EXHIBIT D

TO THE DECLARATION OF MITCHELL S. BERNARD

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August 25, 2010

2010 AUG 26 A 8:00

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

Docket No. FDA–2010–D–0094; Draft Guidance For Industry #209 (GFI #209): The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

Alpharma, LLC, a sponsor of over 100 new animal drug applications (NADA) and abbreviated new animal drug applications (ANADA) potentially affected by the proposed policy, is pleased to submit these comments on the draft GFI #209.

SUMMARY

The Center for Veterinary Medicine's Draft GFI #209 summarizes current concerns regarding feed and water approved uses in food producing animals in the U.S. relative to resistance concerns for drugs used in both animals and people, and the agency's current thinking based on cited references. While Alpharma understands the general concern and concepts presented in this Draft Guidance, we believe that several underlying assumptions put forward deserve additional discussion and critical analysis. Much of the scientific underpinning is based on a limited set of publications which assert some overly-broad and in some cases unsupported definitions and assumptions. While Alpharma recognizes CVM's intended direction based on public health concerns related to medically important antimicrobial drugs, we also believe additional discussions, critical reviews of the science and, in particular, specifics on drug categorization are needed prior to any subsequent regulatory initiatives. For example, bacitracin products have only topical uses in humans and no cross resistance issues versus other antimicrobials used in humans. Thus, there is no need to change or restrict existing bacitracin indications for use in animals. Other antimicrobials used mostly for therapeutic reasons in animals (*e.g.* chlortetracycline, oxytetracycline, procaine penicillin, and sulfonamides), while related to older human-use agents, have already been extensively scrutinized for potential resistance impacts using microbiologically-specific, data-driven risk assessments, Guidance for Industry #152 (GFI #152) reviews, and have been tracked for resistance by NARMS and other surveillance programs for over a decade. We maintain approved uses of our products--which help to safely and efficiently provide high quality, affordable meat, milk and eggs for a growing world population-- are in fact in the interest of protecting and promoting public

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health; *i.e.,* these are judicious uses. Alpharma intends to actively coordinate and cooperate with the agency in developing sound, science-based and fair regulatory policies. That having been said, Alpharma notes this proposed broad policy statement does not indicate the current approved growth promotion uses of antibiotics are unsafe within the meaning of section 512(e) of the Federal Food, Drug and Cosmetic Act.

Comments Pertaining to Specific Sections of Draft GFI #209:

I. Executive Summary

P3. "*Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers .....*"

Virtually all antimicrobial uses can create direct selective pressure that allows resistant subpopulations to survive and grow, not just under supposed conditions of "misuse and overuse", which is not well defined in this document (other than strongly implying growth promotion claims fall into this category). As pointed out below, therapeutic as well as subtherapeutic dosing regimens can select for resistant bacteria. Our ongoing reviews of published experimental studies directly related to subtherapeutic uses show that relative to current U.S. approvals, there are no imminent or serious public health concerns that warrant banning or taking more stringent risk management actions.

II Introduction, P4. "*..key scientific reports..* "

The references cited include U.S. governmental summaries along with selected international and other expert reviews and reports. While the citation list covers much of recent current thinking by some governmental and international expert bodies, there are numerous additional expert scientific reviews and scientific organizations who have similarly and extensively reviewed this subject matter; for example, the Institute of Food Technologists expert report on this topic (IFT, 2006). It's clear that not all relevant sources agree with the implicit and explicit conclusions put forward in this Guidance. Several of the international reports cited were often comprised of the same limited set of individuals and came to similar conclusions and recommendations in regard to growth promotion uses. WHO expert groups are not, however, beyond criticism. For example, Oxman et al. (2007) in a Lancet article investigated WHO recommendation processes and concluded:

"systematic reviews and concise summaries of findings are rarely used for developing recommendations. Instead, processes usually rely on experts in a particular specialty, rather than representatives of those who will have to live with the recommendations or on experts in particular methodological areas".

Specific to animal antimicrobials, Phillips (2007) described similar difficulties and biases in the EU growth promoter debates. The limitations inherent in the papers

cited likely biased CVM's 'weight of evidence' finding toward a particular point of view favoring overly-precautionary actions rather than regulations based strictly on scientific evidence and likely to effect actual improvements in public health.

We submit the FDA should more thoroughly review the broader set of literature available on this topic. We question whether a truly scientifically objective, conclusive "weight of evidence" finding can be made using such a limited subset of cited references. The term 'weight of evidence' itself, is imprecise in that it does not rely on any comprehensive or standardized criteria. According to Weed (2005):

"Several problems are identified: the frequent lack of definition of the term "weight of evidence," multiple uses of the term and a lack of consensus about its meaning, and the many different kinds of weights, both qualitative and quantitative, which can be used in RA."

We propose CVM should include a more comprehensive set of publications from different disciplines when finalizing this Guidance. Further, any kind of 'weight of evidence' analysis should be based on some type of objective, preferably quantitative methodology (*e.g.*, a meta-analysis), explaining how literature sources are included and how their conclusions are integrated.

Page 4—Footnote and FAQ Question 6. Antimicrobial resistance was defined as:

"***the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial resistance, as it relates to bacterial organisms, occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to treat bacterial infections***".

FDA should define resistance in a more accurate way and differentiate a measurement (resistance) from subsequent risk impacts (loss of effectiveness in treating bacterial infections). Raw resistance data by itself does not automatically correlate to loss of medical effectiveness. The scientific definition of antimicrobial resistance is the ability of a microorganism to grow in the presence of a drug concentration that is normally inhibitory. This is the result of *an in vitro* test. Vegetative bacteria may under certain conditions survive exposures to normally inhibitory drug concentrations. The stated "*ability to resist effects of a given drug*" can be caused by inoculum density or other conditions that temporarily halt or slow bacterial growth. For example, the ability to resist cell wall inhibitor antibiotics can be the result of limiting nutrients or other conditions preventing rapid cell growth. The draft GFI and FAQ's proposed definition of antimicrobial resistance should therefore be changed..

Changes in bacterial susceptibility related to the broader concept of "loss of effectiveness" which the agency is concerned about from a public health perspective, are usually attributed to "acquired resistance" due to a genetic mutation or acquisition of a resistance determinant resulting in the ability of a specific pathogen to grow in the presence of higher, clinically relevant concentrations of a given drug used for the treatment of that pathogen. The

medical "loss of effectiveness" of a given drug is best assessed by medical surveillance programs and quantitative risk assessments, not just resistance data by itself.

III "Key Scientific Reports"

Pages 4-5- 1969 Swann Report

This report is over 40 years old and was specific to the U.K.. While historically interesting, the conclusion that subtherapeutic feeding posed a hazard to human health was based on rudimentary and incomplete knowledge. For example, it is well known that people may ingest resistant bacteria from a variety of sources, not just undercooked meat. We question whether the subsequent restrictions on feed antimicrobials in the U.K. resulting from this report actually yielded meaningful reductions in resistance impacting humans in that country.

We would also point out this early report recognized antibiotics used to enhance production work in part through control of microorganisms, stating "*animals kept under commercial conditions are held back from their potential growth rates by micro-organisms in the environment, and that antibiotics somehow reduce this restraint*". The Swann Committee rejected as a generalization the allegation the growth effect is a compensation for "*deficiencies in method of husbandry*".

