

# Bugs in the System

How the FDA Fails to Regulate Antibiotics in Ethanol Production

By Julia Olmstead

Institute for Agriculture and Trade Policy

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### **EXECUTIVE SUMMARY**

Basic microbiology and the principle of natural selection dictate that antibiotic use will tend to spur bacteria to become resistant to antibiotics. This fact underlays growing concern about the public health effects of the 29 million pounds of antibiotics sold annually for animal agriculture, weighing in at over four times the tonnage sold for use in treating sick humans. The U.S. Food and Drug Administration (FDA), tasked with protecting public health, has taken a lax stance on the use of antibiotics in livestock or poultry feed, refusing to place binding regulations on producers that would limit their antibiotic use. Despite rising problems with antibiotic resistance linked to antibiotic use in food animals, and the fact that most antibiotics given to livestock are used for growth promotion, rather to than to treat illness, making their use unnecessary, the FDA has asked that industry to make voluntary reductions and, and essentially, to self-regulate.

Three years ago food safety and public health advocates began to recognize that another sector of agriculture-the corn ethanol industry—also played a role in antibiotic misuse. Many ethanol producers routinely add antibiotics such as penicillin and erythromycin (both important for human health) and virginiamycin and tylosin (both have analogues used to treat humans) to the tanks where they mix corn mash with warm water to ferment ethanol. Bacterial outbreaks are common in ethanol plants (the bacteria like the warm, moist conditions and the corn sugar), and can lead to yield (and therefore profit) losses. Antibiotics help keep bacterial counts low, but fuel isn't the only product that leaves ethanol plants. Producers also sell what is known as "distillers grains" (DGS), the nutrient-rich, leftover corn mash, to cattle, dairy, swine and poultry producers for use as a livestock feed. In 2008 the FDA found antibiotic residues in DGS samples taken from ethanol plants across the country, results that have been confirmed by subsequent studies.

As with antibiotics added directly to livestock feed, the FDA has not restricted the marketing or use of antibiotics in ethanol production, nor have they prohibited or limited sales of DGS that are contaminated with antibiotic residues. The FDA has ruled, however, that antibiotics used in ethanol production should be treated as food additives, and thus require FDA approval before they can be used. This IATP report shows that the FDA has not enforced its own ruling. Companies marketing these antibiotics, and the ethanol producers using them, are therefore doing so unlawfully; and the FDA is violating federal code in not regulating them.

For life-threatening bacterial infections in humans, there are no alternatives to antibiotics. Once resistant bacteria develop from antibiotic misuse, we have forever lost the corresponding tools needed to treat bacterial illness. As with

non-therapeutic antibiotic use in livestock, however, ethanol production does not require antibiotics. Effective, cost-competitive antimicrobial alternatives are readily available to producers. In fact, many ethanol producers have already begun to substitute these products for antibiotics. Given these alternatives, and the very real threat antibiotic misuse poses to public health, there is no good argument for their continued use.

### **Background**

For at least two decades, antibiotics have been an important component of the fermentation process used to make ethanol.¹ Corn ethanol is the product of starches broken down into sugars by yeast. The sugars are then fermented and distilled, all of which happens in tanks full of warm water, a perfect environment not only for yeast but also for growing bacteria. Bacterial contamination is a significant problem for ethanol producers, because the bacteria compete with the yeast for sugar and nutrients and outbreaks can cause significant losses in the yield of the ethanol plant, or even halt the fermentation process.²

To prevent bacterial outbreaks and limit yield losses, many ethanol producers routinely dose fermentation tanks with antibiotics also important to human medicine, like penicillin, erythromycin and tylosin, and virginiamycin. These antibiotics, distributed by animal drug manufacturers and chemical suppliers, are readily available without a prescription. They are inexpensive, and completely unregulated by the FDA. Ethanol producers have full discretion over the quantity and frequency with which they dump antibiotics into their plants. As ethanol production has exploded, from 4.5 to 12.5 billion (Figure 1) gallons per year between 2005-06 and 2009-10, antibiotic use also has undoubtedly increased, although currently the FDA does not appear to track antibiotic sales to ethanol producers, as it does sales for use in animals.<sup>3</sup>

