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

Re: Docket No. 2005P-0139 - Citizen Petition Seeking  
Withdrawal of Approvals of Herdwide/Flockwide Uses of Critically  
Important and Highly Important Antibiotics Pursuant to Guidance #152

The ANIMAL HEALTH INSTITUTE ("AHI") is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy. These comments are submitted by the AHI in response to the petition filed on April 7, 2005 by Environmental Defense, The American Academy of Pediatrics, The American Public Health Association, and The Union of Concerned Scientists, requesting that FDA withdraw the herdwide/flockwide uses of penicillins, tetracyclines, aminoglycosides, streptogramins, macrolides, lincomycin, and sulfonamides in chickens, swine, and beef cattle for weight gain and feed efficiency, and disease prevention and control (except for non-routine use where a bacterial infection has been diagnosed within a herd or flock). Specifically, the petitioners seek to have FDA take "immediate action" to withdraw all claims for these drugs meeting these criteria on the basis that the Center for Veterinary Medicine Guidance for Industry #152 categorizes these drugs as critically important or highly important to human medicine.

Similarity to a previous FDA rejected petition

A citizen petition was filed on March 9, 1999 by the Center for Science in the Public Interest (CSPI), the Environmental Defense Fund (ED), The Food Animal Concerns Trust, The Public Citizen's Health Research Group, and the Union of Concerned Scientists. That petition also requested a ban on the same antimicrobial drugs because of their similarity to drugs used in human medicine. The FDA responded on two occasions to that petition, the most recent in a letter signed by Dr. Stephen Sundlof, Director, Center for Veterinary Medicine, on February 28, 2001. In essence, Dr. Sundlof informed the petitioners that the agency cannot simply withdraw approved new animal drug applications or approved uses en masse for a variety of different compounds marketed by different companies. Specifically, the letter stated:

*"For legal, scientific and resource reasons, withdrawal actions for the petitioned drugs need to be considered on a drug by drug basis. Data and information will need to be reviewed and analyzed for each drug. Thus the petition can only be denied on a drug by drug basis as reviews are completed and resources permit."*

*"The Center's determination on whether to initiate action to withdraw an approval is primarily an internal process, although participation by drug sponsors and the public may be requested."*

*This process may include among other things, an in-depth review and evaluation of available data and information related to the particular drug, collection of additional data if needed, and a risk assessment. These reviews will be used to determine whether statutory grounds exist to support a withdrawal action."*

AHI completely agrees with the response by the CVM to that petition. We see very little that has changed since the issuance of that response and the current petition requesting essentially the same action to alter the process for determining the safety of individual new animal drugs, notwithstanding the issuance of new agency guidance. The matter of antimicrobial resistance is a complex one and much has been learned over the last five years. As we will discuss in our comments, there have been a number of attempts to critically evaluate the contribution of animal drug use to resistance problems in human medicine. Most of the arguments cited by the petitioners, in an attempt to support their case that antimicrobials present such a risk to public health that FDA must take the drastic action they propose, cite the same speculative findings of what *may happen* rather than what *has been shown to happen*. When investigated further along the food production and processing chain, it is clear that there are significant hurdles to the actual transfer of antibiotic resistant foodborne bacteria between the farm and the table.

First and foremost, is the strict regulatory process and monitoring that is required of the veterinary pharmaceutical industry in the approval and marketing of animal antibiotics which restricts the use of these products to labeled indications. For example, medicated feeds are blended at FDA licensed and inspected feed mills to ensure quality. Moreover, it is illegal for a producer to use feed additive antibiotics in an extralabel manner. Second, there have been documented reductions over the last five years in the contamination of meat and poultry with food borne bacteria through implementation of pathogen reduction measures in slaughter and processing plants by the USDA and food industry. These reductions reduce the rate of both susceptible and antimicrobial resistant microorganisms on raw meat and poultry. Third, there have been stricter standards for handling and cooking of meat and poultry in food service establishments. Fourth, there have been educational campaigns directed to consumers on the safe preparation of meat and poultry with mandatory safe handling labels required of all raw products. Fifth, producers and veterinarians are acutely aware of resistance concerns related to production practices, and have responded with voluntary guidelines and programs, both within their industries and in conjunction with regulatory authorities to emphasize that judicious uses of antimicrobials should be implemented as part of good husbandry practices.<sup>27,28</sup>

Current food borne pathogen surveillance data from USDA, the CVM Office of Research, and the Centers for Disease Control does not support the assertion that there is an "emerging medical crisis", as the petitioners claim, from agricultural use of antibiotics in food animals, that would require FDA to alter its usual deliberative and science driven process to determine the safety of marketed antimicrobials.