Additionally, the report identifies three criteria for feed (production claim) antibiotics to be used without veterinary prescription: *"(a) that the proposed 'feed' antibiotic would have little or no applications as a therapeutic agent, (b) that the efficacy of other prescribed therapeutics would not be impaired through the development of strains of pathogens resistant to the proposed 'feed' antibiotic, and (c) that the proposed 'feed' antibiotic would be of economic value in livestock production..."*. Zinc bacitracin is identified in this report as one antibiotic which could satisfy these criteria. Subsequent to this report, numerous papers have affirmed the overall safety and beneficial effects of bacitracin used in food production (Butaye *et al.*, 2003, Phillips, 1999).

1970 FDA Task Force

The 1970 FDA Task Force report likewise needs to be taken in context of the time; there were numerous initial findings of plasmid-encoded resistance in enteric bacteria. These were relatively new findings at the time, therefore regulations requiring the intentional feeding of resistant Salmonella strains (21 CFR 558.15) and following the shedding with and without fed antimicrobials was conducted. These were to demonstrate that the agents did not promote bacterial drug resistance. In most cases, there were insignificant differences found between medicated and control feeds. If anything, these studies can now be

seen as early evidence that low-level uses did not impose any unique level of selection impact; to the contrary there was little selection found overall and in some cases there was reduced shedding of resistant bacteria.

Page 6- 1977 Ban Initiative for Penicillin and Tetracyclines

We continue to agree with the (> 30 year old) decision to conduct further studies and hold in abeyance the implementation of blanket withdrawal actions for penicillins and tetracyclines. Numerous published *in vitro*, *in vivo* and risk analysis studies following this action have shown a lack of data linking any actual harm to human health due to approved feed and water animal usage of these antimicrobials. While this does not prove that hazards do not exist (as stated in the 1980 NAS report), subsequent surveillance data on sentinel bacteria (Alpharma Comments, 2010), and more recent risk assessments continue to show that such risks are extremely low (possibly zero) for all animal uses regardless of route of administration of penicillin and tetracycline under current conditions (Cox et al., 2009, Cox & Popken, 2010).

Page 7- 1988 IOM Report

This report used a risk-analysis model using *Salmonella* infections causing deaths. The Committee was unable to find a substantial body of direct evidence demonstrating that the subtherapeutic use of penicillin or tetracycline in animal feed posed a human health hazard. We believe this Committee accurately determined that both subtherapeutic *and* therapeutic use of antimicrobials can select for resistant bacteria that may be potential hazards.

Page 7- 1997 WHO Report

This expert group stated "low level, long-term exposure to antimicrobials *may have* greater selective potential than short-term, full-dose therapeutic use" (italics added). This very general and qualified assertion used to bolster the group's recommendations, was not, however, backed up by experimental studies on relevant individual drugs. To the contrary, we can cite numerous peer-reviewed papers showing feed and water uses of approved antimicrobials do not select for problematic resistance resulting in loss of effectiveness in contemporary human medicine.

Pages 8-13.
Several studies mentioned (1999 EC Report, 2000 WHO Report, 2003 FAO/OIC/WHO Expert Workshop, 2003 IOM Report, 2004 FAO/OIE/WHO Expert Workshop, 2004 GAO Report, 2005 Codex Code of Practice).

These reports had overall general recommendations to conduct additional studies. We note the sole U.S. government report in this set (GAO, 2004) stated that researchers disagree about the extent of the human health risk caused by the passive transfer of antibiotic resistant bacteria to humans. The GAO

recommended advancing the risk assessment process, which in fact was followed by FDA, industry, and Codex. We note that 2004 Codex Code of Practice further specified responsible use of growth promoting agents did not include drugs belonging to classes of antimicrobials used in humans *in the absence of appropriate risk analysis*. We submit both FDA and industry have so far successfully engaged and expanded the use of risk assessment approaches for currently used subtherapeutic antimicrobials.

Additionally, Alpharma actively participates in and supports the efforts of the Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance to develop guidelines for risk analysis for minimization and containment of foodborne antimicrobial resistant micro-organisms and resistance determinants to protect consumers' health and ensure fair practices in food trade at the national/regional level. While not intended for veterinary product registration purposes, any FDA policies or regulations should take into account the principles contained this Codex document, when adopted.

Pages 13-15.
IV. Strategies for Controlling Antimicrobial Resistance Are Needed

An important statement is made in this section that based on the previous information presented in the Guidance: "*FDA has reviewed the recommendations provided by the various published reports and, based on this review, believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health*".

We noted in earlier comments for sections I and II that it's unlikely a truly conclusive "weight of evidence" finding can be made using such a limited subset of cited references; we therefore question it. We refer the authors of this Guidance and statement to a contemporary article published in CVM Veterinarian (Sechen, 2006), which summarized in detail how production animal health needs are met while also protecting the public health. Providing high quality, affordable protein in the form of meat, milk and eggs for a growing world population we submit *is* in fact in the interest of protecting and promoting public health.

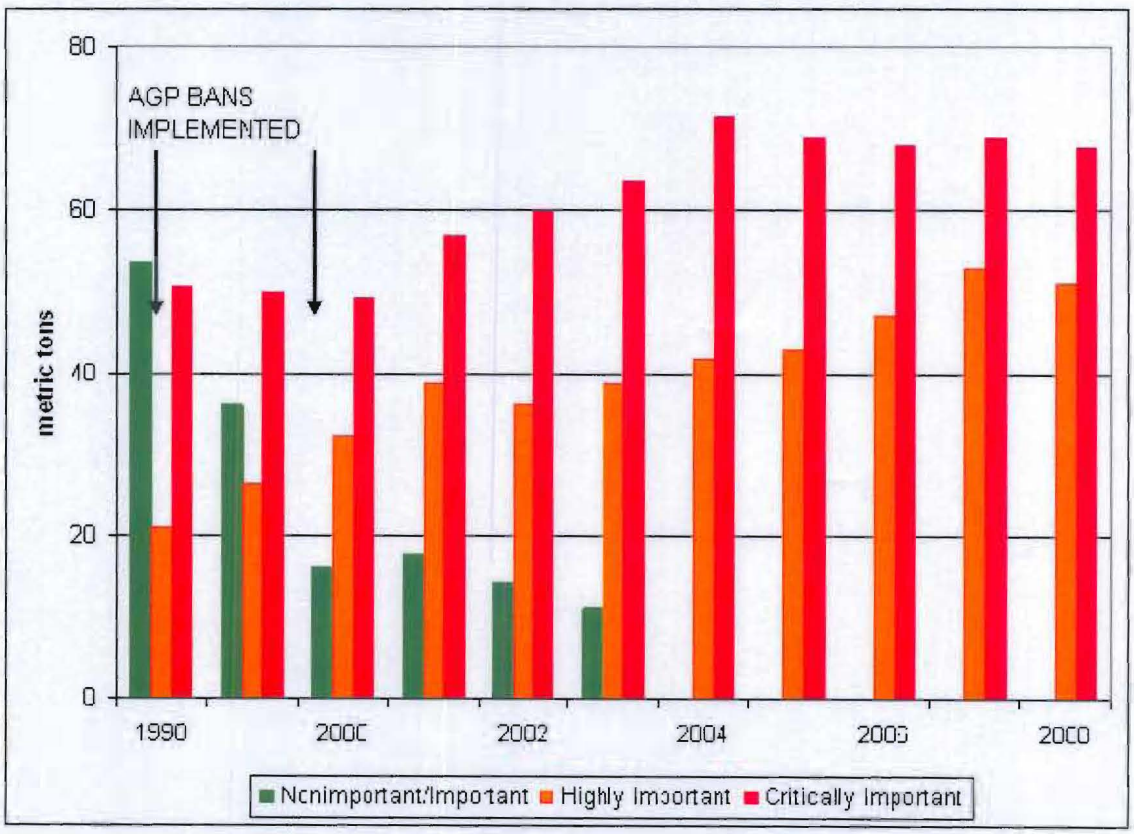
V. Current Regulatory Framework

We generally concur with this section, which describes the GFI#152 qualitative risk assessment paradigm. We also note the inherent limitations of only using a qualitative process. We agree risk-related concerns associated with approved NADAs can sometimes be better addressed through informal processes and dialog with sponsors. We would, however, point out GFI #152 is better suited to pre-approval evaluation of new antimicrobials than to assessing the microbial safety of antimicrobials which have been used for decades in animal feed or water and for which resistance rates and patterns remain stable.