Until recently, there was little concern about the unintended side effects of using antibiotics in this way. For example, could widespread use of these antibiotics in making ethanol undercut the effectiveness of their close human analogues in treating sick people? That very real health threat led the FDA to recognize that adding antibiotics to livestock feed contributes to the spread of antibiotic-resistant infections in people. FDA data reveal more than 80 percent of all antimicrobials sold in the U.S. are sold for use in agriculture.<sup>4</sup>

Fuel isn't the only product that leaves an ethanol plant. After the ethanol is distilled, the remaining corn mash and liquid slurry is sold either wet or dry as an animal feed, a product known as distillers grains with solubles (DGS) (the solubles are a nutritious, molasses-like liquid created when some of the slurry water is separated from the mash and condensed; it's typically added back into the distillers grains to boost nutrition values) (see box). In the last decade, accompanying the increase in ethanol production, DGS production and sales have exploded. From 2000 to 2010, DGS production increased 1,264 percent, from 2.5 to 34.1 million metric tons per year. The beef industry uses 41 percent of all DGS, the dairy industry consumes 26 percent, 5 percent are fed to swine and 4 percent to poultry; 22 percent are exported for use by meat producers overseas. DGS have rapidly become a mainstay of the conventional livestock diet, replacing 914 million bushels of traditional corn feed in the 2010-11 production year. Much of U.S. conventional beef and dairy cattle consume some amount of distillers grains.

# Distillers grains definition from an Ohio State University Extension Fact Sheet:

In the United States most of the ethanol produced currently is made from corn but other grains can be used. The corn is processed and mixed with yeast that converts the starch into ethanol and carbon dioxide. The ethanol is distilled off and the remaining liquid is centrifuged to remove some water. This residue is called wet distillers grains and usually has 30 to 35% dry matter (DM) and contains most of the fiber, fat, protein, and minerals found in the original grain used to make the ethanol. The liquid removed by centrifuging is usually partially dried and becomes condensed distillers solubles. Condensed solubles are a good source of protein, energy, and vitamins but have the consistency of molasses, making feeding difficult. Most distilleries add the condensed solubles back to the wet distillers grains making wet distillers grains with solubles (WDGS). The wet products are either fed as-is or are heatdried producing dried distillers grains with solubles (DDGS).

Most of the distillers grains fed to livestock are dried distillers grains with solubles, and in the popular press, the abbreviation "DDGS" is commonly used. Many of the studies and documents referenced in this report, however, discuss either wet distillers grains with solubles or dried distillers grains with solubles, or both. To be comprehensive and minimize confusion, we have decided to use the abbreviation "DGS" throughout the report to refer to both wet and dried distillers grains with solubles.

Figure 1: U.S. Ethanol Production 1993-2011

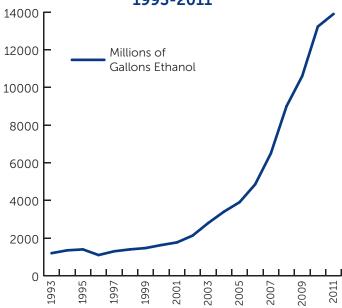
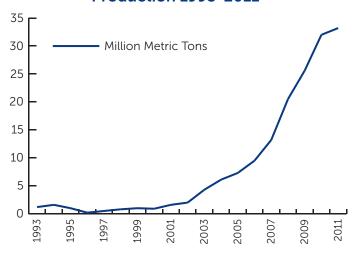


Figure 2: U.S. Distillers Grain Production 1993-2011<sup>7</sup>



In 2008, amid increasing public concern over the use of antibiotics in animal production, the Food and Drug Administration (FDA) collected and tested 60 DGS samples for residues of virginiamycin (a streptogramin antibiotic with an important human analogue, Synercid), erythromycin and tylosin (another macrolide antibiotic, like erythromycin, that may spur crossresistance to the latter). Of the 45 samples analyzed, 24 (53 percent) came back positive, according to Dr. Daniel McChesney, director of the FDA/Center for Veterinary Medicine's (CVM) Office of Surveillance and Compliance. Fifteen of the samples contained residues of virginiamycin, twelve contained residues of erythromycin, and five contained residues of tylosin. Some

were detected at levels considered significant, according to the FDA, including residue levels exceeding 0.5 parts per million (ppm).9

