KEEP ANTIBIOTICS WORKING

The Campaign to End Antibiotic Overuse

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA–2010–F–0510

Keep Antibiotics Working (KAW) and the undersigned groups are writing to provide comments on the Ferm Solutions, Inc. Food Additive Petition (Animal Use) for Virginiamycin, Docket No. FDA–2010–F–0510. The Ferm Solutions petition asks that the Food and Drug Administration (FDA) approve the feeding of distiller grains, a by-product of ethanol production, to food producing animals even when the distiller grains contain the medically important antibiotic virginiamycin. Virginiamycin enters the distiller grains when it is used during ethanol production to inhibit bacterial growth. Distiller grains are often used as animal feed, including the feed of food producing animals like beef cattle.

Keep Antibiotics Working is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than eleven million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in food animals.

The FDA should not approve the Ferm Solutions food additive petition for virginiamycin in distiller grains. To do so would: a) ignore the availability of safer, cost-effective alternatives; b) contradict basic public health principles; c) set a poor precedent for a public health agency; and d) contradict the agency's own stated policy and internal guidance on antimicrobial resistance.

Safer, cost-effective alternatives. Viable alternatives to antibiotics generally, and to virginiamycin in particular, exist to control microbes in ethanol production, a fact demonstrated by the large number of ethanol producers who have already phased out or decreased their use of antibiotics in fermentation (Deutscher, 2009; Lushia and Heist, 2005; Nixon, 2009; Olmstead, 2009).

The public health threat. Antibiotic resistance poses a threat to every one of us. Basic microbiology demonstrates that any use of antibiotics can potentially add to the selection pressure in the broader environment for antibiotic resistance. Their use in ethanol

production is no exception. As KAW has previously argued, the existence of effective, cost competitive alternatives to antibiotics for ethanol production means there are no public health grounds for permitting the use of antibiotics in livestock feeds, since there are no animal or human health benefits.

Virginiamycin is a member of the streptogramin class of antibiotics that includes Synercid, an important drug for treating patients with severe infections associated with Gram-positive bacteria, including strains resistant to other antibiotics. Synercid is approved for the treatment of "serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia" and "complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible) or *Streptococcus pyogenes*" (FDA, 2008).

In the FDA's risk assessment on the use of virginiamycin as a feed additive (an assessment that was never completed), the agency found that feed additive use would lead to between 2 and 391 people being adversely affected each year due to resistance in *Enterococcus faecium*, just one of the 3 pathogens for which streptogramins are approved in humans (FDA, 2004). Extrapolating this finding to the more than 16,000 patients treated annually with streptogramins means that up to 1 in 50 could be negatively impacted by virginiamycin use in feed. The risk assessment was not completed because there was not sufficient data to determine to what extent *E. faecium* from livestock are able to cause human disease or to transfer resistance genes to humans. Since then, studies have provided compelling evidence that resistant *enterococci* from livestock are able to cause human illness (Larsen, 2010) and that resistance determinants can be transferred from livestock to human strains of *enterococci* in the human gut (Lester, 2006; Hammerum, 2010). Linezolid is an alternative drug for treating VREF and other serious gram positive infections, but globally resistance is on the rise to linezolid (Rossolini, 2010), so streptogramins likely will become even more important in the future.

While the food additive petition does not state the allowed level of virginiamycin contamination in distiller grains the sponsors are seeking, it does state that virginiamycin has been found at .54 ppm in distiller grains. It is unclear from the data provided whether levels much higher might be found in distiller grains, but even at this level there is a real risk for the selection of streptogramin resistant microorganisms. The level found in distiller grains is close to the clinical breakpoint for resistance in the organisms for which streptogramins are approved in humans. Clinical breakpoints for *Enterococcus faecium*, *Staphylococcus spp*., and *Streptococcus spp*. are 4 ppm for resistance. Organisms with a MIC of equal to or less than 1 ppm are considered susceptible. Because of this, the use of distiller grains contaminated with virginiamycin in livestock feed will likely result in the selection of streptogramin resistant organisms similar to what occurs when virginiamycin is intentionally fed to food producing animals for growth promotion or disease prevention. The feeding of streptogramin contaminated distiller grains to food-producing animals puts the use of streptogramins at risk for the treatment of these and other important diseases in humans and animals.

The widespread feeding to animals of low levels of viginiamycin in distiller grains could also contribute to the selection and spread of resistance to drugs other than streptogramins, including drugs in other antimicrobial classes through multiple mechanisms. This includes co-selection, selection for bacteria resistant to related drugs that work by stopping protein synthesis like macrolides, lincosamides, and oxazolidinones, and increasing the mutation rate of exposed bacteria.