Page 15- VI. Status of FDA's Current Activities

We generally concur with statements in this section. We agree the scientific understanding regarding antimicrobial resistance has advanced significantly over time, and while some expert groups and governments have raised public health concerns, it is also true the discipline of quantitative risk assessment homing in on specific microbes and relevant drugs has also advanced. Potential new regulatory initiatives should realize solely concern-driven risk management has a high potential for unanticipated consequences; for example, some EU countries which unilaterally banned production agents, even those having "nonimportant" or "low-level important" categorizations, ended up using higher percentages and amounts of "highly important" and "critically important" agents with potentially greater resistance risk to humans than those banned.

The following figure shows an example of this for Denmark, subsequent to the ban on growth promotion uses of antimicrobials:



Changes in the amounts and types of antimicrobials used in food-producing animals in Denmark(DANMAP, 2008). Arrows show years where bans of growth promoters were implemented. Antimicrobials were grouped as categorized for their importance to human medicine by FAO/WHO/OIE (2007): "Critically Important: Glycopeptides, avilamycin, penicillins, aminoglycosides, streptogramins, macrolides, fluoroquinolones and cephalosporins/other penicillins. Highly Important: Tetracyclines and sulfonamides. Nonimportant/Important: Flavofosfolipol, quinoxalines, coccidiostats and bacitracin".

There have been no demonstrable improvements in human health or resistance rates in major food borne pathogens in the EU following these AGP bans, and there were notable deleterious effects on animal health. Moreover. the prevalence of some foodborne bacteria such as *Campylobacter* increased after bans were implemented across the EU. As summarized by Phillips (2007), "*The relentless increase in the prevalence of human campylobacteriosis in the EU is so far unexplained, but we are not aware of any effort to investigate its potential relationship to the cessation of use of growth-promoting antibiotics*".

VII. Recommended Principles Regarding Judicious Use in Animals.

We agree with the statement: "***The continued availability of effective antimicrobial drugs is critically important for combating infectious disease in both humans and animals. This Includes the continued availability of feed and water uses of such drugs for managing disease in animal agriculture***". We also recognize that FDA believes additional steps are needed in the area of judicious use guidance.

Pages 16-17. Commenting on the first stated 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.

We believe this statement of principle needs to be addressed and mainly accomplished by consulting expert sources in the field of veterinary pharmacology, epidemiology, animal production science, and related agricultural fields not just the cited sources or other individuals/organizations who believe they can accurately estimate this parameter. The term "medically important" needs to be further refined. Many categorization schemes have been developed by expert groups, FDA and other countries. We submit that drugs having only nominal human use should warrant less regulatory restrictions.

As a prime example, the narrow-spectrum peptide antibiotic bacitracin is only used topically in humans and has been extensively documented as having no important residues, resistance or cross-resistance impacts on pathogens (Butaye et al., 2003, Jones, 2001, Jones, et al., 2006, Phillips, 1999). Though the 2007 WHO expert group had placed bacitracin into an 'Important' category based on its limited topical human usage, bacitracin zinc or bacitracin methylene disalicyclate products for feed use clearly warrant lower priority when considering regulation of approved animal therapeutic or growth promotion uses. Indeed GFI #152 in 2003 did not even list ionophores or bacitracin in the Appendix A list of compounds of human medical importance, based on the collaborative expert (CDER) review. Furthermore, bacitracin has subsequently been removed from the NARMS surveillance drug testing panels for enterococci to allow space for other drugs that are of greater human medical relevance. Medical experts in infectious disease confirm since the bacitracin peptide is highly nephrotoxic when injected, its human medical importance is inherently very minor (Jones, 2001,

attached). We therefore submit bacitracin feed and water products as prime examples of agents that should continue to be allowed as production improvement tools in U.S. animal agriculture.

For several other older drug classes which are listed in GFI #152 (*e.g.*, natural penicillins, tetracyclines and sulfas), while they are still used in human medicine thus medically important, in many cases are no longer preferred drugs for human infection and have been shown by quantitative risk analyses to pose extremely limited microbiological resistance risks (Cox et al., 2009, Cox & Popken, 2010). Current NARMS data moreover shows resistance and multi-resistance 11+ year patterns to be low, stable and even declining among human *Salmonella* isolates (Alpharma Comments, 2010, attached). These facts plus a long background of safe usage after over 5 decades in food-producing animals should provide the proper context when proposing new policies or regulations for feed and water applications of these agents.

We firmly agree with the statement "...***FDA believes some prevention indications are necessary and judicious***". Judicious uses of feed and water agents for prevention and control have long been recognized as appropriate tools for keeping populations of domestic livestock and poultry healthy and thriving. We believe there is good evidence that the five criteria specified in this section have been addressed by numerous studies submitted to CVM, as well as in published literature.

On page 17, a second Principle is stated: *"The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation."*

While many situations already involve such oversight, we believe label indications have historically been safely and effectively used by responsible parties. The shortage of veterinarians specializing in food production agriculture, along with geographic distances and climates across our continent-spanning nation suggests that reasonable accommodations on this principle could and should be made. We are not aware of any recent cases of mis-application or misuse of most feed and water products by farmers, ranchers, or animal nutrition professionals resulting in problematic resistance outbreaks or residue violations. Most of the violations involving residues are related to therapeutic administrations. We note other uses of antimicrobials (*e.g.*, antibacterial soaps, some pet medications and fruit crop uses) often do not involve such oversight or consultation. We question whether the paperwork, costs and administrative burden of such requirements are justified given the extremely low-level risks associated with mostly older-generation approved feed and water products being reviewed in this Guidance.

VIII. Conclusion

Alpharma agrees with and supports FDA's commitment to working with animal drug sponsors, the veterinary and public health communities, the animal agriculture community and other interested stakeholders in developing a strategy

to address resistance concerns in a manner protective of both human and animal health. We believe reserving the formal regulatory authority for cases presenting actual public health threats is the best policy. These can be better defined through comprehensive and, wherever possible, quantitative risk assessments and reviewing surveillance program findings. Working with drug sponsors and professionals in the industry will help enable FDA to accomplish its mission of minimizing adverse resistance impacts on animal and human health without seriously disrupting U.S. animal agriculture.

Sincerely,

Sondra C. Flick

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Director, Government & Industry Affairs

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A Brief Review of U.S. NARMS Data Pertaining to Relevant Feed and Water Antimicrobials used in Animal Agriculture

July 2, 2010

Alpharma, LLC, manufacturer and distributor of medicated feed and water additives in the U.S. and worldwide, appreciates the opportunity to comment on the U.S. National Antimicrobial Resistance Monitoring System (NARMS) programs and data.