These test results were exceedingly important because they disproved the belief that antibiotic use in ethanol production was benign vis-à-vis public health. This study showed the opposite: Antibiotic use in ethanol production increases the load of nontherapeutic antibiotics being fed to livestock, which the FDA itself acknowledges is a public health threat needing to be addressed.<sup>10, 11</sup>

To date, the FDA has refused to publish the full results of their 2008 survey of antibiotic residues in DGS. It has given no rationale for this failure in transparency. At a 2010 meeting of the Association of Animal Feed Control Officials (AAFCO), an employee at the FDA's Center for Veterinary Medicine (CVM) stated the FDA would never publish the study results. IATP obtained the numbers from a National Grain Council Association newsletter; a CVM official later confirmed them via email.<sup>12</sup>

In 2010, the FDA carried out a second round of antibiotic residue testing, the results of which were recently published in a CVM bulletin. The FDA collected and analyzed 46 samples—18 import samples and 28 domestic samples—for residues of 12 antibiotics (ampicillin, penicillin G, chlortetracycline, oxytetracycline, tetracycline, clarithromycin, erythromycin, streptomycin, virginiamycin M1, bacitracin A, chloramphenicol, monensin, and tylosin). They found four positive samples. In the three positive domestic samples (Table 1): sample 1 contained virginiamycin M1 detected at 0.16 ppm, sample 2 contained erythromycin detected at 0.58 ppm, sample 3 contained virginiamycin M1 detected at 0.15 ppm and penicillin detected at 0.24 ppm. The positive import sample, from Canada, had a detected residue of 0.18 ppm of virginiamycin M1.<sup>13</sup>

Table 1: Positive antibiotic residue results from 2010 FDA distillers grains testing

Positive Sample	Antibiotic Found	Residue Level (parts per million)	
1	Virginiamycin M1	0.16	
2	Erythromycin	0.58	
3	Virginiamycin M1	0.15	
4	Penicillin	0.24	
Import	Virginiamycin M1	0.18	

These results were also reported in an abstract for an as-yet unpublished paper, "Impacts of low level microbial residues in distillers grains," to be presented at an academic conference in May 2012. <sup>14</sup> In the abstract, CVM researchers report on further

testing they carried out to analyze the impact of exposure to antibiotics at the levels found in the 2010 survey on two species of bacteria that can cause disease. From the abstract:

Enterococcus sp and Campylobacter sp with known minimum inhibitory concentrations were exposed to low levels (≤1.0 µg/ml) of pen, vir, a pen/vir blend (93%/7%), and ery. The strains were evaluated for decreased susceptibility to the test antimicrobials. Results indicate that low levels of pen, vir and the pen/ vir blend did not select for strain variants with decreased susceptibility. In contrast, ery gave mixed results. There was no selection for resistance in Campylobacter sp. (0.5 µg/ml) or in Enterococcus sp. (0.1 µg/ml). However, resistant variants of Enterococcus sp were observed with 0.25 and 0.5  $\mu g/ml$  ery. It was concluded that pen and vir (≤1.0 µg/ml) or ery (0.1 µg/ml) did not select for resistant variants. However exposure of Enterococcus sp. to ery (0.25 and 0.5  $\mu$ g/ml) did select for resistant phenotypes. Given these results it is suggested that ery residues in distillers grains be more fully evaluated given the importance of this antimicrobial in clinical medicine.

Put more simply, their study found that virginiamycin and penicillin at the levels present in the DGS samples did not select for resistance (i.e., allow the susceptible bacteria to die off and the resistant bacteria to thrive) among Campylobacter bacteria (a major cause of food poisoning) or Enterococcus bacteria (resistant strains of which cause significant problems in hospitals).