Environmental Defense (ED) “Grounds for Action” and what has changed to justify this new petition?

The petitioners request that FDA withdraw current approvals for “herdwide/flockwide uses” of seven antimicrobial classes in chickens, swine, and beef cattle for weight gain/feed efficiency and disease prevention and control claims except for non-routine use where a bacterial infection has been diagnosed within a herd or flock. The apparent basis for the difference between this petition and the aforementioned 1999 petition that FDA rejected is the publication of Guidance for Industry #152 by the Center for Veterinary Medicine in 2003. Environmental Defense, et.al., states that subsequent to a re-review by CVM of several approved NADAs containing penicillin for feed use under the new guidance, that the agency implicitly requested sponsors to “...voluntarily remove these substances from the market.” This is completely untrue and does not at all reflect the content of the three letters appended to the petition. CVM actually concluded that some of the claims on these products may be unacceptable based on a review of data in the file and by simply assigning default “high risk” rankings where specific data was unavailable. The primary reason for the letters was to invite the companies to meet with the agency to discuss their preliminary findings. **CVM did not implicitly or explicitly ask these companies to remove any approved product from the market.** It is understood that the company may have additional information or would be given an opportunity to collect additional information to address the CVM concerns before any action would be taken.

In requesting the action to withdraw “continuous use” claims, the petitioners state “*FDA has never determined that the existing herdwide/flockwide uses covered by this Petition meet modern scientific standards for safety with regard to antibiotic resistance.*” However, they have not been found to be unsafe by modern scientific analysis either. With “science moving on”, the compounds in question continue to be found to be insignificant in regard to clinically important resistance. For example, data from the National Antimicrobial Resistance Monitoring System (NARMS) shows that most resistance levels in *Salmonella* and other indicator microorganisms have maintained a stable pattern for over seven years<sup>29,30</sup> in both human and animal sectors in the U.S. for the classes of drugs listed in the petition.

In addition to NARMS data, broader food safety public health goals were recently reviewed by The U.S. Department of Health and Human Services.<sup>1</sup> Year 2010 targets for the proportion of human isolates of non-typhi *Salmonella* spp. that are resistant to antimicrobial drugs were set at no increase from 1997 baselines. Two antibiotics, gentamicin and ampicillin (in the penicillin class mentioned in the petition), exceeded these goals in 2002! With resistance to the penicillin class of drugs meeting (even exceeding) resistance targets 8 years ahead of time, and with the current health maintenance approvals in place, we must question the petitioners allusion to ‘The Emerging Medical Crisis of Antibiotic Resistance’ as being linked to responsibly used feed additives in the U.S.

It is not clear in the petition what its sponsors believe will be the public health benefit from CVM summarily using GFI #152 to ban all continuous use claims. The evidence from USDA and CDC indicate dramatic reductions in carcass contamination and decreased food borne illness, down 23 % since 1996. Neither does the petition contain any specific data to substantiate

its claims nor provides evidence that removal of these particular claims would in any way “preserve” or extend the useful “life cycle” of these “critically or highly important” antibiotics for human use. Many of the 7 antibiotic product classes listed have been on the market, in multiple animal species, for 50 years or more.<sup>22</sup> It is reasonable to postulate that a steady-state situation with antibiotic resistance has long since been achieved. As mentioned previously, more recent surveillance programs in the U.S. show that most sentinel organisms show relatively stable year-to-year resistance profiles for the individual drugs listed in the petition.

The petition includes a list of human diseases for which the seven classes of antibiotics are used. However, there is no epidemiological connection of these human pathogens to food animal antibiotic use (except for foodborne bacteria), let alone an identified route of transfer of resistance genes. It is recognized that the biggest problem with antimicrobial resistance in humans is with nosocomial infections, that is, those infections acquired in hospitals. The top intensive care unit resistance rates in the United States were published for 2002 in the American Journal for Infection Control.<sup>26</sup> Not one of the top six resistant infections have been associated with food or antibiotic use in food animals in the United States nor are the antibiotics involved used as feed additives. In the case of vancomycin resistant enterococci (VRE), neither vancomycin or any other glycopeptide antibiotic has ever been approved in the United States for animals either in feed or as therapeutic dosage forms.