The primary stated objectives of NARMS include:

- To provide descriptive data on the extent and temporal trends of antimicrobial drug susceptibility in *Salmonella* and other enteric bacterial organisms from human and animal populations, as well as retail meats.
- To facilitate the identification of antimicrobial drug resistance in humans, animals, and retail meats as it arises;
- To provide timely information to veterinarians and physicians on antimicrobial drug resistance patterns. (FDA NARMS, 2010)

Another goal of these activities is to have data available that will serve to help inform national policy aimed at prolonging the lifespan of approved drugs by promoting prudent and judicious use of antimicrobial drugs and to identify areas needing more detailed investigation. The NARMS program is also an important post-approval monitoring program for approved antimicrobials used in human and animal sectors. The following review used data available from the most recent NARMS annual reports from all three program arms. The review emphasized trends and contrasts for multi-drug and single resistances among older classes of antimicrobials relevant to feed and water uses in food-producing animals.

Human NARMS Multidrug Resistance

For 2007 (most recent year having a final summarized report), 18.9% (406/2144) of non-typhoidal *Salmonella* isolates from human clinical cases were resistant to one or more CLSI antimicrobial classes (81.1% were therefore pan-susceptible). Multidrug resistance is described in the NARMS program by both number of antimicrobial classes and also by specific co-resistant phenotypes. The penta-resistant ACSSuT phenotype (acronym for ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline co-linked resistance markers), is commonly found among several Gram-negative bacterial types including *Salmonella* and *E. coli.* Of 239 non-typhoidal *Salmonella* resistant to three or more classes, most were *Salmonella* Typhimurium (57.7%) serotype. Some interesting observations on the individual drug resistances are also discussed relative to hypotheses about antibiotics use in agriculture. From the CDC 2007 report, the following highlights were reported:

• 6.3% (136/2144) of non-typhoidal *Salmonella* isolates had the pentaresistant ACSSuT pattern.

•1.7% (19/1100) of *Campylobacter* had resistance to three or more antibiotic classes. None were reported with pentaresistance patterns.

• 2.1% (4/190) of *E. coli* O157 isolates were resistant to three or more classes, 0.5% to five or more, and none (0%) were found with an ACSSuT phenotype.

• 33.2% (160/482) of *Shigella* isolates were resistant to three or more classes and 3.7% (18/482) possessed the ACSSuT phenotype. (Note: *Shigella* only has a human colonizing reservoir).

Trends: Figure 1 was taken directly from page 18 of the 2007 CDC NARMS Summary Report. Overall, multidrug resistance patterns have shown an 11 year downtrend since 1996.

Figure 1.07: Proportion of non-typhoidal *Salmonella* isolates resistant to 3 or more antimicrobial classes, by year, 1996-2007.

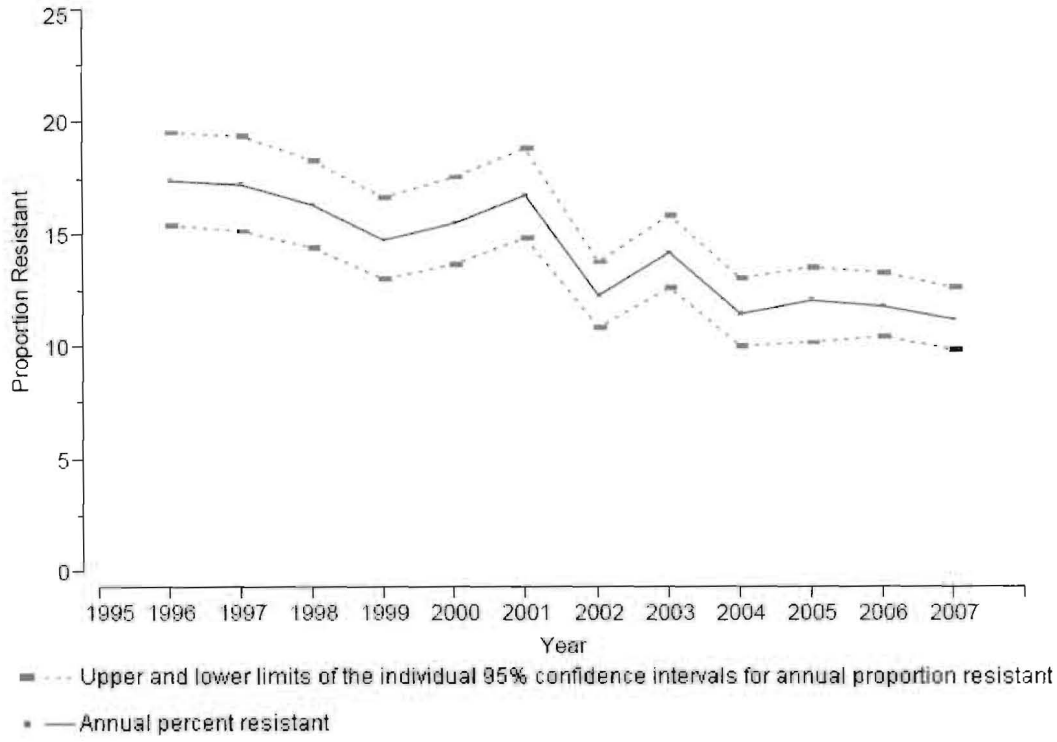

Figure 1. Human NARMS overall multi drug resistance trend for *Salmonella*.

Comparison of Multi-Drug Resistant *Salmonella* from USDA/FSIS Slaughter, FDA Retail, and CDC Human Clinical Sources

Non-Typhi *Salmonella* multiple drug resistance was compared by plotting the weighted average resistance of four food-producing animal species associated with USDA NARMS (FSIS slaughter carcass rinsates), along with the resistance prevalence for all FDA retail meat and CDC human strains reported through 2007 (Figure 2). The CDC human isolates have shown an 11-year downtrend, with the USDA and FDA sets showing stable or declining patterns

since 2000 and 2002, respectively. The overall multidrug resistance prevalence levels are lower than 10%.