Erythromycin, however, at the 0.58 ppm level found in DGS samples, did select for resistance in Enterococcus bacteria. While the results bear follow-up research—which one would hope a public agency would make public—the bottom line is this: Residues of antibiotics in DGS—the predictable result of adding antibiotics to ethanol fermentation vats—have the potential to cause increased antibiotic resistance impacting the human population.

The ethanol and antibiotics industries have often claimed that any lingering antibiotic residues in DGS are rendered inactive through processing. In combination with the FDA findings, other recent research may have put a definitive stake through that claim. Researchers at the University of Minnesota did quarterly collections of 20 distillers wet grains with solubles samples and 20 distillers dried grains with solubles samples from ethanol plants throughout the U.S. and tested them for virginiamycin, penicillin, tetracycline, erythromycin and tylosin residues. They then tested the residues they found on so-called sentinel species of gut bacteria, E. coli and Listeria monocytogenes, to see if antibiotics at that level were active. All of the 117 DGS samples tested to-date contained antibiotic

residues; one sample was found to have antibiotic residue active enough to inhibit E. coli growth. <sup>16</sup> These study results have yet to be published in the scientific literature but were confirmed in a phone call with one of the study's authors. <sup>17</sup>

Despite the FDA's clear indication of concern about the safety of antibiotic residues in DGS, and all the data that confirm those concerns are well founded, the FDA has taken no steps to begin to limit this antibiotic use or to make public the full results of its research on the issue.

# Failure to regulate

Federal law requires the FDA to regulate any substance that alters human or animal food. The Food Additives Amendment of 1958 (Public Law 85-929, 72 Stat. 1784, which will be referred to as "the Amendment" in this report), an amendment to the Federal Food, Drug and Cosmetic Act of 1938 (FFDCA), put forth a mandate and framework for the regulation of substances that are added to food.

Food, according to the U.S. Congress, is "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article" (21 USC 321 (f)). The Amendment created a separate, and very specific, definition for substances that are added to food. The statutory definition is as follows:

The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include -

- 1. a pesticide chemical residue in or on a raw agricultural commodity or processed food; or
- 2. a pesticide chemical; or
- 3. a color additive: or

- 4. any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph 4 pursuant to this Act [enacted Sept. 6, 1958], the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following);
- 5. a new animal drug; or
- 6. an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

Clearly, the definition leaves much room for interpretation. In the context under consideration in this report, however, it seems to follow that the use of a given antibiotic in ethanol production (1) "results or may reasonably be expected to result directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food [distillers grains]" and (2) does not fit into any of the categories 1–6 (these substances/uses are excluded because they are regulated elsewhere) that would exempt the given antibiotic from being classified as a "food additive." If, then, the antibiotics used in ethanol production and present in DGS are Food Additives, they must be regulated as such.

The law's definition of a food additive, however, leaves room for another mechanism of exclusion (and regulation), known as "generally recognized as safe" (GRAS), delineated in this section of the statement:

[...]if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use[...]

Soon after the Amendment was passed in 1958, the FDA created a list of food substances that were, when used for the intended purposes and under good manufacturing practices, generally recognized as safe. Substances considered GRAS are exempted by the Amendment from the FDA approval requirement, and can be marketed for and used in food without the FDA's knowledge.

Citing the impossibility of listing all substances that are GRAS for their intended use, the FDA allowed that manufacturers themselves can determine whether there is sufficient scientific data to support a GRAS determination. A GRAS determination requires "a reasonable certainty in the minds

of competent scientists that the substance is not harmful under its intended conditions of use" (21 CFR 570.3(i)). In 1997, the FDA proposed a rule creating a voluntary process for manufacturers to submit notice of their GRAS determinations, along with supporting information, to the FDA for review. The FDA does not then "approve" or "deny" the GRAS determination, but may state in a letter that it does or does not have questions about the manufacturer's GRAS determination. Again, this process is voluntary and not required prior to the marketing or use of a substance.

# Placing public safety in the hands of the animal agriculture industry

It is the GRAS framework under which antibiotics manufacturers have been marketing products to the ethanol industry and adulterating the U.S. food supply.