The antibiotic product classes listed, although described as “critically or highly important” to human medicine, are not drugs of last resort for treating foodborne infections. In fact, for the treatment of food borne bacteria of most concern with antibiotic resistance, there are other antibiotic classes that are available as therapeutic options. It is difficult to understand how penicillin which is rated as critically important to human medicine because it is used to treat neurosyphilis, is compromised by use in food animals since there is no epidemiological connection. Similar issues are present with sulfonamides (actually trimethoprim/sulfa in Appendix A, which is not used in premixes) which is characterized in GFI #152 as critically important because it is used to treat a protozoal infection.

Furthermore, the petition requests withdrawing approvals for penicillins that were never approved for feed uses in the U.S. (penase resistant penicillins, antipseudomonal penicillins and aminopenicillins). Only the natural form of penicillin has animal health applications in feed. Thus, listing all of the modified forms is misleading. In terms of hazard characterization, there are no listed foodborne disease microbes for which natural penicillin is indicated in humans.

Sulfonamides were one of the first approved antimicrobial classes for poultry, and their application since 1948 helped to control diseases like coccidiosis that inevitably took hold when larger numbers of animals were housed for commercial production. These drugs have been credited with helping to reduce the high cost of chicken.<sup>24</sup> We question the wisdom of completely removing these important classes of drugs from a consumer economic as well as animal health perspective.

Finally, the relief that ED is requesting by removal of certain claims on “fixed dose” combination antimicrobial approvals would result in complete disruption of the original basis for the approval, therefore jeopardizing any of the claims ED considers acceptable.

### Selective Use of Literature

The petition selectively quotes from several sources that have addressed the antibiotic resistance issue but does not cite other publications, which fail to turn up convincing evidence that banning many uses of antimicrobials in food animals will yield human health benefits.<sup>3-15, 19, 20</sup> The limited set of literature reviews put forward as grounds for removal of the compounds in question is certainly not conclusive when carefully analyzed.

The petition reviews only the Phillips paper<sup>5</sup>, which presents a contrary conclusion on the potential risks, and several critical letters to the editor, as if that were the concluding part of the debate.<sup>31,32,33</sup> In fact, a detailed, documented rebuttal to the critics (published in the same volume) comprehensively addressed each objection.<sup>6</sup> In that response, Phillips, et al. indicate their overriding concern is that overly aggressive risk management actions such as proposed in this petition may not benefit human health at all because antimicrobials prevent and control animal disease and reduce pathogen loads on food potentially reducing human illness. They state “... we are concerned that well-meaning efforts to avert hypothetical dangers may create real ones.”

The petition cites expert organizations selectively while conveniently omitting animal science-related scientific groups which disagree with the thesis presented. Although most of the organizations mentioned (Institute of Medicine, World Health Organization (WHO), Alliance for Prudent Use), are in favor of “reducing inappropriate use of antibiotics” in all sectors, there is no consensus that antibiotic growth promoter (AGP) uses were or are significant drivers of clinically important, resistant human pathogens. The underlying philosophy behind this petition seems to be a rigid belief in a heavy-handed version of the precautionary principle. Indeed the APHA (one of the petitioning groups) has endorsed the concept of massive large-scale precautionary bans for U.S. agriculture production practices.<sup>2</sup> This is unrealistic, contrary to our U.S. regulatory process, and potentially damaging to veterinary medicine, animal health, animal welfare, and food safety.

The best information available for whether or not removal of these antibiotics has had a measurable public health impact is from Europe where restrictions have been in place for several years. There is no evidence that the European experience of withdrawal of production claims of these several antibiotic classes would have resulted in any measurable decrease in the prevalence of antibiotic resistance to these classes in human food borne pathogens isolated from humans (except for possibly the macrolides and campylobacter).<sup>9</sup> A conference sponsored by WHO held in Foulum, Denmark, also concluded that due to the narrow spectrum gram-positive activity of many of the feed antimicrobials banned in Denmark-”...direct effects of the termination of growth promoters on resistance in Gram-negative bacteria (e.g. *E. coli*, *Salmonella*) was neither expected nor observed.”<sup>3</sup>