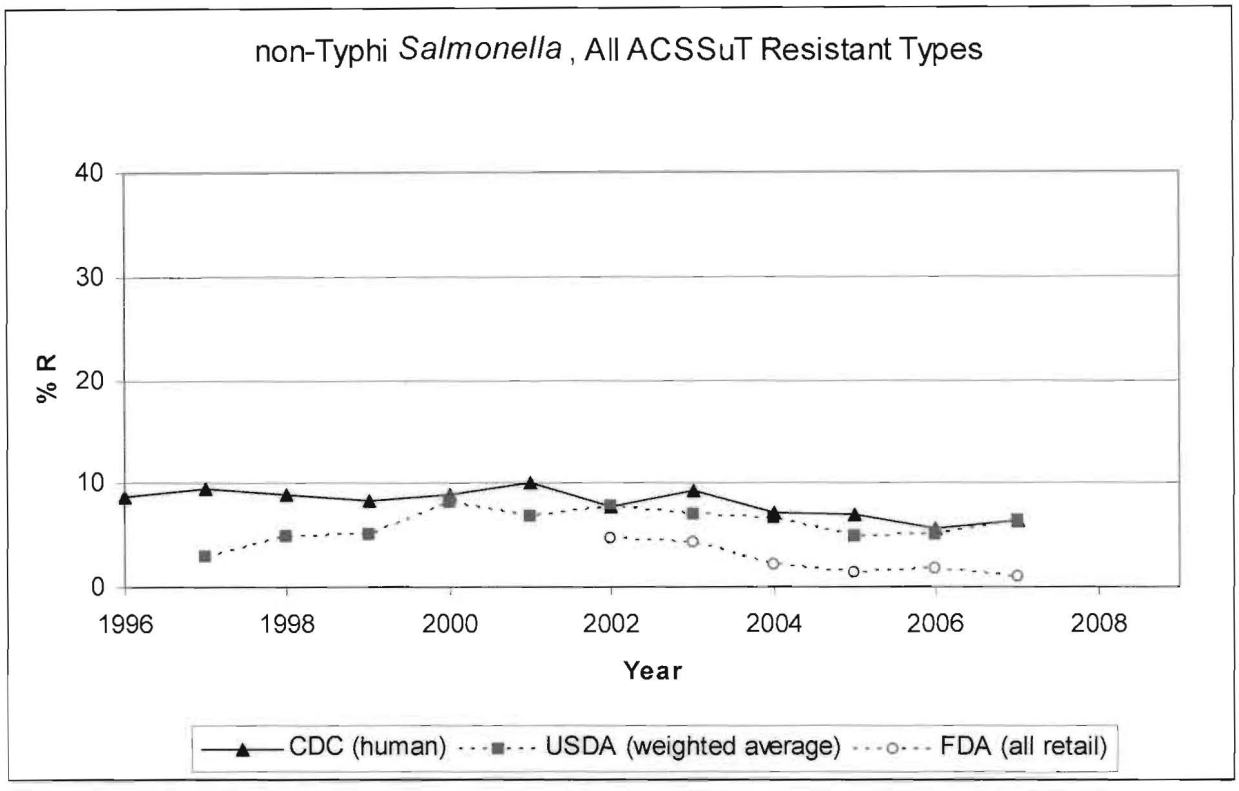

Figure 2. Overall multi-drug resistance trends as reported by three arms of the NARMS program.

For animal carcass-sourced multi-drug resistant types (as measured by the USDA NARMS program from associated slaughter carcasses), there are distinctive levels of resistance associated with animal species, with cattle and swine recently having somewhat higher proportions of ACSSuT types. In Figure 3, the legend also lists the top 2 *Salmonella* serotypes in 2007 for each species. It is known that different colonizing serotypes possess varying stable MDR phenotypes, or alternatively virtually no resistance. An example from human

source *Salmonella*; the second most prevalent non-Typhi *Salmonella* found in human clinical cases (ser. Enteritidis) by NARMS has essentially no multiple drug resistance, and very low single resistance levels yet has remained an important disease causing pathogen in people.

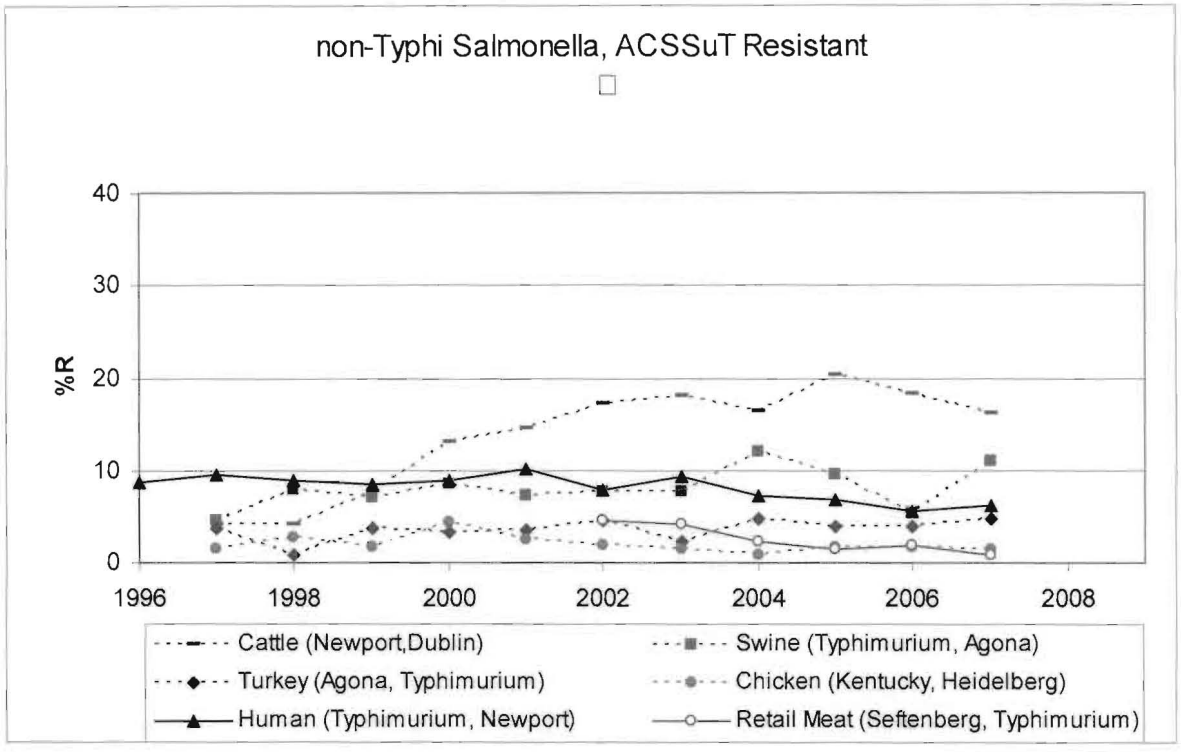

Figure 3. Specific animal-associated carcass isolate ACSSuT resistance prevalence levels, as reported by USDA NARMS relative to CDC (human) and FDA (retail meat) levels. Top two serotypes associated with MDR phenotypes in parentheses.

Other Enterics with Pentaresistant (ACSSuT) and MDR Phenotypes Reported by NARMS

Campylobacter jejuni, although an important foodborne pathogen, demonstrates relatively low levels of multi-drug resistance. The USDA NARMS carcass *C. jejuni* showed <15% and CDC showed <3% resistance to three or

more drugs. Althougn non-Typhi *Salmonella* serovars can colonize animals and thus serve as reservoirs for human infection, other enterics such as *Shigella* and *Salmonella* Typhi only have known natural reservoirs in humans and other primates (Tauxe, 2002). *Salmonella* Typhi causes typhoid fever and *Shigella* spp. shigellosis; both acute human enteric diseases. Athough present at less than 15% of total, the ACSSuT phenotype in both bacteria have been consistently detected since 1998 from human clinical cases. The prevalence levels of these phenotypes have been greater than for E. coli 0157:H7 (rare) which may be carried in livestock (Figure 4), also greater than from generic *E. coli* isolated from humans and chickens in CDC and USDA pilot projects. These observations raise questions as to whether humans rather than food-producing animals could be the most important reservoirs and/or sources of multi-drug resistance determinants.