Until 2010, the voluntary GRAS notification program had applied only to substances added to human food. In that year, the FDA announced the pilot of a companion program for substances in animal food to be administered by its Center for Veterinary Medicine (CVM).18 Since the launch of that pilot, four GRAS determination notices have been submitted to the CVM19 (table 2). In December 2010, Lallemand Specialties, Inc., a Milwaukee, Wisconsin-based company that manufactures and markets yeasts, bacteria, and antimicrobials, submitted a notice for penicillin G potassium, and in March 2011, submitted a GRAS notice for virginiamycin. For unknown reasons, in August 2011 Lallemand asked the CVM to cease reviewing these notices and submitted new notices for the same products in September 2011. The CVM has not made publicly available the information submitted by Lallemand in support of the determination. In addition, Lallemand has issued three public announcements of its GRAS determinations, for its products Lactoside V (virginiamycin), Lactoside 247 (virginiamycin), and Allpen Special (penicillin).

Phibro Animal Health Corporation, a Ridgefield Park, New Jersey-based company that manufactures and markets animal feed additives and specialty chemicals, made a public announcement in June, 2010, of its GRAS determination for its Lactrol (virginiamycin) product. To date, the company has not submitted a notice of this determination to the CVM. Because GRAS determination notices are voluntary, it is unknown if others have been carried out. Lallemand and Phibro are not the sole marketers of antibiotics to the ethanol industry.

Table 2: GRAS notices submitted to the FDA

Company	Product	Date Submitted	Status
Lallemand Specialties, Inc.	Penicillin G. Potassium	12/23/2010	"At notifier's request, FDA ceased to evaluate the notice."
Lallemand Specialities, Inc.	Virginiamycin	3/16/2011	"At notifier's request, FDA ceased to evaluate the notice."
Lallemand Specialities, Inc.	Penicillin G. Potassium	9/15/2011	Pending
Lallemand Specialities, Inc.	Virginiamycin	9/15/2011	Pending

In all four public announcements the companies made clear their belief that their own GRAS determination represented full compliance with federal regulations. Lallemand's announcement regarding Lactoside 247 (virginiamycin), reads "The Lactoside 247 TM GRAS determination achieves full regulatory compliance and obviates the need for a Food Additive Petition." (emphasis added) Phibro's Lactrol (virginiamycin) announcement states, "To meet FDA requirements and protect Lactrol's proprietary active ingredient, Phibro pursued a GRAS determination, an equally acceptable option for regulatory compliance (emphasis added)." Indeed, Lallemand and Phibro do appear to have correctly followed the procedures for GRAS self-determination, as stipulated by the Amendment.

But the antibiotics used as processing aids in ethanol production are considered food additives by the FDA, and are therefore not eligible for GRAS status. As food additives, antibiotics in ethanol production instead are subject to FDA regulation, and are not allowed to be marketed before the FDA has approved a Food Additive Petition for the substances. In other words marketing and use of antibiotics in ethanol is and has been unlawful.

## Skirting the law?

There is mounting evidence that some antibiotics suppliers have been fully aware that the FDA considers antibiotics used for ethanol processing food additives, and have been exploiting the FDA's failure and unwillingness to follow its Congressional mandate to regulate these substances.

At a January 19, 2011 meeting of the AAFCO ("a voluntary membership association of local, state and federal agencies charged by law to regulate the sale and distribution of animal feeds and animal drug remedies") Laboratory Methods and Services Committee, Dr. John McCurdy, a CVM chemist, presented the FDA's position on antibiotics in distillers grains in a memo distributed to committee members.

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### FDA Thinking/Position

Distillers grains are fed continuously to animals, and may constitute a significant portion of their diet. FDA is concerned because the continuous consumption of distillers grains containing low level antibiotic residues by food-producing animals may impact antimicrobial resistance in humans and animals.