The only attributable effect in humans of the ban of growth promoters by the European Commission in 1999 has been a diminution in acquired resistance in enterococci isolated from human fecal carriers.<sup>9</sup> However there has been an increase in human infections from vancomycin resistant enterococci (VRE) in Europe probably related to the increased usage of vancomycin to treat methicillin resistant *Staphylococcus aureus*.<sup>4,9</sup> It is important to note that VRE was the primary motivation for the European Commission to implement the precautionary principle and ban all product label claims for growth promotion in feed additive products regardless of whether or not there was any evidence they had a specific impact on this hospital acquired pathogen. As a result, the ban has failed to achieve its purpose.

Several quantitative risk assessments and other papers, published in peer reviewed journals or released in draft form, were not mentioned at all in the petition<sup>10-13, 19</sup>. In fact, the majority of risk evaluations to date suggest an alternative view; that the risks to human health from these products are likely inconsequential, and the mechanisms of resistance transfer are complex, having many sources.<sup>7-21</sup>

#### Guidance for Industry #152

FDA guidance for industry documents are not binding on FDA or the company; guidance documents are neither law nor regulations, they have no legal standing. They merely represent an approach available to drug sponsors to meet the statutory and regulatory requirements that a product be shown to be safe and effective. They do not provide the only mechanism for meeting the statutory and regulatory requirements. GFI #152 cannot be literally interpreted to require FDA to immediately take action to withdraw approvals of several antimicrobial products or their claims. Each product must be reviewed individually with the sponsor given the opportunity of either providing additional data to alter the risk management process outlined in Table 7 of GFI#152 or to present another and more accurate means of assessing the risk of the product such as using a quantitative farm to fork risk assessment model.

A great deal of selective quoting of CVMs GFI #152 is presented by ED, claiming an overall thesis that existing feed additive products don't match the risk management usage conditions in the Guidance. As noted in the petition, this Guidance is aimed mainly at new entities coming on the market. Notably missing from the analysis is the fact that several quantitative risk assessments on some of the named compounds have been completed before, during, and after the GFI#152 was published.<sup>10-13,19</sup> AHI supported GFI #152 in terms of presenting a basic, rational framework for risk assessment. Alternative means of detailing hazard characterization and risk estimations are specifically allowed, because FDA (rightly so) presents a conservative regulatory approach when deciding on allowing new entities on the market.

What's left out of the petitioner's analysis is that the estimated numerical risk for virginiamycin, a drug for which CVM initiated a quantitative risk assessment, is very low in regard to a potential linkage to clinically problematic *Enterococcus faecium* (VRE) and Synercid<sup>®</sup> treatment of same.<sup>10-13</sup> Similarly, the risk of tylosin versus *Campylobacter jejuni* derived from chicken is shown to be acceptably low when subjected to a systematic risk

estimation.<sup>19, 25</sup> These risk estimations were openly published and communicated in a transparent manner. The petitioners conveniently ignore these and seek instead to focus on letters to the editor and documents favorable to their case instead of discussing additional clarifying information such as quantitative risk analyses of the products in question.

While GFI #152 is useful as a preliminary means of identifying potential risks, published quantitative assessments expose the inherent flaws in using the guidance as a final authoritative means of determining actual risks. For example, if there is the potential for zero human exposure to resistant bacteria, strict adherence to the guidance would still lead to the conclusion that there is a moderate to high risk for many antimicrobials. This is counter to the basic logic of a risk assessment which is based on the degree of risk being directly related to the degree of exposure.

#### Legal Standard/ Regulatory Process

The petition completely ignores the due process required by the FFD& C Act and the Constitution. CVM cannot simply withdraw products. CVM must determine, based upon reliable scientific information, that one of the conditions set forth in §512(e) are met, provide the applicant notice and an opportunity for hearing to consider the scientific argument on both sides.

Despite assertions to the contrary, by petitioners or in GFI #152, the legal standard under § 512 of the FFDCA under which FDA reviews New Animal Drugs is whether they have been shown to be safe. It is settled law that an assessment of “safety” under the FFDCA requires a risk/benefit analysis. *Hess & Clark*, 495 F.2d at 993–94; *Rhone-Poulenc v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980); *Brown & Williamson*, 529 U.S. at 140. Notably, the *Rhone-Poulenc* court flat-out rejected the FDA’s contention that the “risk/benefit” requirement is not binding on the FDA. *Rhone-Poulenc*, 636 F.2d at 754.

