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–2011-F-0225

Dear Sir or Madam,

Keep Antibiotics Working (KAW) and the undersigned groups are writing to provide comments on the Ferm Solutions, Inc. **Food Additive Petition (Animal Use) for Erythromycin Thiocyanate**, Docket No. FDA–2011-F-0225.

The Ferm Solutions petition asks that the Food and Drug Administration (FDA) approve the feeding of distillers grains, a by-product of ethanol production, to food producing animals even when the distillers grains contain the medically important antibiotic, erythromycin. Erythromycin enters the distillers grains when it is used during ethanol production to inhibit bacterial growth. Distillers grains are often fed to food producing animals like beef and dairy 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 erythromycin thiocyanate in distillers grains. To do so would:

- contradict basic public health principles;
- set a poor precedent for a public health agency;
- contradict the agency's own stated policy and internal guidance on antimicrobial resistance; and
- ignore the availability of safer, cost-effective alternatives.

Erythromycin is the treatment of choice for serious Campylobacter infections (IDSA, 2001). Erythromycin use and the resulting contamination of distillers grains, followed by feeding of these grains to food producing animals, will add to the selection pressure for erythromycin resistance in bacteria in these animals and the meat derived from them.

The public health threat. Antibiotic resistance poses a threat to every one of us. Fundamentals of microbiology dictate that any use of antibiotics can add to the selection pressure in the broader environment for antibiotic resistance. Antibiotic use in ethanol production is no exception.

Ferm Solutions acknowledges that erythromycin will be present in distillers grain products at levels estimated to be 0.5 ppm in wet distillers grains and 1.2 ppm in dry distillers grains. These levels are at the same order of magnitude as the approved levels for growth promotion in food producing animals of 5 to 10 ppm, and therefore likely will be providing antibacterial activity (and selection pressure) at this level. The Joint FAO/WHO Expert Committee on Food Additives (WHO, 2006) summarized studies for minimum inhibitory concentrations of erythromycin in multiple bacterial species and found MICs from .1 to 1 ppm, many well below the levels expected in distillers grains if erythromycin is used as proposed. To reiterate, therefore, erythromycin will be biologically active in feed resulting from the proposed use and will therefore select for antimicrobial resistance.

Erythromycin, like other macrolides, 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., 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 erythromycin will likely contribute to the spread of resistance determinants that not only put at risk macrolides but numerous other classes of antibiotics.

Erythromycin is the treatment of choice for serious Campylobacter infections (IDSA, 2001). The main alternative, ciprofloxacin, is not recommended for use in children, and more than 20% of Campylobacter isolates from sick humans are ciprofloxacin resistant (CDC, 2008). Food producing animals including cattle often carry Campylobacter without any signs of illness (Horrocks, 2009). Campylobacter from livestock can lead to human illness through direct contact with animals, consumption of contaminated animal products, and through untreated or improperly treated drinking water contaminated with livestock wastes (Wagenaar, 2006; Cools, 2003). Subtherapeutic doses of macrolides have been shown to lead to increased resistance in Campylobacter in food producing animals as compared to animals treated at a therapeutic doses or untreated controls (Ladely, 2007.) Macrolide resistance in Campylobacter is mainly linked to point mutations in ribosomal genes that modify the binding site of macrolides making them ineffective (Gibreel and Taylor, 2006). Because of this, low level macrolide use could select for the clonal spread of macrolide resistant Campylobacter in food animal reservoirs.

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

Inconsistent with FDA policy and guidance. The proposed use of erythromycin 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 (FDA, 2003). Both the FDA and the

World Health Organization (FDA, 2003;WHO, 2009)consider the macrolide class of drugs including erythromycin to be critically important, the highest ranking, for human medicine. For the FDA, macrolides are one of only four classes of antimicrobial considered to be critically important. In addition, the World Health Organization includes macrolides as one of the top three antimicrobial classes needing attention.

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). The FDA (2011) includes within it Strategic Priorities for 2011-2015 measures to "limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation". The proposed use of distillers grains containing erythromycin meets neither of the conditions that FDA has stated should be met for the appropriate use of this medically important antimicrobial in food producing animals. On this basis alone the FDA should not approve this feed additive petition and should use its existing authority to prohibit the sale of feed containing these unapproved additives.

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 (GFI152). According to the consequence assessment described in Appendix A of GFI152, the FDA considers erythromycin to be "critically 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 distillers grains feeding, is high. Combining the "critically important" consequence assessment with the "medium" or "high" exposure assessment, based on GFI152 Table 6, gives an overall risk estimate of high, or category 1.

Because distillers grains containing erythromycin as a result of antibiotic use in ethanol production 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 high risk uses of antimicrobials under GFI152. Table 8 of that guidance recommends that category 1 drugs be limited to low use, which means they should not be used on a flock or herd wide basis. And should only be used for a limited duration.

Failure to consider impact of resistant organisms on environment. The Ferm Solutions petition fails to consider the environmental impact of resistant organisms that result from the proposed use and then migrate from the livestock feeding operation into the environment through multiple pathways including air, water, and through wildlife. The petition does note that the level in distilled grains is lower than approved levels in livestock, but the anticipated level is still high enough to be biologically active. The Ferm Solutions petition supplies no information on what is the anticipated impact on resistance in the microbial community on farms where animals are fed distillers grains with erythromycin at this level.

