EXHIBIT C

TO THE DECLARATION OF MITCHELL S. BERNARD

ANIMAL HEALTH INSTITUTE
Representing manufacturers of animal health products

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Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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Re: Docket No. FDA–2010–D–0094; Draft Guidance: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Availability

The Animal Health Institute (AHI) submits these comments to draft Guidance #209 published June 28, 2010 on FDA's current thinking with regard to the use of medically important antimicrobial drugs in food producing animals. AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

General Comments:

AHI companies have developed and marketed antimicrobials for use in livestock and poultry for many years. These products have become a critical part of maintaining animal health and productivity leading to safe, abundant, and affordable animal protein. We understand the concerns which prompted FDA to publish this guidance setting forth the agency's intention to limit antimicrobials to assuring animal health and to expand veterinary oversight over the use of those products currently used in feed. AHI strongly supports the use of antibiotics in feed for therapeutic claims. The use of antimicrobials in feed must be maintained for the assurance of animal health. AHI further believes any changes to the current situation must be made with sufficient involvement of all stakeholders so as to minimize any disruptions in animal agriculture.

AHI appreciates that "*FDA is committed to working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community, and all other interested stakeholders in developing a strategy to address antimicrobial resistance concerns in a manner that is protective of both human and animal health.*"

- AHI is also committed to working with the agency to address the concerns outlined in the guidance with the intention of assuring the availability of these products to prevent, control and treat animal disease.

AHI notes FDA/CVM in the proposed guidance does not claim existing uses are unsafe, but rather not judicious. This suggests current science cannot implicate existing indications for

growth promotion as unsafe uses of antibiotics, but certain opinion leaders believe the use is inappropriate.

AHI believes use of antimicrobials can benefit animal health when approved labels are followed. There are almost assuredly judicious disease control and prevention effects that occur with antibiotic growth promotants. While FDA has articulated a regulatory policy on production claims, the agency has not identified in this guidance specific safety issues with approved antimicrobials used in animal feed.

Certainly, there has been a misunderstanding with the public and a negative perception of the value of low dose uses of antibiotics for growth promotion. These claims were established many years ago when antibiotics were first being used in animal production. There has not been a new growth promotion indication approved in more than 20 years for any antimicrobial considered medically important for human medicine. While the so-called growth promotion indications imply these uses simply "fatten" the animal, in fact, what many veterinarians and researchers believe is their use functions in maintaining gut health by suppressing bacteria causing subclinical disease. Current scientific technologies may allow proof subclinical disease is safely and effectively controlled or prevented by medicated feeds. Subclinical infections may not be readily apparent but can affect the animals' ability to efficiently utilize nutrients and resources to reach its optimal production potential. It's important to remember the best measures of a healthy animal are rate of weight gain and feed efficiency. This was most evident in Denmark when withdrawal of antibiotic growth promoters from pig production resulted in the outbreak of intestinal disease in weaners, leading to increased incidence of scouring with attendant increase in mortalities.

Specific comments:

III. Key Scientific Reports on the Issue

This is a very controversial issue which has been studied for over 4 decades. There is an abundance of scientific reviews and opinions rendered both favorable and unfavorable on the significance of animal antibiotic use to human health. The referenced reports discussed in the guidance represent only some of the information available and are only those that have emanated from governmental or international organization studies. There is another side to the story not presented in the guidance that comes to a different conclusion as to the actual impact of animal antimicrobial use on human health. The following is a partial listing of key publications that do not support the contention that animal use of antibiotics necessarily represents a significant risk to human health:

- **Antimicrobial Resistance: Implications for the Food System, Comprehensive Reviews in Food Science and Food Safety, Vol. 5, 2006.**

  This report was conducted under the auspices to Institute of Food Technologists and the IFT foundation. The panelists found the extent to which antibiotic use in food animals produces clinically important antibiotic resistant infections in humans is unknown. They further concluded regulatory targeting of specific antibiotic-resistant foodborne

pathogens may not be the most successful or cost effective means to reduce overall foodborne illness. Thus, applying interventions to control foodborne pathogens in general, rather than focusing on antibiotic-resistant strains specifically, would have the greatest impact in reducing foodborne illness.