Any attempt to impose a “reasonable certainty of no harm” standard on New Animal Drugs runs afoul of settled law as declared by the U.S. Court of Appeals for the D.C. Circuit. CVM’s attempts to apply a “reasonable certainty of no harm” standard have been rejected. CVM initially asserted that the “reasonable certainty of no harm standard” applied in the course of the DES (diethylstilbestrol) proceedings in the early 1970s. The D.C. Circuit, in reviewing CVM’s proceedings, clearly held that a risk/benefit analysis is inherent in determining the safety of a new animal drug: “[T]he issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue *invariably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use.*” *Hess & Clark*, 495 F.2d at 993–94 (emphasis supplied).

The *Hess & Clark* court remanded the proceedings to the FDA, which conducted a hearing. The agency’s findings, which were published in the Federal Register, addressed, in part, the effect of the *Hess & Clark* decision. The Commissioner essentially announced that he would ignore the court’s instruction to consider the risks and benefits of use of an animal drug, because he considered that instruction to be dictum. 44 FR 54,852, 54,881–83 (1979).

However, when the matter returned to the D.C. Circuit, the court reiterated that the *Hess & Clark* risk/benefit analysis requirement was indeed binding upon the FDA (and, of course, CVM), stating that

[t]he Commissioner's arguments regarding the propriety of risk-benefit analysis are repeated in the agency's brief. We decline the invitation to overrule our prior holding, however. The language quoted above was not dictum. Rather, it expressly set forth one of the issues to be considered at the hearing. Whatever the merits of the Commissioner's arguments on this point may be, we are bound by the holding of the *Hess & Clark* court until we are instructed otherwise by the Supreme Court or an en banc determination of this Court.

*Rhone-Poulenc v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980).

Thus, it is clear that, regardless of whatever terminology one wants to use to describe the analysis of "safety," the standard used must include a risk/benefit analysis. It is therefore equally clear that, if a proposed standard does not include a risk/benefit analysis, that standard cannot apply. Because the FDA has made it clear that its "reasonable certainty of no harm" standard has no room for a risk/benefit analysis, that standard cannot apply.

#### Benefits of Antimicrobials used in Food-Producing Animals

The petition seeks to have FDA summarily remove uses of antimicrobials in animals that have been safely and effectively applied in animal agriculture for more than 40 years. The efficient production of available, affordable and high quality protein to feed the world has in part been made possible by the use of antimicrobials. They help reduce necessary resources and spare land that would otherwise be required if these production tools were unavailable. Experts in animal health and veterinary science can cite several examples of preventive uses of antibiotics in maintaining herd and flock health. Subtherapeutic uses of most of the drugs on the petition list often have favorable prophylactic and even therapeutic results when administered according to label directions. Health maintenance claims of the 7 antibiotic product classes confer important levels of disease suppression based upon the European experience following the discontinuation of these same classes of antibiotics as growth promoters.<sup>3,5,9,17,20</sup>

The petitioners fail to consider the unintended consequences that could result if all the approved uses they have targeted are withdrawn. For example, antimicrobials in feed are used to prevent the expression of several diseases such as liver abscesses in feedlot cattle, ileitis in swine, and necrotic enteritis in chickens, to name a few. These are diseases that can affect literally millions of animals leading to lowered production and significant economic impacts on producers and consumers of meat and poultry. There are, in some cases, no therapeutics labeled for the diseases, let alone the lack of ability to inject hundreds or thousands of animals.

Health maintenance claims of the 7 antibiotic product classes help to protect the environment. Since healthy animals will reach market sooner, less feed is needed (preserving cropland), less manure is excreted (less to dispose of), water is conserved, fewer dead animals

require disposal, and less disease may be present, reducing the need for therapeutic antibiotic use. A comprehensive review of over 2000 published papers and books was conducted in 2003 on the role of enteric antibiotics in livestock production through the Australian Association for Crop Protection and Animal Health (AVCARE).<sup>23</sup> This extensive worldwide literature review has documented the diversity of benefits from antimicrobial feed additives that have previously gone unrecognized.

