

MRL

PHARMACEUTICAL SERVICES

January 28, 1999

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Dear Steve:

Thank you for permitting me to have a part in the recent VMAC. I hope you realize that I did not come there to be for or against the document but rather to speak to the science as I saw it. Hopefully I did that.

Away from the public forum, however, I do wish to express some of my feelings. While I do think the document has some good features, the major meaning leaves me completely flabbergasted and somewhat stunned. As I understand it, the FDA would have the option and authority to not approve a drug because at some future date (post approval) there might be a bacterial strain that might develop resistance to that drug and it might cause an infection in a patient so that this patient could not be treated with that drug. That is like saying lets outlaw cars because someone may be killed in a wreck, or don't build a satellite because a piece might fall, etc. I would think that, at the very best, this would be a grossly unfair approach. With this process we would not have any antimicrobials in human medicine. Even vancomycin would not be retained for MRSA (no resistance) because it could select for vancomycin-resistant enterococci.

As to human problems with bacterial resistance, you and I (as well as others at the meeting) know that animals had very little to do with it. Even if you consider vancomycin-resistant *E. faecium* to be a big problem (I do not because it is much to do about very little) it is unlikely that avoparcin use in Europe had anything to do with it. We do not – yet, anyways – have a problem with *E. coli*. Animals did not cause our MRSA problem, etc, etc.

As I indicated in an aside in my presentation, I am also concerned that this was a meeting that was concerned with problems that were almost totally microbiological yet the "table" did not have anyone who truly understood the nuances of bacteria, resistance, and the epidemiology of resistance.

One speaker used her time to mostly talk about the tetM gene, which anyone who has studied resistance at all, knows to be the most ubiquitous of all resistance genes (for reasons not understood). I think your document was perfectly correct in saying the transfer of resistance from enterics to respiratory organisms would be a rare occurrence, particularly in *S. pneumoniae*. (An argument that the TEM-1 gene came from *E. coli* to *H. influenzae* would have made much more sense). I am also concerned about the examples that were constantly being used. For example, the term VRE was used as if it meant vancomycin-resistant *E. faecium* instead of vancomycin-resistant

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enterococci. Essentially all the vancomycin resistance occurs in *E. faecium*, which causes very few of the enterococcal infections (much less than 10%). Although the vanco resistance has sharply risen in *E. faecium* in the last three years, the level in *E. faecalis* (between 1 and 2%) has not changed at all, and this species cause most infections. Furthermore, *E. faecium* is a very poor pathogen. I know the argument is that if I had a patient with vancomycin-resistant *E. faecium* infection, I would look at it differently and I appreciate that, but major decisions cannot be based on such rare occurrences. I have similar feelings about *Salmonella*. Even though it is a very uncommon pathogen, I understand its epidemiologic niche for your use. *Salmonella* is one of those organisms that seems to have a knack for gathering resistance genes but if you study it over the years, outbreaks with particular resistances come and go. I also seriously doubt that patients died with *Salmonella* because they could not be treated with a fluoroquinolone or that we are likely to see "bodies strewn around" because of this problem. I also do not think it is appropriate to consider pulling a drug because you get 25 patients with an FQ-resistant *Salmonella* or even 25 deaths – it must all be put into the context of all other factors.

On a somewhat different microbiological question, the industry's argument about breakpoints for ciprofloxacin has no merit. The important thing is whether the MICs are increasing, i.e. whether there is decreased susceptibility.

I could make other arguments, but I hope I have made a case for microbiologists with the right kind of expertise (I am not looking to be that person if that thought occurred to you).

My other major point to make to you (even though I had this point in my presentation) is that I believe antimicrobial resistance should not be a part of the food safety initiatives. Resistance should be studied for resistance's sake. I suspect you don't have control of this issue but if you do I would urge you to separate them because "resistance" loses if they are together.

My comments and suggestions on the document are enclosed.

Thanks for letting me have my say.

With kindest regards,

Sincerely,



Clyde Thornsberry Ph.D.

Enclosure