Gram positive bacteria on farms, at slaughter, and in animal products sampled at retail are often resistant to multiple antibiotics including streptogramins (CVM, 2007; Diarra, 2010; Fluckey, 2009). Co-selection where organisms have linked genes conferring resistance to multiple drugs has been shown to be a likely cause of the persistence of drug resistance in the absence of selection pressure in *enterococci* in food producing animals (Aaerstrup, 2000). In this manner, the feeding of grains containing virginiamycin could contribute to the spread of resistance to drugs in unrelated antimicrobial classes.

Virginiamycin, like other streptogramins, can be grouped with other antibiotic classes that work by disrupting bacterial protein synthesis by binding to the same site on the bacterial ribosome, i.e., macrolides, lincosamides, streptogramins, ketolids, and oxazolidinones (Roberts, 2008). There are numerous genetic determinants that confer resistance to members of this group, creating the likelihood that the use of one of these drugs can select for resistance to other members of the group. Of particular concern are *erm* genes which confer resistance to macrolides, lincosamides, and streptogramins and *cfr* genes which confer resistance to pleuromutilins and oxazolidones, in addition to those conferred by *erm* genes. Both *erm* and *cfr* genes can be transmitted horizontally between bacteria and have been identified in isolates from food producing animals sometimes with a single organism harboring both types of gene (Martel, 2005; Kehrenberg, 2009). Because of the related mechanisms of action, the widespread feeding of virginiamycin will likely contribute to the spread of resistance determinants that not only put at risk streptogramins but numerous other classes of antibiotics.

Finally, the exposure of bacteria to low levels of bactericidal antimicrobials has been shown to lead to multidrug resistance though increasing the mutation rate (Kohanski, 2010).

Clearly, it is not in the interest of public health to allow the feeding of virginiamycin to potentially billions of animals for no medical purpose, as proposed in this petition.

Inconsistent with FDA policy and guidance. The proposed use of virginiamycin in livestock feeds is inconsistent with the FDA's stated policy on the inappropriateness of the non-therapeutic use of antimicrobials in food producing animals and the current risk management framework for antimicrobial resistance as described in Guidance for Industry #152 (GFI152).

The FDA has publicly stated its opposition to the use in food animals of medically important antibiotics for purposes other than animal health in testimony before Congress (Sharfstein, 2009; Sharfstein, 2010) and in its release of a thinking paper on the non-therapeutic use of antimicrobials in food animals (FDA, 2010). Virginiamycin, as part of the streptogramin class of antibiotics, is a medically important antimicrobial and the proposed use in feed provides no animal health benefit.

This proposed use is also inconsistent with the FDA's current policy on assessing the safety of using antimicrobials in food producing animals as described in Guidance for Industry #152. According to the consequence assessment described in Appendix A of GFI152, the FDA considers virginiamycin to be "highly important" for human health. Under GFI152 Table 5, the exposure assessment will be either "medium" or "high" because consumption of beef, the commodity associated with the livestock sector currently associated with distiller grains feeding, is high. Combining the "highly important" consequence assessment with the "medium" or "high" exposure assessment, based on GFI152 Table 6, gives an overall risk estimate of either high or medium, or category 1 or 2.

Because virginiamycin contaminated distiller grains are not intended as a drug for at risk animals, they would be fed to whole flocks or herds. This is inconsistent with the risk management recommendations for both high and medium risk uses of antimicrobials under GFI152. Table 8 of that guidance recommends that category 1 and 2 drugs be limited to low or medium use, which means they should not be used on a flock or herd wide basis.

Conclusion

Allowing the feeding of virginiamycin to potentially billions of animals for no medical purpose as proposed in this petition is not in the interest of public health. We are also concerned that this petition, if approved, because it is so clearly inconsistent with the risk management framework set out in GFI152, would undermine the guidance and undermine the FDA's entire approach to managing resistance related antimicrobial use in livestock. The feeding of large numbers of animals with low doses of medically important antimicrobials for non-medical purposes contradicts the FDA's own policy statements and guidance on addressing the problem of antimicrobial resistance. Granting this petition would signal that the FDA is not serious in its stated intent to address antimicrobial resistance by reducing the inappropriate use of antimicrobials in food producing animals.

For these reasons, KAW and the undersigned groups recommend that the FDA decide against this petition and not approve the feeding of distiller grains containing virginiamycin to animals.

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