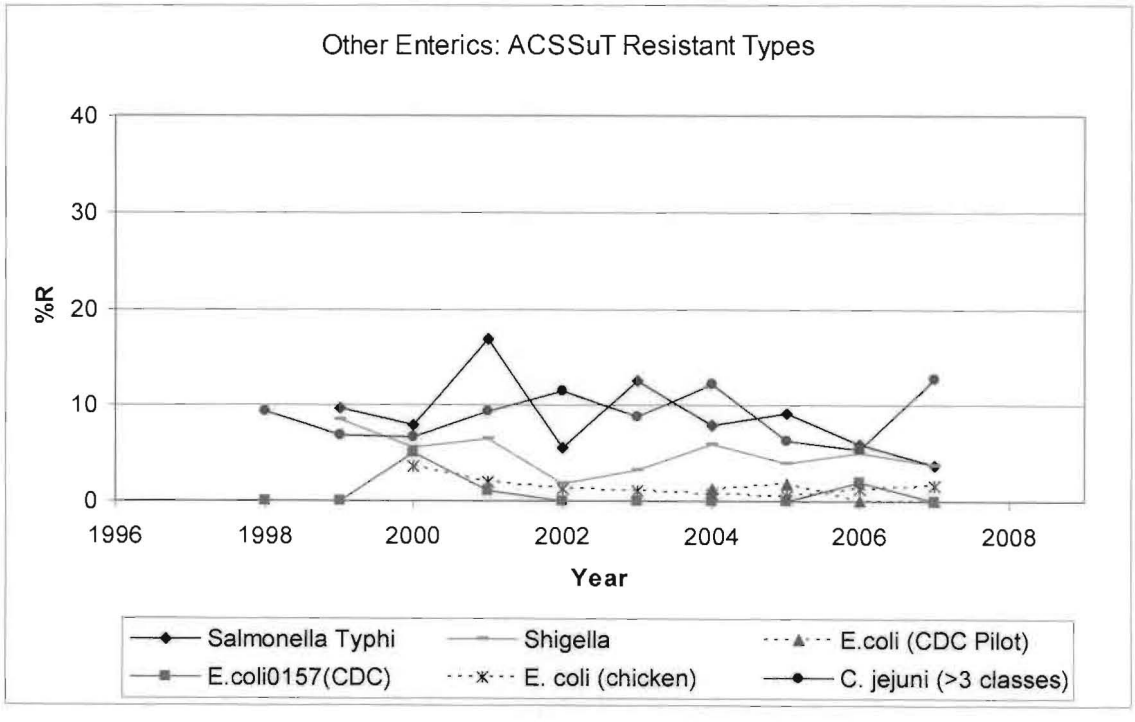

Figure 4. Pentaresistance (ACSSuT) trends for enterics other than nontyphoidal *Salmonella*.

A popular hypothesis has been that commensal bacterial selected by antimicrobials could be driving multi-drug resistance among foodborne pathogens. The disparate animal and human resistance levels and trends measured by the NARMS program, however, offer very limited empirical data supporting this hypothesis.

Are older antimicrobials used in agriculture driving resistance in food-producing animals and humans?

This question is one that NARMS can help answer, since single as well as multiple drug resistance to relevant classes have been measured since 1996 and 1997 in both humans and from animal-associated carcass sources. Some evidence can be found by looking at the prevalence trends, and also reviewing which drug classes are/are not used in animal feeds and water. Figure 5 shows the single-resistance trends for animal-associated slaughter types (USDA NARMS) and human (CDC NARMS), for the older drugs streptomycin, ampicillin, sulfonamide and tetracycline.

The resistance lines show slightly declining 11-year human-source trends for all four antibiotic classes, with overall stable resistance levels for animal-associated slaughter (weighted averages shown). The average resistance levels are plotted in the next graph (Figure 6) that for all four classes, human resistance prevalence levels are essentially the same. Animal carcass-associated (USDA), while showing relatively high tetracycline resistance also reveals there is also significant resistance to streptomycin at a level higher than for ampicillin or sulfa.

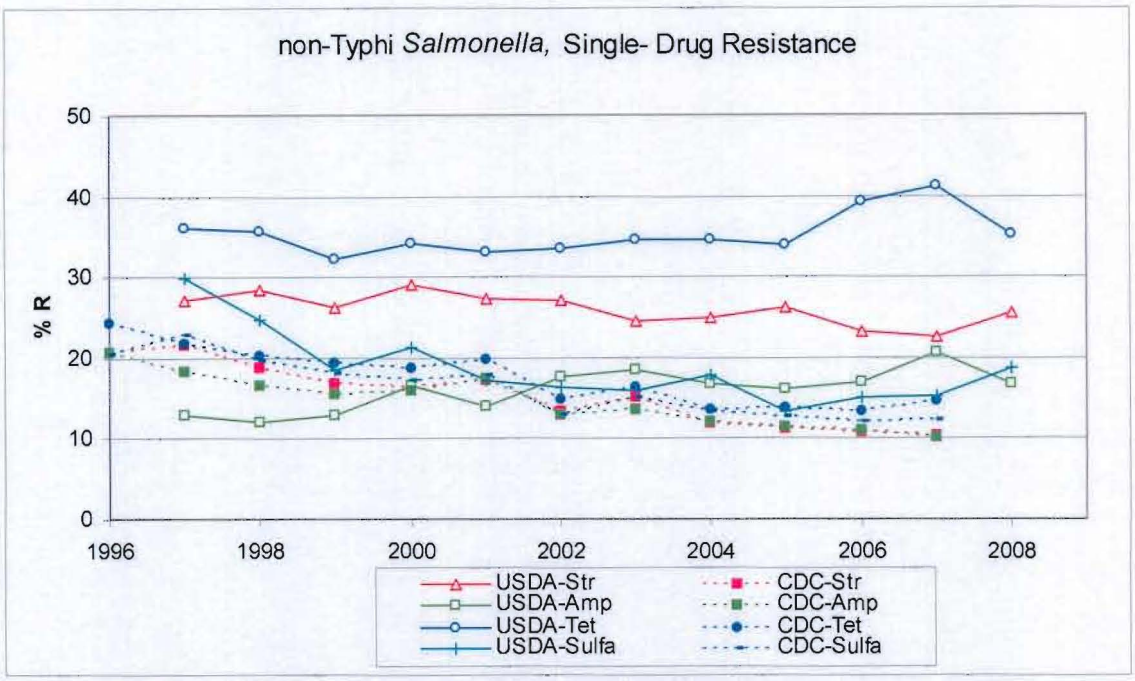

Figure 5. Single-drug resistance among carcass slaughter (USDA) and human source (CDC) *Salmonella* as reported by NARMS.

Penicillin and sulfas have some feed and water approved uses in U.S. food producing animals, but at relatively low total volumes (< 6.5 % of total for both classes combined) in comparison to all antimicrobials sold each year according to AHI sales statistics (AHI, 2007). Streptomycin, however, is only used for mammary infusions and some injectable treatments for leptospirosis; essentially having no feed or water approved uses. Among related aminoglycosides (kanamycin, gentamycin and neomycin) there are some uses of neomycin in livestock and poultry. All aminoglycosides make up < 0.8% of all antimicrobials sold, however (AHI, 2007). The enteric bacterial exposure to these antibiotics would thus be expected to be extremely low for streptomycin relative to others. If drugs associated with oral administrations in agriculture were forcing significant resistance levels among enteric *Salmonella*, we would predict relatively low streptomycin resistance and a correlation among single-drug resistances among *Salmonella* according to the relative amounts sold or used

among classes used in feed and water mostly for disease prevention, control, or therapy.

