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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–N–0159

To Whom It May Concern:

We are writing to provide comments on the **North American Bioproducts Corp. (NABC) Food Additive Petition for Erythromycin Thiocyanate (Animal Use), Docket No. FDA-2010-N-0159**.

The Institute for Agriculture and Trade Policy (IATP) works locally and globally at the intersection of policy and practice to ensure fair and sustainable food, farm and trade systems. *Keep Antibiotics Working* (KAW) 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 Food and Drug Administration (FDA) should not approve the NABC food additive petition for erythromycin thiocyanate. 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 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.

The public health threat. Antibiotic resistance poses a threat to every one of us. Basic microbiology demonstrates that antibiotic use – any use – can potentially add to the selection pressure in the broader environment for antibiotic resistance. Their use in ethanol production is no exception. As IATP and KAW have previously argued, the existence of effective, cost-competitive alternatives to antibiotics for ethanol production means there can be no public health rationale for permitting the use of unnecessary antibiotics such as erythromycin thiocyanate. The FDA is a public health agency.

Inconsistent with FDA policy and guidance. The proposed use of erythromycin thiocyanate in livestock feeds is inconsistent with the FDA's stated policy on the inappropriateness of the nontherapeutic use of antimicrobials in food producing animals and the current risk management framework for antimicrobial resistance 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 described in the section of the petition in question, 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 erythromycin-contaminated distillers 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 high risk uses of antimicrobials under GFI152. Table 8 of that guidance recommends that category 1 drugs be limited instead to low extent of use.

If the anticipated level of drugs fed to cattle in the distillers grains were at a level so low as to not have biological activity perhaps then it may not have been appropriate to apply GFI152. But this is not the case. A steer close to slaughter may consume 25 pounds of feed a day. If DDG are fed as 50 percent of the ration, then the amount consumed per day will be over 8 mg erythromycin per head. Similarly, a dairy cow may consume 100 pounds of feed per day so even at a lower inclusion rate of 20 percent would end up consuming over 13 mg of erythromycin per head per day.

Given that the FDA-approved rate for growth promotion is 37 mg of erythromycin per head per day, the amount fed in distillers grains is very close to the effective growth dose so would likely be active at that level. The 66th report of the Joint FAO/WHO Expert Committee on Food Additives referred to in the NABC assessment discussion states that "lowest relevant MIC_{50} for erythromycin" was 0.1 ppm – well below the 1.5 ppm proposed level in the petition.

IATP AND KAW strongly question the wisdom of feeding large quantities of medically important antimicrobials to large numbers of livestock for no medical purpose whatsoever. We are also concerned that this petition, if approved, because it is brazenly inconsistent with the risk management framework set out in GFI152 , would undermine the guidance and undermine the FDA's whole approach to managing resistance related antimicrobial use in livestock.

Inadequate and error-filled environmental assessment discussion. While KAW believes that the proposed use of distillers grains should not be approved, based upon a human safety assessment derived from application of the agency's own GFI152, we also find that the

environmental assessment discussion of the petition is grossly inadequate, with factual errors, methodological flaws, and important omissions. The greatest omission is its failure to discuss the potential for the use of distillers grains contaminated with erythromycin to contribute to the pollution of surface waters and rural environments with resistant disease-causing bacteria. While the assessment discusses the release of bacteria from the ethanol production facility, it does not address the release of bacteria from the livestock production facilities where distillers grains will be fed. Of particular concern is *Campylobacter spp*. because erythromycin is a treatment of choice for this important pathogen (Skirrow) and the potential for *Campylobacter spp.* to contaminate water and the rural environment and cause human illness (Van Dyke).

In addition to failing to consider the impact of the proposed use of erythromycin on pathogens in the environment, the assessment discussion fails to provide any information on the number and types of animals likely to be fed distillers grain containing erythromycin on an annual basis. Without this information assessing the environmental risk is impossible. The discussion does include a highly misleading comparison between feeding erythromycin in distillers grains and treating cattle with erythromycin by injection. The comparison is misleading because distillers grains will be fed to whole herds or flocks of animals over long periods of time while injection will only be done to individual sick animals at a particular point in time. The comparison also is misleading because it is based on feeding only 20 percent distillers grains while the petitioners note in the same section that a significantly higher level of 50 percent may also occur and the amount of feed consumed is low for some types of cattle (dairy animals or heavier beef cattle).

The NABC assessment discussion refers repeatedly to the 66th report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). However, the petitioners clearly misunderstand the role of JECFA, as well misquoting the report. The assessment discussion wrongly refers to an FAO/WHO "approved formulation and dose of erythromycin thiocyanate for food animals", failing to recognize that FAO/WHO is not a drug approval agency. The background material in the 66th report of the Joint FAO/WHO Expert Committee on Food Additives does refer to a maximum recommended therapeutic dose but this is not a FAO/WHO "approved formulation and dose" and it is unclear what is its relevance (if any) for assessing the safety of the erythromycin included in distillers grains. The NABC assessment discussion also misstates the findings of the JECFA report with respect to the potential for erythromycin to persist in the intestinal track. The assessment discussion states that the JECFA report found that "70% to 90% of erythromycin is destroyed in the gastric acid after 15 minutes". The JECFA report did not find this. It only mentions that "erythromycin is sensitive to degradation by gastric acid" but then sets a microbiological ADI based on the assumption that 50 percent of the oral dose would be present in the colon and fecal contents. This is consistent with other studies (Aust, 2008) that found that between 50 percent and 100 percent of the related macrolide drug tylosin fed to cattle is excreted.

The NABC assessment does not provide any information on the extensive literature on the fate of macrolides in manure, soils, and surface waters or any information on ecotoxicity. It

does misleadingly make a comparison with the amount likely to be found in manure after a treatment dose, but as we noted above this is misleading because a single treatment dose is not comparable to continuous feeding of all animals in a herd. Also stating that this risk is less than another risk is meaningless unless the risk associated with the other use has been evaluated. The assessment discussion provided no information on the environmental impacts of current uses of macrolides.

Conclusion

IATP and KAW recommend that the FDA decide against this petition and not approve the addition of the critically important human drug, erythromycin, to feed due to the risk to public health from the development of antimicrobial resistance. 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 clearly 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.

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Supporting materials and references:

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