In the past, CVM has issued letters stating that we would exercise enforcement discretion with respect to the use of certain antibiotics in ethanol production. However, because of the increasing amount of distillers grains being produced and consumed by animals, as well as FDA's concerns about antimicrobial resistance and other food safety concerns, CVM has decided to no longer exercise enforcement discretion for antibiotics in ethanol production. When the distillers grains are used as a feed or feed ingredient the antimicrobial would be considered a Food Additive and regulated by the FDA.

FDA is strongly recommending that athanol producers research alternatives for controlling bacterial contaminations.

### Industry Response

FAP Submissions: erythromycin thiocyanate; virginiamycin; penicillin G procaine

GRAS Notification: penicillin G potassium GRAS self-determination: virginiamycin

Figure 3: Excerpt from CVM memo.

The memo includes this statement: "CVM has decided to no longer exercise enforcement discretion for antibiotics in ethanol production. When the distillers grains are used as a feed or feed ingredient the antimicrobial would be considered a Food Additive and regulated by the FDA."<sup>20</sup> (Fig. 3)

In confidential follow-up conversations with two CVM staff members (names withheld), this classification of antibiotics used in ethanol production as Food Additives was confirmed.<sup>21</sup> IATP was told that **the FDA had determined the Food Additive status five or six years ago** and that the determination meant that these antibiotic uses could not therefore be considered GRAS. When IATP asked for further documentation of this determination, we were told that none was publicly available. However, the CVM's own Annual Report for Fiscal Year 2008 corroborates this position (Fig. 4):

the use of antibiotics during fuel ethanol production. FDA regulates distiller byproducts from both potable and fuel ethanol production when the byproducts are used as animal feed and/or feed ingredients, regulating antibiotic residues as food additives (emphasis added). If the distiller byproduct is burned as fuel or disposed of in another non-food/non-feed manner, however, the antibiotics would be considered pesticides and regulated by the Environmental Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act.<sup>22</sup>

Antibiotics manufacturers, and likely the ethanol producers, knew this was the case. In 2010 and 2011, three Food Additive Petitions (FAPs) were submitted to the FDA for antibiotics to be used specifically in ethanol production. Ferm Solutions, Inc., a Danville, Kentucky–based company that markets antimicrobials and other products to the ethanol industry, submitted an FAP for virginiamycin, a notice of which was published in the Federal Register on October 12, 2010.<sup>23</sup> North American Bioproducts Corporation (NABC), a Georgia–based company, submitted FAPs for Penicillin G Procaine and for Erythromycin thiocyanate, notices of which were published in the Federal Register on September 14, 2010 and April 25, 2011, respectively.<sup>24</sup> Decisions on these FAPs are pending.

These FAP submissions were likely prompted by communications to antibiotics manufacturers of the FDA's position. NABC put out a press release on August 30, 2010, announcing the FDA's acceptance for filing of its FAP for erythromycin thiocyanate. According to the release:

In 2008 and 2009, the FDA/CVM gave clear direction to the ethanol industry and certain antibiotic suppliers that because they can reasonably be expected to become a component of the feed, i.e. distiller by-product, antibiotics are considered food additives and expressly stated that antibiotics are not recognized as GRAS for use in Fuel Ethanol Production.<sup>25</sup>

The FDA/CVM has not made available to the public its communications to the industry. However, numerous

the use of antibiotics to prevent bacterial growth during ethanol fermentation. Any residual antibiotics in distillers grains could transfer to animals and pose a potential health risk to the animals as well as to humans that consume food derived from the animals.

In 2008, CVM worked with the Environmental Protection Agency to clarify the respective roles of the agencies with regard to regulatory jurisdiction over the use of antibiotics during fuel ethanol production. FDA regulates distiller byproducts from both potable and fuel ethanol production when the byproducts are used as animal feed and/or feed ingredients, regulating antibiotic residues as food additives. If the distiller byproduct is burned as fuel or disposed of in another non-food/non-feed manner, however, the antibiotics would be considered pesticides and regulated by the Environmental Protection Agency under the Federal Insecticide, Fungicide, and Rodenticide Act.

