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The Campaign to End Antibiotic Overuse

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February 23, 2005

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

Rockville, MD 20852

Re: Docket No. 2004N-0479

Dear Sir or Madam:

Keep Antibiotics Working (KAW) appreciates this opportunity to submit comments concerning the 'Draft Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals,' as requested by FDA's Center for Veterinary Medicine (69 Federal Register 68384-68385). Keep Antibiotics Working (www.KeepAntibioticsWorking.com) is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than nine million members dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in farm animals.

Our comments on the draft risk assessment are of two types. First, we discuss why the draft risk assessment seriously underestimates the risks associated with virginiamycin use in animals. Second, we explain how the draft risk assessment deviates seriously from FDA's recommended approach for assessing the safety of antimicrobial new animal drugs, as laid out in Guidance #152, and why the draft risk assessment should be discarded in favor of a new assessment consistent with Guidance #152.

FDA's draft risk assessment does not focus on the affected population and thus dramatically underestimates risk

FDA estimates the risk per year of Synercid therapy failing for humans with resistant *E. faecium* infections, due to the ingestion of resistant strains of *E. faecium* on food. The draft risk assessment focuses on two broad populations – for all hospitalized patients and for the general population. Unfortunately, the draft does *not* calculate a risk estimate for the population of most interest – people who might actually need treatment with Synercid – in other words, people with vancomycin resistant *E. faecium* (VRE) infections.

To put FDA's estimates in perspective, consider for comparison the risk over a year of suffering a particular ailment during pregnancy. FDA's focus on broad populations is

comparable to estimating the risk of a pregnancy-related ailment for all women of child-bearing age (the great majority of whom would not be pregnant during any given year), or for the general population (which would include men, women too young or old to have children, as well as women of childbearing age who are not pregnant). Obviously, the most meaningful statistic for pregnancy-related ailment would be the risk for women who are actually pregnant. This risk estimate would of course be much higher than if the risk was averaged out over either all women of childbearing age, or the general population.

Now consider FDA's one-year risk estimates for Synercid resistant *E. faecium*. If only 10% of the risk of acquiring resistant *E. faecium* is attributed to food, FDA estimates this risk as 6 to 120 chances in 100 million for a random hospitalized member of the US population and 0.7 to 140 chances in 100 million for a random member of the US general population. If 100% of the risk of acquiring resistant *E. faecium* is attributed to food, the FDA's estimate is 10-fold greater: 60 to 1200 chances in 100 million for a random hospitalized member of the US population and 7 to 1400 chances in 100 million for a random member of the US general population.

According to the draft risk assessment, there may be as many as 70,000 vancomycin resistant *E. faecium* infections a year[1] in the total US population of roughly 280 million. Using these figures, only about one person out of every 4,000 in the United States is infected each year by vancomycin resistant *E. faecium*. To get a rough sense of the risk to these people – those who might actually need Synercid to treat a resistant *E. faecium* infection – one can multiply FDA's risk estimates for the US general population by 4,000. The result is a risk estimate of 2800 to 980,000 chances in 100 million, if there is a 10% risk of acquiring resistant *E. faecium* from food, and 28,000 to 9,800,000 chances in 100 million, if there is a 100% risk of acquiring resistant *E. faecium* from food. **In other words the risk of treatment failure may be as high as one in ten people with vancomycin resistant *E. faecium* infections.**

The following chart summarizes the effects of these assumptions and populations:

% of risk assumed attributable to food	US population considered	Risk estimated
10%	Hospitalized persons	6-120 chances in 100 million
	General population	.7 to 140 chances in 100 million
100%	Hospitalized persons	60-1200 chances in 100 million
	General population	7 to 1400 chances in 100 million
10%	70,000 persons experiencing vancoymcin resistant infections annually	2800 to 980,000
100%	70,000 persons experiencing vancoymcin resistant infections annually	28,000 to 9,800,000 in 100 million ***(i.e., as high as 1 in 10)***

Although these numbers are hardly precise, our general point is clear: FDA's risk estimates are misleading because they consider the overall population, thus greatly diluting the impact on the <u>most-affected subpopulation.</u>

[1] FDA draft risk assessment, p. 1.

FDA's draft risk assessment also underestimates risk for other reasons

The draft risk assessment focuses only on the acquisition of Synercid resistant *E. faecium* from food, and thus fails to account for a number of other means by which Synercid resistance arising from the use of virginiamycin in animals may harm people. These other means include:

- ***Infection by Synercid-resistant* Staphlycoccus aureus.** Synercid is used to treat skin and soft tissue infections caused by *S. aureus* and *Streptococcus pyrogenes* as well as vancomycin resistant *E. faecium*. *S. aureus* is a major cause of nosocomial infections and the incidence of community-acquired *S. aureus* infections is increasing. Staphylococcus spp. and Streptococcus spp. commonly cause illness in farm animals and also cause skin infections in poultry plant workers[2] and resistant infections in meat plant workers.[3] At least one recent scientific paper suggests that agriculture may be a source of resistance determinants in human *S. aureus* infections.[4] Thus, the use of virginamycin in animals may now or in the future decrease the effectiveness of Synercid in treating *S. aureus* infections in humans.

- ***Transfer of plasmids carrying determinants for streptogramin resistance***. The use of virginiamycin in animals selects for streptogramin resistance genes, which may then be transferred among different types of bacteria. Such inter-species transfer may be significant; indeed, evidence suggests that vancomyin resistance in some *S. aureus* may have been transferred from *E. faecalis*.[5] Yet, FDA's draft risk assessment considers only gene transfer from animal to human strains of *E. faecium*. Determinants for streptogramin-resistance may be transferred from enterococci to *S. aureus* – or vice versa[6] – or among different species of enterococci or other gram positive bacteria. Gene transfer likely increases the prevalence of Synercid-resistance among bacteria that are treated with this drug.