- **Ian Phillips, Mark Casewell, Tony Cox, Brad De Groot, Christian Friis, Ron Jones, Charles Nightingale, Rodney Preston and John Waddell, *Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data,* Journal of Antimicrobial Chemotherapy (2004) 53, 28–52.**

  This is a critical peer reviewed article by a group of independent experts who examined over 250 published studies to draw distinctions among events that do happen, may happen, might happen, or do not happen relative to the potential for transfer from animal derived food to humans of various bacterial species. They found little data to suggest resistant bacteria transferred from animals have had a significant adverse impact on human and animal health.

  Wassenaar, T. *Use of Antimicrobial Agents in Veterinary Medicine and Implications for Human Health.* Critical Reviews in Microbiology, 2005; Number 3 / July-September (31):155-169.

  This review discusses why veterinary usage of antimicrobial agents is wrongly accused of causing a substantial part of the problem of resistant human pathogens. Although resistant organisms in animals are selected by veterinary antimicrobials, the author concludes these are not a major human health risk either because the role of veterinary usage in selection or propagation is insignificant, or because resistant populations selected by veterinary usage do not pose a substantial risk to human health. Indeed, resistant bacterial infections in humans causing serious quantitative and qualitative health consequences are rarely food-borne and are not the same as those selected by veterinary usage of antimicrobial agents.

- **Bywater R. and Casewell M. *Assessment of the impact of antimicrobial resistance in different bacterial species and of the contribution of animal sources to resistance in human infection.* Journal of Antimicrobial Chemotherapy 2000; 6: 643-645.**

  Individual bacterial species vary in prevalence and the extent of multiple antibiotic resistances. This paper attempted to quantify this variation, or to assess the contribution from animal sources to the overall antibiotic resistance problem in humans. The publication presents the results of a questionnaire directed to recognized experts in the UK and elsewhere chosen on the basis of their experience and wide knowledge of clinical microbiology, and not on prior knowledge of their attitudes to the topics in question. The perceived contribution of animal sources to the overall impact of resistance was estimated to be very low. Overall, the mean scores indicate animal sources might account for 3.88% of the human antibiotic resistance problem.

- **Phillips, I. *Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health (review).* Int. J. Antimicrob. Agents 2007; 30:101-107.**

  Several growth promoters were withdrawn in the European Union between 1995 and 1999 on the basis of the Precautionary Principle. Analyses suggest the added risk to human health from resistance among enterococci and campylobacters selected by growth promoter use is small, whilst the benefit to human health from their use, hitherto largely ignored, might more than counterbalance this.

- **Louis Anthony (Tony) Cox Jr*. and Douglas A. Popken, *Assessing Potential Human Health Hazards and Benefits from Subtherapeutic Antibiotics in the United States: Tetracyclines as a Case Study,* Risk Analysis, Volume 30 Issue 3, Pages 432 – 457. Published Online: 2 Feb 2010.**

  As a case study, examining specific tetracycline uses and resistance patterns suggests there is no significant human health hazard from continued use of all tetracyclines in food animals regardless of route of administration. Simple hypothetical calculations suggest an unobservably small risk (between 0 and 1.75E-11 excess lifetime risk of a tetracycline-resistant infection), based on the long history of tetracycline use in the United States without resistance-related treatment failures.

- **Louis Anthony (Tony) Cox, Jr. , Douglas A. Popken , and Jeremy J. Mathers, *Human Health Risk Assessment of Penicillin/Aminopenicillin Resistance in Enterococci Due to Penicillin Use in Food Animals,* Risk Analysis, Volume 29 Issue 6, Pages 796 – 805. Published Online: 26 Mar 2009.**

  This article considers the possibility such uses might increase the incidence of ampicillin-resistant *Enterococcus faecium* (AREF) of animal origin in human infections, leading to increased hospitalization and mortality due to reduced response to ampicillin or penicillin. Multiplying the total at-risk population of intensive care unit (ICU) patients by a series of estimated factors suggests that not more than 0.04 excess mortalities per year (under conservative assumptions) to 0.14 excess mortalities per year (under very conservative assumptions) might be prevented in the whole U.S. population if current use of all penicillin drugs (regardless of route of administration) in food animals were discontinued and if this successfully reduced the prevalence of AREF infections among ICU patients. These calculations suggest current penicillin usage in food animals in the United States presents very low (possibly zero) human health risks.