CVM also worked actively during the year with the U.S. Department of Agriculture's Food and Agricultural Service and the Canadian Food Inspection Agency to address potential distillers grain trade issues between the United States and Canada as a result of the issuance of the Canadian Food Inspection Agency's Regulatory Guidance Document on Ethanol Distillers Grains for Livestock Feed in July 2008. The goal is to harmonize policies in this area.

Figure 4: Excerpt from CVM's Annual Report for Fiscal Year 2008.

In 2008, CVM worked with the Environmental Protection Agency to clarify the respective roles of the agencies with regard to regulatory jurisdiction over industry newsletters and other sources clearly cite the FDA's directives on the issue.

In the September/October 2009 edition of Chaff, the American Association of Grain Inspection and Weighing Industries newsletter, the editors report "FDA/CVM has emphasized that no antibiotic residues are currently allowed in DGS intended for use as a feed ingredient."<sup>26</sup>

An April 9, 2009, article about the first round of FDA antibiotic residue testing in DTN/The Progressive Farmer, a widely-read online agriculture news journal, reported the following:

Perhaps the bigger concern is that ethanol producers were found to be using four types of antibiotics, when virginiamycin is the only antibiotic receiving a "no objection letter" from the FDA.

Charlie Staff, executive director and CEO of the Distillers Grain Technology Council, agreed that is a concern.

"That is very troubling," Staff said. "We are hopeful those using other antibiotics will stop using them because they are unapproved.

"They could be opening themselves up to regulatory action," he said.<sup>27</sup>

The National Grain and Feed Association reported the following on its website on January 28, 2010:

Pursuant to the use of antibiotics during the production of distillers grains, FDA has issued a "letter-of-no-objection" for the use of only virginiamycin-based products when such use results in residue levels not exceeding 0.5 parts per million (p.p.m.). Further, FDA now is requiring that such virginiamycin-based products, as well as all other antimicrobial products to be used during the production of distillers grains that will be distributed as a feed ingredient, be approved through a formal food additive petition process administered by the agency (emphasis added).<sup>28</sup>

Other federal agencies seem to have gotten the same message from the FDA. An October 2011 report from the United States Department of Agriculture's Economic Research Service on DGS usage states:

In the past, the Center for Veterinary Medicine (CVM) did not object to specific uses of antibiotics through enforcement discretion which was provided on a temporary basis. This enforcement discretion has expired and currently no antibiotic residues are allowed in distillers' grains intended for use as a feed ingredient.<sup>29</sup>

As referenced in the latter two articles, the FDA released a "no-objection" letter to Phibro Animal Health (then known as SmithKline Beecham Animal Health) in 1993 for a virginiamycin product, and stated that it would exercise enforcement discretion (in other words, it would essentially ignore its use). The letter addresses only the Lactrol formulation of virginiamycin, and allows a maximum residue level of 0.2-0.5ppm.

In a January 2009 address at an International Feed Regulator's meeting in Atlanta, Georgia, CVM Office of Surveillance and Compliance Director Daniel McChesney said the agency was reviewing the appropriateness of the "no-objection" letter.³0 According to reports from the National Grain and Feed Association, McChesney expressed concerns that virginiamycin residues found during the 2008 FDA DGS sampling exceeded the 0.5 ppm threshold.³1

This report documents clearly that DGS containing antibiotics residues are food additives, and should be regulated as such. It is clear that antibiotic manufacturers and marketers have been aware since at least 2009 that the FDA does not consider antibiotics in DGS to be GRAS. Given the FDA's prohibition on marketing unapproved food additives, the antibiotics manufacturers must immediately stop marketing the drugs to the ethanol industry and pursue (or continue to pursue) FAP approval.

Moreover, the FDA—as authorized by the Federal Food, Drug, and Cosmetic Act—must immediately put an end to this regulatory breach and issue an order to antibiotics manufactures to stop marketing these products, and to the ethanol industry to cease unapproved antibiotic use in ethanol production.

# Readily available alternatives

Bacterial contamination is a real problem for the ethanol industry. Fortunately, effective non-antibiotic antimicrobial products are widely available to ethanol producers.