In short, FDA's draft risk assessment is overly narrow in its scope and considers only one among several pathways whereby virginiamycin use in animals may lead to Synercid resistance that harms humans. As a result, the risk estimated very likely understates possible harm to humans resulting from the administration of virginiamycin in animal feeds.

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[2] Barnham, 1984. A profile of skin sepsis in meat handlers. The Journal of Infection, 9(1):43-50.
[3] Sims, 1996. A prolonged outbreak of streptococcal infection among workers at a meat plant. Public Health, 110(2):81-4.
[4] Lee, J.H. 2003. Methicillin (oxacillin)-resistant *Staphylococcus aureus* strains isolated from major food animals and their potential transmission to humans. Applied and Environmental Microbiology, 69: 6489–6494.
[5] Ferber, D. 2003. Triple-Threat Microbe Gained Powers From Another Bug. Science 302: 1488.
[6] According to the risk assessment (p. 27), many – but not all - determinants for streptogramin resistance are typically found in either enterococci or staphylococcus.

FDA's draft risk assessment is inconsistent with FDA Guidance for Industry #152 and should be discarded in favor of a new assessment that is consistent with Guidance #152.

The draft risk assessment deviates seriously from the FDA's own recommended approach for assessing the safety of antimicrobial new animal drugs, as laid out in Guidance for Industry #152. The Guidance establishes a semi-quantitative approach under which three elements – release, exposure, and consequence – are each assigned a high, medium, or low ranking; those three elements are then integrated into an overall risk ranking (also characterized as high, medium, or low). The Guidance also lays out management criteria associated with high, medium, and low overall risks.

FDA's publication of Guidance #152 was the culmination of a multi-year process in which FDA first tried and rejected several other approaches. Indeed, the Guidance's overall structure constitutes an acknowledgment that quantitative risk assessment methods are simply not adequate at the current time to provide an appropriate evaluation of risk from antimicrobial resistance determinants, particularly those that are transferable.

The draft risk assessment differs from the approach spelled out by Guidance #152 in several ways. Most significantly, it combines qualitative risk assessment in the release and exposure segments with a quantitative risk assessment in the consequence section. This use of a quantitative approach for evaluating consequence is misguided. Key data needed for a quantitative approach do not exist, particularly in relation to both the extent of human carriage of animal derived strains and the rate of exchange of resistant determinants from animal derived strains to humans. This and other limitations – some of which are described below – are so profound that a quantitative risk assessment for Synercid resistance is unlikely to be reliable. Accordingly, FDA should discard this draft and start over again, utilizing the semi-quantitative approach taken in Guidance #152.

In addition to abandoning the approach of Guidance #152 in the consequence section, the draft risk assessment also departs significantly from Guidance #152 with regard to the release and exposure assessments. Both Guidance #152 and the draft risk assessment define the release as the likelihood that the use of the animal drug will result in the emergence of the resistant bacteria in the animal. However, the draft fails to come to any conclusion regarding the likelihood of release, even though the draft's summary of the available evidence makes clear that virginiamycin use on farms **does** select for streptogramin-resistant *E. faecium* and that the resistance-conferring elements are mobile. By contrast, the Guidance provides that the available evidence should be integrated into a conclusion that the likelihood of release is high, medium, or low. If FDA revises this draft (instead of abandoning it as we urge), at the least the conclusion of the release assessment should make clear that the bulk of available evidence suggests that use of virginiamycin in farm animals has a high probability for selecting for streptogramin resistant *E. faecium* in these animals.

The draft risk assessment also departs from Guidance #152 with regard to the exposure assessment. The Guidance recommends that exposure be estimated by combining

information on the level of food contamination by the bacteria in question with the amount of food likely to be consumed. This is the internationally accepted method for estimating exposure foodborne risks from microbiological hazards.[7] The draft risk assessment starts with this approach, but then deviates from it by examining the prevalence of bacteria in the community as an indicator of exposure. A much clearer picture of the risk could be had by focusing on the available exposure data, which, in this case, is limited to food. (That said, disregard of nonfood pathways is a serious flaw in both the Guidance and the draft risk assessment.)

Finally, Guidance #152 ranks the streptogramin class of drugs (of which virginiamycin is a member) as "highly important" because streptogramins are used to treat vancomycin resistant *E. faecium* (VRE) infections. As the draft risk assessment notes, Synercid was specifically approved to address the problem of VRE; since Synercid's approval, the number of VRE cases has increased. By describing the risk in terms of number of patients potentially affected, the draft risk assessment miscommunicates the importance of this class of drug to human medicine – particularly if the number of vancomycin-resistant infections continues to increase. It is telling that the conclusions section does not include a discussion about the severity of the risk, focusing instead only on number of patients affected.

Conclusion

FDA's draft risk assessment on Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals grossly underestimates risk to the most relevant population – namely, individuals infected by vancomycin-resistant *E. facium.* By our calculations, these individuals may face as much as a 10% failure rate for Synercid treatment. Moreover, the draft assessment is inconsistent with FDA's recommended approach for assessing the safety of antimicrobial new animal drugs.

We strongly recommend that the agency discard the current draft, and create a new assessment consistent with Guidance #152. As it stands, the failure to either comply with the Guidance or to justify a departure from the Guidance leaves the impression that the agency was not satisfied with the outcome when using the Guidance and therefore modified the approach to achieve a desired result.

Thank you for considering these comments.

Submitted on behalf of Keep Antibiotics Working by:

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[7] WHO, 1999. Principles and Guidelines for the Conduct of Microbiological Risk Assessment, CAC/GL-30 (1999).

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