- **Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals *"Virginiamycin Risk Assessment", FDA Center for Veterinary Medicine,* November 23, 2004. *http://www.fda.gov/downloads/AnimalVeterinary/NewsEvents/CVMUpdates/UCM054722.pdf*.**

  The FDA CVM's own draft risk assessment for this drug found it difficult to assess the extent of transfer of streptogramin resistance from virginiamycin-exposed *E. faecium* to *E. faecium* found in human infections based on the available data. Literature reports demonstrate there are differences in the characteristics of resistant *E. faecium* isolated from animal and human sources, with respect to minimum inhibitory concentration (MIC) distributions and the presence of known resistance genes. These two findings, along with the current incomplete knowledge of the genetic basis of streptogramin resistance, prevents the risk assessment from making firm conclusions as to whether, and, if so, how much, the use of streptogramins in food animals contributes to the occurrence of streptogramin-resistant *E. faecium* infections in humans via a foodborne pathway.

- **Cox L.A. *Potential Human Health Impacts of Banning Antimicrobials Used in Food Animals: A Case Study of Virginiamycin.* Environ Int. 2005; 31(4):549-63.**

  This paper presents a quantitative human health risk and benefits assessment for virginiamycin (VM), a streptogramin antibiotic recommended for withdrawal from use in food animals in several countries. 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).

- **Hurd, H. S.; S. Doores; D. Hayes; A. Mathew; J. Maurer; P. Silley; R. Singer; RN Jones. *Public Health Consequences of Macrolide use in Food Animals: A Semi-quantitative Risk Assessment.* J. Food Protection 2004; 67:980-992.**

  Using the CVM Guidance for Industry # 152 this paper presents a deterministic model to assess the risk from two macrolide antibiotics, tylosin and tilmicosin. The scope of modeling included all label claim uses of both macrolides in poultry, swine, and beef cattle. Risk was defined as the probability of this hazard combined with the consequence of treatment failure due to resistant Campylobacter spp. or Enterococcus faecium. The risk assessment demonstrated that use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure, with an approximate annual probability of less than 1 in 10 million Campylobacter-derived and approximately 1 in 3 billion E. faecium-derived risk.

VI. Status of FDA's Current Activities

Medically Important Antimicrobial Drugs

- AHI recommends the principles articulated in draft GFI #209 be restricted in application to only those antimicrobials drugs identified in Appendix A of GFI #152 as critically important, highly important, or important.

The guidance defines medically important antimicrobial drugs, "*…as those that are important for therapeutic use in humans.*" There are some antimicrobials used in animals that are not used for therapeutic purposes in humans, and would logically be exempted from the guidance. Many human infections have no origin in animal hosts, thus are unlikely to be affected by the use of antimicrobials in animals, even if the same or similar antimicrobial is used to treat those human infections. The elimination of claims or restriction of marketing status for these antimicrobials would also seem to be unnecessary.

The agency has already considered the issue of what drugs constitute medically important antimicrobials during the development of Guidance for Industry # 152. That guidance includes Appendix A, "*Ranking of antimicrobial drugs according to their importance in human medicine.*" That listing includes criteria to classify antimicrobials as either critically important, highly important, or important based on their use in foodborne illness and use as the sole therapy for an important non-foodborne human infection. The development of this list was accomplished as a cooperative effort between the Center for Veterinary Medicine and the Center for Drug Evaluation and Research utilizing the advice and counsel of the FDA Advisory Committee on Anti-infective drugs. As a stakeholder in the process AHI presented information in support of that classification. Until that guidance is updated we believe it should be the operative listing for defining what is medically important for the purposes of this guidance.

We agree with FDA there are significant differences in applying GFI # 152 to products presented for approval as opposed to applying the guidance to products that have been approved and safely marketed for many years. Conditions of use for marketed products were approved by the agency based on the data submitted to the NADA's establishing dose rates, duration of therapy and extent of use. GFI #152 is based on certain assumptions as to risk and has built in risk management limitations on conditions of use for products presented to FDA for approval. Simple application of the criteria in that guidance to approved products could cause inappropriate actions to propose to withdraw products that are not a risk to public health.