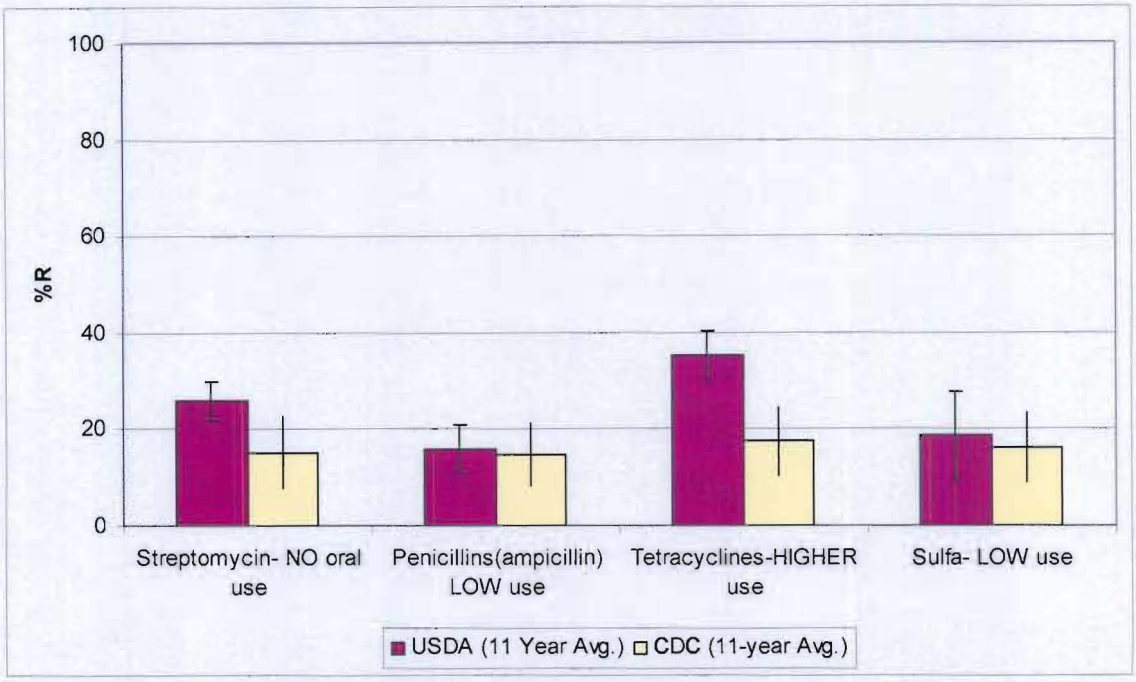

Figure 6. Lack of correlation of older antibiotic single-drug resistance levels and relative amounts used in animal agriculture. Error bars, 95% confidence limits of prevalence levels.

Except perhaps for some possible selection effects from tetracycline in USDA (remembering that major colonizing serotypes heavily influence resistance patterns and tetracycline being the most common resistance type), Figures 5 and 6 illustrate how little correlation there is between relative animal usage versus single-drug resistance and 11-year trends in human (CDC) isolates.

Among the entire set of human clinical isolates reported by NARMS, single resistance among older drugs are uniformly low and shows declining trends over the 11 year period (Fig. 5). *Salmonella* and other enterics in people likely have significant non-food animal reservoirs, but importantly the total volumes used in food-producing animals are not good predictors of human clinical resistance, when measured by isolates from associated slaughter animals

or from people. Another indication of this can be seen by looking at resistance patterns for *E. coli* 0157 (Figure 4), which may be carried in livestock but which still demonstrate very low resistance to single drugs, and virtually no multiresistance despite potentially greater exposure to antimicrobials.

Another example of non-correlation with use, is chloramphenicol resistance (the "C" of the ACSSuT phenotype), a commonly detected single and multiple-associated resistance in many bacteria (6-10% prevalence level among human NARMS *Salmonella*). This class is not approved for use in animal feeds or water, however. If total agricultural use volumes were correlated with resistance, one would predict this marker to have a very low prevalence among sentinel bacteria such as those tracked in the NARMS program. This is shown to not be the case.

NARMS Data and 'PAMTA' Bills

To highlight the need for verifiable scientific information informing public policy, House Bill H.R. 1549 (questionably titled "Preservation of Antibiotics for Medical Treatment Act of 2009"), for example contains many scientifically erroneous statements and assertions regarding antimicrobials used in food-producing animals relative to human diseases, such as:

"An estimated 70 percent of the antibiotics and other antimicrobial drugs used in the United States are fed to farm animals for nontherapeutic purposes, including i) growth promotion; and ii) compensation for crowded, unsanitary, and stressful farming and transportation conditions; ..."

The "70% nontherapeutic" and broad-brush value judgments on crowding and sanitation conditions originate from non-peer reviewed advocacy group sources that have overstated the total volumes of relevant antimicrobials (AVMA, 2009). Similarly, a Consumer Reports article, a 2001 *editorial opinion* in a medical journal and similar "references" were used as the basis of the bill. After mentioning specifically tetracyclines, macrolides, aminoglycosides, penicillins, sulfonamides and others, the bill further states:

"these drugs are used in people to treat serious diseases such as scarlet fever, rheumatic fever, venereal disease, skin infections, and even pandemics like malaria and plague, as well as bioterrorism agents like smallpox and anthrax."

Several of the diseases specified in this bill (scarlet fever, rheumatic fever, malaria, plague) are older (in some cases obsolete) diseases that have become rare in the past 170 years in the United States (Quinn, 1989). Penicillin (either oral penicillin V or injectable benzathine penicillin) remains the agent of choice for preventing rheumatic and scarlet fever, because it is cost effective, has a narrow spectrum of activity, has long-standing proven efficacy against pharyngeal diseases, and group A streptococci resistant to penicillin have not been documented (Dajani et al. 1995). Various macrolides, oral cephalosporins, and other β-lactam agents are acceptable alternatives for rheumatic and scarlet fevers, particularly in penicillin-allergic individuals, with no or very low resistances reported for any of these older drugs.

Venereal diseases, skin diseases and anthrax are not foodborne infections, malaria is a parasitic disease and smallpox is a virus that has been eradicated worldwide (Henderson, 1980)—being a virus no animal feed related antibiotic could treat it even if it were somehow resurrected as a bioterror agent. These diseases were apparently listed in the bill either due to inadequate literature review or perhaps for the ominous sounding impact achieved by listing them. The list of diseases in H.R. 1549 is certainly not an accurate or realistic representation of public health impacts that could be related to the targeted drugs' resistance.

In contrast, data from NARMS show single resistance and multi-drug resistance prevalence levels and 11-year trends among potentially relevant foodborne bacteria remain low, stable, and even declining among human sentinel and indicator isolates from 1996-2007. The actual data thus run contrary to erroneous assertions made by advocacy groups and drafted into scientifically misinformed legislative bills focusing on agricultural antibiotics uses. In addition to this review's focus on NARMS data, microbiology-specific quantitative risk

assessments have been published in scientific journals and by governmental sources for streptogramin, macrolide, penicillin and tetracycline classes; all showing vanishingly low levels of potential resistance impacts.

Alpharma, LLC, as a responsible manufacturer and marketer of antimicrobial products remains concerned about antimicrobial resistance. Alpharma therefore supports continuing and improving the U.S. NARMS surveillance programs as a source of relevant, timely, and science-based antimicrobial resistance data.

Jeremy J. Mathers, MS, PhD
Senior Manager, Product Support-Microbiologist

References

USDA NARMS

http://www.ars.usda.gov/Main/docs.htm?docid=14491

FDA NARMS

http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm

CDC NARMS

http://www.cdc.gov/narms/

2007 Annual Survey. Active Antibacterial Ingredients Sold by AHI Members:

http://www.ahi.org/files/Media%20Center/Antibiotic%20Use%202007.pdf

Tauxe RV. 2002. Emerging foodborne pathogens. Int. J. Food Microbiol 78:31.

Quinn, RW. 1989. Comprehensive review of morbidity and mortality trends for rheumatic fever, streptococcal disease, and scarlet fever: The decline of rheumatic fever. Rev. Infect. Dis. 11(6): 928.