It is insufficient to state that the level in distillers grains is lower than the level in existing drug approvals, because the condition of use will be different for distillers grains. In the case of antimicrobials used as approved drugs, the drug will only be used in certain circumstances when the livestock owner determines there is adequate reason. The erythromycin in distillers grains will be fed for no reason whatsoever, and has the potential to occur on a much wider level. In addition,

resistance selection is not simply correlated with dose; in fact, lower doses may result in greater selection pressure. Selection pressure is also dependent on other factors such as duration and number of animals receiving the antimicrobial.

The Ferm Solutions petition states that an environmental assessment was submitted for the new drug application for Gallimycin, the veterinary drug Ferm Solutions wishes to repackage for use in ethanol production, but does not give the date of the assessment or what impacts were considered. Since Gallimycin was first approved in 1960, there has been a considerable body of scientific research on the impact of antimicrobial use in food producing animals on the spread of resistant organisms into the environment. The Ferm Solutions petition completely fails to consider this extensive literature and fails to even mention the potential for resistant bacteria to arise from the proposed use and then spread into the environment.

Safer, cost-effective alternatives. Viable alternatives to antibiotics generally, and to erythromycin 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).

Conclusion

The petition before the FDA would allow the feeding of erythromycin, a critically important human drug, to potentially billions of animals for no medical purpose. This is clearly not in the public's health interest.

Because this petition is so clearly at odds with the FDA's own risk management framework as set out in Guidance 152, we are concerned if approved it would undermine the Agency's entire approach to managing resistance-related antimicrobial use in livestock. In short, granting this petition would signal 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 distillers grains containing erythromycin to animals.

Submitted by:

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Steven Roach, Food Animal Concerns Trust
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Supporting materials and references:

CDC. 2008. National Antimicrobial Resistance Monitoring System - Enteric Bacteria (NARMS) 2008 Annual Report. Available from: http://www.cdc.gov/narms/annual/2008/NARMS_2008_Annual_Report.pdf

Cools. 2003. Survival of Campylobacter jejuni strains of different origin in drinking water. J Appl Microbiol. 94(5):886-92.

Deutscher. 2009. Report: Ethanol Industry Moving Away from Antibiotic Use. Ethanol Producer Magazine, July 2009. Available from: http://www.ethanolproducer.com/article.jsp?article_id=5855

FDA. 2003. Guidance for Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern. Available from: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

FDA. 2010. Draft Guidance #209. The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. Available from: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf

FDA. 2011. Strategic Priorities 2011 – 2015 Responding to the Public Health Challenges of the 21st Century. Available from: http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm227527.htm

Gibreel and Taylor. 2006. Macrolide resistance in Campylobacter jejuni and Campylobacter coli. J Antimicrob Chemother. 58(2):243-55.

Horrocks et al. 2009. Incidence and ecology of Campylobacter jejuni and coli in animals. Anaerobe. 15(1-2):18-25.

ISDA. 2001. Practice Guidelines for the Management of Infectious Diarrhea. CID 32:331–50. Available from: http://cid.oxfordjournals.org/content/32/3/331.full

Kehrenberg et al. 2009. Methicillin-resistant and -susceptible Staphylococcus aureus strains of clonal lineages ST398 and ST9 from swine carry the multidrug resistance gene cfr. Antimicrob Agents Chemother. 53(2):779-81.

Ladely et al. 2007. Development of macrolide-resistant Campylobacter in broilers administered subtherapeutic or therapeutic concentrations of tylosin. J Food Prot. 70(8):1945-51.

Lushia and Heist. 2005. "Antibiotic-Resistant Bacteria in Fuel Ethanol Fermentations," Ethanol Producer Magazine, May 2005. Available from: http://www.ethanolproducer.com/article.jsp?article_id=511

Martel et al. 2005 Comparison and transferability of the erm (B) genes between human and farm animal streptococci. Microb Drug Resist. 11(3):295-302.

Nixon. 2009. CMEC [Central Minnesota Ethanol Cooperative] does not use antibiotics. St. Cloud Times, April 2009. Available from: http://www.centralmnethanol.com/index.cfm?show=10&mid=35

Olmstead. 2009. Fueling Resistance? Antibiotics in Ethanol Production. Institute for Agriculture and Trade Policy, July 2009. Available from: http://www.agobservatory.org/library.cfm?refID=106420

Roberts. 2008. Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. FEMS Microbiol Lett. 282(2):147-59 Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1574-6968.2008.01145.x/full

Sharfstein. 2009. Testimony before the U.S. House of Representatives Committee on Rules, July 13, 2009.

Sharfstein. 2010. Testimony before the U.S. House of Representative's Committee on Energy and Commerce, Subcommittee on Health, July 12, 2010. Available from: http://energycommerce.house.gov/documents/20100714/Sharfstein.Testimony.07.14.2010.pdf

Wagenaar et al. 2006. Campylobacter in primary animal production and control strategies to reduce the burden of human campylobacteriosis. Rev. sci. tech. Off. int. Epiz., 25 (2), 581-594. Available from: http://web.oie.int/boutique/extrait/10wagenaar581594.pdf

WHO. 2006. 66th report of the Joint FAO/WHO Expert Committee on Food Additives. Available from: http://whqlibdoc.who.int/publications/2006/9241209399_eng.pdf
WHO. 2009. 2nd Revision WHO list of Critically Important Antimicrobials. Available from: http://www.who.int/foodsafety/foodborne_disease/CIA_2nd_rev_2009.pdf