We would also like to correct the record with regard to the impression suggested in the guidance that currently approved antimicrobial products for production or growth promotion purposes were never subject to a safety assessment for antimicrobial resistance since their original approvals. The discussion fails to discuss the specific requirements which were imposed on all sponsors of feed use antimicrobials in 1975 under 21 CFR 558.15 – "Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals". Specific studies were required to determine effects of antimicrobials in the feed to both the Salmonella reservoir as well as antimicrobial resistance selection pressure on *E. coli* gut flora. The regulation stated these evaluations were necessary for continued approval and were conducted and submitted to CVM

for review. While the scientific approach for assessing resistance may have changed since that time, considerable effort was expended to satisfy the agency that human health was not being jeopardized

VII. Recommended Principles Regarding Judicious Use in Animals

Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.*

- AHI recommends FDA remove this factor from the final guidance or clarify that it is not a regulatory requirement that will be enforced by the agency.

As previously stated, AHI believes use of antimicrobials can benefit animal health when approved labels are followed. There are almost assuredly judicious disease control and prevention effects that occur with antibiotic growth promotants. AHI strongly agrees with FDA that the continued availability of effective antimicrobial drugs is critically important for combating infectious disease in both humans and animals. We appreciate that FDA acknowledges antimicrobials are necessary for use in animal feed, as this may be the most effective means of administering medications to large groups of animals and birds in preventing or controlling disease.

We generally support the criteria suggested in the guidance on page 16 for justifying preventive use of antimicrobials and agree veterinary involvement is important in assuring these uses are judicious. However, we do take issue with the final criteria (5) *evidence that no reasonable alternatives for intervention exist.* While a veterinarian may consider a range of options which could be used to prevent bacterial disease, including the use of an antimicrobial, we believe this is not a factor that FDA has authority to apply in the course of deciding on the safety and efficacy of label indications. There is no statutory requirement in 512 of the Act or in 21 CFR 514 of the regulations for sponsors to demonstrate an approved product or one submitted for approval is the only intervention available for preventing a particular disease. While we understand the guidance is not binding, this factor could be used to prevent or block an indication from being approved or used to request approved indications be withdrawn when this document becomes finalized and is applied.

Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.*

- AHI recommends the agency consider all options to achieving the goal of increasing veterinary oversight, including application of the Veterinary Feed Directive. We encourage FDA to work with the AVMA and veterinary specialty groups to seek out alternative solutions.

From a practical standpoint antimicrobials and other animal drugs were historically approved for use as over the counter products due to the nature of animal agriculture and the difficulty of obtaining veterinary services in rural areas of the country. The FD&C Act recognized the difference between animal and human medicine and the need for producers to be able to maintain their animals' health when a veterinarian was not readily available. The Act

requires adequate directions for use be written for a drug to be properly labeled. It was assumed that producers could read and follow label directions for production and preventive uses of medicated feed and regulatory controls are in place to assure feed mills were properly mixing antimicrobials into the feed according to label conditions of use. Although veterinarians have been frequently involved with decisions on the use of antimicrobials in food animals, until 1996 there was no specific legislative requirement for veterinary feed directive labeling and there was no regulatory provision for product labels to restrict use by or on the order of a licensed veterinarian. The Animal Drug Availability Act provided for Veterinary Feed Directive labeling which allowed for the agency to consider all new antimicrobials added to feed to be used under the supervision of a veterinarian.

AHI recognizes the intention to increase veterinary oversight but points out the logistical difficulties if the agency intends to require products that contain antimicrobials considered medically important to only be labeled as VFD drugs. AHI is commenting separately on the Advance Notice of Proposed Rulemaking for Veterinary Feed Directive. Conversion of currently approved OTC product labels to VFD labels is a complex task and would likely require a lengthy phase-in time for veterinarians, feed mills, and producers to successfully implement.

In conclusion AHI appreciates the FDA's willingness to work with sponsors and the veterinary and agriculture community to achieve the stated goals in this guidance.

Sincerely,

Richard A. Carnevale, VMD