A 2009 IATP paper estimated that 45 percent of ethanol production facilities in the U.S. were, at that time, using antibiotic alternatives (either to partially or entirely replace antibiotics). Based on figures provided by antibiotic-alternative vendors, 56 percent of ethanol producers now use some form of antibiotic alternative. POET, the largest ethanol producer in the world, recently announced that all of its 27 plants are antibiotic-free. A small number of those plants are third-party certified antibiotic-free, a step that allows the company to market antibiotic-free DGS to the layer hen industry, where DGS with antibiotic residues are prohibited. According to a POET spokesperson, all plants are antibiotic-free and can be certified as market demand

for antibiotic-free DGS increases. The POET process is proprietary, and the company has not released details as to how they are avoiding antibiotics.

There are two commercial alternative antimicrobial products available. "Stabilized chlorine dioxide" (sold under the DuPont brand name "Fermasure") is buffered sodium chlorite, a salt with antimicrobial properties activated by the fermenter's own bacteria. The acidic nature of the bacteria converts the sodium chlorite to chlorine dioxide, a disinfectant used frequently in water treatment facilities, which degrades to a residue of chloride and sodium ions (salts). According to the manufacturer, no free chlorine or dioxins are produced in the process.

At least 65 producers are using an enzyme derived from hops, the same type as those used in breweries.<sup>34</sup> Hops extract is a natural antimicrobial, and the makers of IsoStab, the brand name for a hops extract produced for the ethanol industry by BetaTec, Inc., say adding the right hops-based enzymes not only controls bacteria, but also creates conditions under which yeast thrive.

Eliminating antibiotics from ethanol production would represent a significant production change for many producers, and may result in a temporary increase in expenses during the testing and installation phases. The risks to public health potentially posed by antibiotic use in ethanol production, however, far outweigh the modest costs of this transition. To ease the burden on producers, federal and state governments could offer technical support to the industry to make the switch as rapid and as burden-free as possible.

# **Policy recommendations**

This report has presented substantial evidence that antibiotics used in ethanol production are food additives and not GRAS. In light of that evidence, the Institute for Agriculture and Trade Policy makes the following policy recommendations:

THE FDA SHOULD IMMEDIATELY ENFORCE THE LAW AND BAN SALES OF UNAPPROVED ANTIBIOTICS TO ETHANOL PRODUCERS. There is ample evidence indicating the FDA considers antibiotics used in ethanol production a food additive and therefore not GRAS. As a result, pursuant to 21 C.F.R. 570.38(b)(1), the FDA should immediately "issue a notice in the FEDERAL REGISTER proposing to determine that [antibiotics used in ethanol production] [...] are not GRAS and are a food additive subject to section 409" of the FFDCA.

ANTIBIOTICS MANUFACTURERS SHOULD IMMEDI-ATELY HALT MARKETING ANTIBIOTICS TO THE ETHANOL INDUSTRY. The documentation in this report shows that antibiotics producers were likely aware of the FDA's position on the status of antibiotics used in ethanol production but continued to market them anyway. Pursuant to Section 409(a) (2) of the FFDCA, which bars the use of a food additive unless "there is in effect, and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used," sales of antibiotics for ethanol production are unlawful until a FAP for their use has been approved.

THE ETHANOL INDUSTRY SHOULD VOLUNTARILY STOP USING ANTIBIOTICS. IMMEDIATELY. Antibiotic overuse threatens both human and animal health. Antibiotic use in livestock and poultry is a major contributor to this problem, and antibiotic use in ethanol production compounds it. Antibiotic alternatives exist for ethanol production—alternatives proved viable and economical by dozens of producers already. Given these alternatives and the legal status of antibiotics for ethanol production, there are no good arguments for continued antibiotic use by ethanol producers.

USDA, DOE AND OTHER RELEVANT STATE AND FEDERAL AGENCIES SHOULD ASSIST ETHANOL PRODUCERS CURRENTLY USING ANTIBIOTICS. This help could include both direct technical assistance, as well as potential financial support through existing programs to ensure that ethanol producers are able to transition quickly away from antibiotic use.

### **Endnotes**

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