Dajani, A. et al. 1995 (Oct.). Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: A statement for health professionals Pediatrics 96(4),758-764
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AVMA. 2009. Frequently Asked Questions about

Antimicrobial Use *and* Antimicrobial Resistance

http://www.avma.org/public_health/antimicrobial_use.asp

The JONES Group, Inc.*
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371

DATE: June 28, 2001

TO: Eddy Piron
011-32-328-75881

FROM: Ronald N. Jones, M.D
Director, JMI Laboratories
Professor of Medicine
Tuft's Univ. School of Medicine

RE: Human Clinic Role of Bacitracin Injectable in the USA

In response to your questions about the current use of Bacitracin for systemic therapy in the United States, I doubt that this product ever will be used for the indication listed in the approved package insert (PI). This compound by systemic route is extremely toxic as clearly outlined in the PI and numerous alternative agents of greater potency and spectrum are available that carry more acceptable rates of toxic side effects. To my knowledge in nearly 30 years of laboratory medicine and infectious disease practice, we have never considered the use of this product for systemic use.

A query of the most recent edition (21st) of the USP-Drug Information publication fails to show Bacitracin systemic in the "Advice of the Patient" volume. This agent only appears in the "Drug Information" volume (USP-DI, 2001, 21st edition) in the "Orphan Product" list (page 3164) as an off-label treatment of antibiotic-associated enterocolitis. This indication also seems to be of very limited value following preferred regimens with vancomycin and/or metronidazole. This listing in the USP "Orphan Products" dates from 1984.

Furthermore, as the chairholder of the NCCLS Antimicrobial Susceptibility Test Subcommittee in the 1980's, I presided over the withdrawal of Bacitracin and other topically used antimicrobials from the national standard methods. At that time (as now) no significant use as systemic agents (toxic) was documented, and the reporting of in vitro test results were not relevant to drug selection in human practice. In fact, current national and international antimicrobial resistance surveillance programs (SENTRY, Alexander, PROTEKT, MYSTIC, etc.) do not routinely monitor these agents because of their limited or nil use in human medicine as systemic agents.

If I can be of assistance in this matter to a greater degree, please contact me at the numbers on this letterhead. With best regards.

/klm
Attachment: USP-DI Table (1)

CUMULATIVE LIST OF ORPHAN PRODUCT DESIGNATIONS AND APPROVALS *(continued)*

NAME *Generic/Chemical* *TN = Trade Name*	INDICATION DESIGNATED	SPONSOR AND ADDRESS *DD = Date Designated ...* **** = Marketing Approval*
ARSENIC TRIOXIDE	TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA.	POLARX, INC. NEW YORK, NY PHONE: (212) 554-4362 DD 03/03/1998
ARTESUNATE	TREATMENT OF MALARIA.	WORLD HEALTH ORGANISATION SWITZERLAND CH PHONE (202) 331-9081 DD 07/19/1999
ATOVAQUONE*** TN= MEPRON	TREATMENT OF AIDS ASSOCIATED PNEUMOCYSTIS CARINII PNEUMONIA.	GLAXO WELLCOME INC. RESEARCH TRIANGLE PARK, NC PHONE: (919) 483-2100 DD 08/10/1990
ATOVAQUONE*** TN= MEPRON	PREVENTION OF PNEUMOCYSTIS CARINII PNEUMONIA (PCP) IN HIGH-RISK, HIV-INFECTED PATIENTS DEFINED BY A HISTORY OF ONE OR MORE EPISODES OF PCP AND/OR A PERIPHERAL CD4+ (T4 HELPER/INDUCER) LYMPHOCYTE COUNT LESS THAN OR EQUAL TO 200/MM3.	GLAXO WELLCOME RESEARCH AND DEVELOPMENT RESEARCH TRIANGLE PARK, NC PHONE. (919) 483-9324 DD 08/14/1991
ATOVAQUONE TN= MEPRON	TREATMENT AND SUPPRESSION OF TOXOPLASMA GONDII ENCEPHALITIS.	GLAXO WELLCOME INC. RESEARCH TRIANGLE PARK, NC PHONE: (919) 483-9324 DD 03/16/1993
ATOVAQUONE TN= MEPRON	PRIMARY PROPHYLAXIS OF HIV-INFECTED PERSONS AT HIGH RISK FOR DEVELOPING TOXOPLASMA GONDII ENCEPHALITIS.	GLAXO WELLCOME INC. RESEARCH TRIANGLE PARK, NC PHONE: (919) 483-9324 DD 03/16/1993
AUTOLOGOUS DNP-CONJUGATED TUMOR VACCINE TN= M-VAX	FOR ADJUVANT THERAPY IN MELANOMA PATIENTS WITH SURGICALLY RESECTABLE LYMPH NODE METASTASIS (STAGE III AND LIMITED STAGE IV DISEASE).	AVAX TECHNOLOGIES, INC. KANSAS CITY, MO PHONE: (816) 960-1333 DD 02/23/1999
AUTOLYMPHOCYTE THERAPY	TREATMENT OF RENAL CELL CARCINOMA.	CYTOGEN CORPORATION PRINCETON, NJ PHONE: (609) 987-8200 DD 07/12/1994
AZATHIOPRINE TN= IMURAN	TREATMENT OF ORAL MANIFESTATIONS OF GRAFT-VERSUS-HOST DISEASE.	ORAL SOLUTIONS, INC. NEW YORK, NY PHONE: (212) 554-4293 DD 09/14/1999
B2036-PEG TN= TROVERT	TREATMENT OF ACROMEGALY.	SENSUS CORPORATION AUSTIN, TX PHONE: (512) 476-0270 DD 06/24/1997
BACITRACIN TN= ALTRACIN	TREATMENT OF ANTIBIOTIC-ASSOCIATED PSEUDOMEMBRANOUS ENTEROCOLITIS CAUSED BY TOXINS A AND B ELABORATED BY CLOSTRIDIUM DIFFICILE.	A. L. LABORATORIES, INC. FORT LEE, NJ PHONE: (201) 947-7774 DD 03/13/1984
BACLOFEN*** TN= LIORESAL INTRATHECAL	TREATMENT OF INTRACTABLE SPASTICITY CAUSED BY SPINAL CORD INJURY, MULTIPLE SCLEROSIS, AND OTHER SPINAL DISEASES (INCLUDING SPINAL ISCHEMIA, SPINAL TUMOR, TRANSVERSE MYELITIS, CERVICAL SPONDYLOSIS, AND DEGENERATIVE MYELOPATHY)	MEDTRONIC, INC. MINNEAPOLIS, MN PHONE: (612) 572-5000 DD 11/10/1987
BACLOFEN	TREATMENT OF INTRACTABLE SPASTICITY DUE TO MULTIPLE SCLEROSIS OR SPINAL CORD INJURY.	INFUSAID INC NORWOOD, MA PHONE (617) 769-8330 DD 12/16/1991
BACLOFEN TN= LIORESAL INTRATHECAL	TREATMENT OF SPASTICITY ASSOCIATED WITH CEREBRAL PALSY.	MEDTRONIC, INC MINNEAPOLIS, MN PHONE: (612) 572-5647 DD 09/26/1994

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- **Fold the printed label at the solid line below.** Place the label in a UPS Shipping Pouch. If you do not have a pouch, affix the folded label using clear plastic shipping tape over the entire label.
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  Take your package to any location of The UPS Store®, UPS Drop Box, UPS Customer Center, UPS Alliances (Office Depot® or Staples®) or Authorized Shipping Outlet near you. Items sent via UPS Return Services℠ (including via Ground) are also accepted at Drop Boxes.
  To find the location nearest you, please visit the Resources area of CampusShip and select UPS Locations.

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  Your driver will pickup your shipment(s) as usual.

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