Two recent studies have attempted to measure benefits to overall human health by improving the safety of food from contamination with food borne pathogens. Antimicrobial resistant organisms represent a very small subset of the overall microbial loads that can remain on meat and poultry subsequent to slaughter and processing. Effective prevention and control of animal disease can have the net benefit of producing a healthier animal with lower levels of pathogens regardless of their antimicrobial susceptibility patterns. In one study, excess *Campylobacter* illnesses in the human population from the withdrawal of virginiamycin in food animals were estimated to greatly outweigh the risk from antimicrobial resistant organisms that might be selected for by its use.<sup>13</sup> In another study, it is estimated that removal of tylosin from chicken production could result in 11,000 to 70,000 more cases of human *Campylobacteriosis*. Without the disease suppression benefits of tylosin birds would likely carry more subclinical disease, leading to less uniformity of weights, less efficient operation of eviscerating equipment, and increased bacterial contamination of carcasses at slaughter.<sup>25</sup>

If this risk/benefit equation holds for many of the antimicrobials targeted for removal in this petition, then the net negative effect on food safety could be substantial if all of these products are simultaneously made unavailable.

#### Recommended Action

- FDA should reject this petition, as was done with a similar previous petition for the following reasons:
- Nothing has changed since the previous petition to justify mass withdrawals of products and alter the due process requirements under the Act, notwithstanding new guidance issued by CVM.
- Guidance for Industry #152 has no legal standing and is only one means of satisfying safety requirements for a new animal drug.
- There is no “*Emerging Medical Crisis*” as evidenced by government resistance monitoring and food borne illness surveillance statistics. Several published quantitative “farm to table” risk assessments indicate negligible risks from use of antimicrobial feed additives according to approved label indications.
- Unintended negative consequences from removal of whole classes of antimicrobials must be considered because of the benefits that have been documented from the use of

antimicrobials to prevent and control disease, and improve productivity in food producing animals.

- The Center for Veterinary Medicine is properly conducting a reevaluation of existing antimicrobial products according to its priority schedule. These evaluations will be done on a product by product basis with participation by the sponsor of the approved NADA and in accord with the due process requirements under the FFDCA.

Sincerely,

A handwritten signature in black ink, appearing to read "Alexander S. Mathews", with a long horizontal flourish extending to the right.

Alexander S. Mathews

References:

1. *U.S. Department of Health And Human Services-Public Health Services, Healthy People 2010, Progress Review Food Safety, , May 11, 2004*  
<http://www.healthypeople.gov/data/2010prog/focus10/default.htm>
2. *American Public Health Association, 2004. Precautionary moratorium on new concentrated animal feed operations, policy statement, <http://www.apha.org/legislative>*
3. *World Health Organization: Impacts of antimicrobial growth promoter termination in Denmark, The WHO International review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark, Foulum, Denmark, 6-9, November 2002*
4. *Goosens H, Jabes D, Rossi R, et al., 2003. European survey of vancomycin-resistant enterococci in at-risk hospital wards and in vitro susceptibility testing of ramoplanin against these isolates, Journal of Antimicrobial Chemotherapy 51 (suppl S3):ii5-iii12*
5. *Phillips, M, Casewell, T., Cox, T, DeGroot, B, Friis, C, Jones, R, Nightingale, C. Preseton, R and Waddell, J. 2004. Does the use of Antibiotics in Food Animals Pose a Risk to Human Health? A critical Review of Published Data. J. Antimicrobial Chemotherapy 53:28-52*
6. *Phillips, M, Casewell, T., Cox, T, DeGroot, B, Friis, C, Jones, R, Nightingale, C. Preseton, R and Waddell, J. 2004. Does the use of Antibiotics in Food Animals Pose a Risk to Human Health? A reply to critics. J. Antimicrob. Chemother. 54:276-278. [This comprehensive rebuttal to the letters critical of the original 2004 paper was not cited in the petition along with petitioner's favorable analysis of the critics' charges. We include this citation to show that the debate certainly did not end with the critics' letters to the editor in that journal.]*
7. *Bezoen, A., Hare, W., & Hanekamp, J.C. 1999. Emergence of a debate: AGPs and public health. Human health and growth promoters (AGPs): Reassessing the risk. Heidelberg Appeal Foundation: Amsterdam, The Netherlands [literature, expert review indicating minimal risk due to AGP in feed]*
8. *Bywater, R.J. & Casewell, M.W. 2000. An assessment of the impact of antibiotic resistance in different bacterial species and of the contribution of animal sources to resistance in human infections. J. Antimicrob. Chemother. 46:643-645. [Estimates only about 5% of bacterial species for which resistance in human therapy is a problem, are attributable to foodborne sources.]*
9. *Casewell, M. Friis, C., Marco, E., McMullin, P., Phillips, I. 2003. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health,*

*J. Antimicrob. Chemother.* 52:159-161.[AGP bans in Europe showed little to no actual benefit to human health, and created emerging consequences]

10. *Claycamp, H.G. & Hooberman, B.H. (FDA/CVM Draft), November 23, 2004. Risk assessment of streptogramin resistance in Enterococcus faecium attributable to the use of streptogramins in animals*  
[http://www.fda.gov/cvm/Documents/SREF\\_RA\\_FinalDraft.pdf](http://www.fda.gov/cvm/Documents/SREF_RA_FinalDraft.pdf). [FDA quantitative risk assessment for virginiamycin, risk estimate of about 63 in  $1 \times 10^8$  for hospitalized patients, and about 7.4 in  $1 \times 10^8$  for the general U.S. population, assuming a 10% attribution of clinical resistant *E. faecium* to animal sources. The paper also indicated that there was little agreement between the resistance and genetic profiles of animal and human *E. faecium*, so that the real attribution may be closer to zero]
11. *Cox, L.A. & Popken, D.A. 2004. Quantifying human health risks from virginiamycin used in chickens. Risk Analysis 24(1):271-288.*[0- <1 statistical life saved in the U.S. and Australia over 5 years if total ban were implemented]
12. *Cox, L.A. and Popken, D.A. 2004. Bayesian monte carlo uncertainty analysis of human health risks from animal antimicrobial use in a dynamic model of emerging resistance. Risk Analysis 25(5):1153-1164* [Risk estimate less than 1 in  $10^6$  even for ICU patients, <1 hypothetical excess statistical death per year for the U.S. population for virginiamycin]
13. *Cox, L.A., 2005. Potential human health benefits of antibiotics used in food animals: a case study of virginiamycin. Environment International 31 549– 563.* [Increased human health risks from more pathogens reaching consumers if VM use is terminated (6660 estimated excess campylobacteriosis cases per year in the base case) are predicted to far outweigh benefits from reduced streptogramin-resistant vancomycin-resistant *Enterococcus faecium* (VREF) infections in human patients (0.27 estimated excess cases per year in the base case).]
14. *Davis, M.A., Hancock, D.D., Besser, T.E., Rice, D.H., Gay, J.M. 2000. Reply to Drs. Angulo and Collignon [letter to the editor]. Emerging Infectious Diseases.*  
[http://www.cdc.gov/ncidod/eid/vol6no4/davis\\_letter.htm](http://www.cdc.gov/ncidod/eid/vol6no4/davis_letter.htm) [With or without imposition of stringent controls on antibiotic use in the United States and Europe, the future genetic emergence of new epidemic clones of *S. Typhimurium* somewhere in the world is highly likely. Dissemination factors are more important drivers of the spread of multiresistant *Salmonella* strains, than approved tetracycline usage in animals.]
15. *DuPont, H.L. & Steele, J.H. 1987. Use of antimicrobial agents in animal feeds: implications for human health. Reviews in Infectious Diseases 9:447-460.* [conclusion: It does not appear that the banning of drugs as feed additives, with concomitant unrestricted use of these agents for the treatment of both animals and people, would favorably influence the problems of antimicrobial resistance and salmonellosis in human populations.]

16. Guardabassi, L. et al. 2004. Pet animals as reservoirs of antimicrobial-resistant bacteria-review. *J. Antimicrob. Chemother.* 54(2):321-332. [Pets can harbor bacteria with transferable resistance, and may be a significant human source due to direct environment sharing and contact]
17. Hayes, D. L. & Jensen, H. H. (2003, August). Lessons from the Danish ban on feed-grade antibiotics. *Choices magazine*. Retrieved March 9, 2005 from [http://www.choicesmagazine.org/2003-3/2003-3-01\\_print.htm](http://www.choicesmagazine.org/2003-3/2003-3-01_print.htm). [greater use of therapeutic, broader spectrum drugs resulted when safer narrow spectrum feed additives were withdrawn. Reduction in total volumes by banning feed drugs may not be good measurements of risk reduction, in view of the fact that more potent therapeutic drugs with more serious resistance consequences are prescribed].
18. Hooton, T.L. & Samadpour, M. 2005. Editorial Commentary: Is Acute Uncomplicated Urinary Tract Infection a Foodborne Illness, and Are Animals the Source? *Clinical Infectious Diseases* 40:251-257. [The editors of the CID journal, disagreed with the (Ramchandani & Riley, et al.) cited paper's conclusion that UTI-causing E. coli strains have a foodborne origin. The speculative paper was cited in the petition, while the cautionary editorial in the same journal was omitted. This illustrates the very weak nature of the supposed link of animal antibiotics to resistant human infection]
19. Hurd, H.S., Doores, S, Hayes, D., Mathew, A., Maurer, J., Silley, P., Singer, R.S., Jones, R.N, 2004. Public health consequences of macrolide use in food animals: a deterministic risk assessment. *J. Food Prot.* 67(5):980-992. [Tylosin and tilmicosin use had risk probabilities of  $<1$  in  $10^7$  for macrolide-resistant *Campylobacter* infection in humans. Risk for *Enterococcus faecium* 1 in  $3 \times 10^9$ ]
20. Phillips, I. 1999. The use of bacitracin as a growth promoter in animals produces no risk to human health. *J. Antimicrob. Chemother.* 44:725-728. [Qualitative risk assessment of bacitracin. Its banning in the EU demonstrated the non-scientific nature of those actions. Although bacitracin was not listed in the 2005 activist petition, this review is included to emphasize the spurious science used in trying to link AGPs as important sources of clinical resistance].
21. Sarwari, A.R., Magder, L.S., Levine, P. et al. 2001. Serotype distribution of *Salmonella* isolates from food animals after slaughter differs from that of isolates found in humans. *J. Infectious Diseases* 183:1295-1299. [Serotype mismatches suggest the hypothesized direct food animal to human transfer of all foodborne *Salmonella* may be more complex than previously thought.].
22. Stokestad, E.L.R., Jukes, T.H. Pierce, J. et al. 1949. The multiple nature of the animal protein factor. *J. Biol. Chem.* 180:647-654.

23. *Page, Stephen, 2003. The Role of Enteric Antibiotics in Livestock Production.*  
<http://www.avcare.org.au/files/animalhealth/information/The%20Role%20of%20enteric%20antibiotics%20in%20livestock%20production.pdf>.
24. Navia, M.A. 2000, June 23. A chicken in every pot, thanks to sulfonamide drugs [letter to the editor]. *Science* 288.
25. R.S. Singer, L.A. Cox, J.S. Dickson, H.S. Hurd, I. Phillips, G.Y. Miller, Potential Risks and Benefits of Tylosin Use in Poultry, Abstract C2-1986, Interscience Conference on Antimicrobials and Chemotherapy (ICAAC), Washington, DC, 2004.
26. Anon. Nosocomial Infections in the U.S., *Am. J. Infect. Cont.*, 2003; 31: 481-492
27. National Pork Board 2005, *A Producer's Guide to Using Antibiotics Responsibly.*  
<http://www.porkscience.org/documents/TC%20Manual%20Page%20by%20Page.pdf>
28. U.S. Food and Drug Administration, CVM and Judicious Use Guidelines  
<http://www.fda.gov/cvm/JudUse.htm>
29. USDA Agricultural Research Bacterial Epidemiology and Antimicrobial Resistance; NARMS reports; <http://www.ars.usda.gov/Main/docs.htm?docid=6750>
30. National Antimicrobial Resistance Monitoring System: Enteric bacteria;  
<http://www.cdc.gov/narms>.
31. L. Tollefson (2004). Factual errors in review article, *Journal of Antimicrobial Chemotherapy* 54:271-271
32. B.E. Karp and J. Engberg (2004). Comment on: Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data., *Journal of Antimicrobial Chemotherapy*, 54(1): 273-274.
33. V.F. Jensen, J. Neimann, A.M. Hammerum, K. Mølbak, and H.C. Wegener (2004). Does the use of antibiotics in food animals pose a risk to human health? An unbiased review?., *Journal of Antimicrobial Chemotherapy*, 54(1): 274-275.