Industry Viewpoint on Therapeutic Antimicrobial Use in Food Animals

Dr. Richard Carnevale

The AHI is very pleased to present views of the animal health industry on this very important and complex topic. For the last two days we have heard a lot of scientific data and opinions rendered as to the problem of antibiotic resistance and animal and human health. Clearly this is a worldwide issue of importance to all of us in the pharmaceutical industry as it threatens to decrease the effectiveness of products to treat the diseases they were intended for.

Let's step back and take a look at the AHI position:

- We support strong government regulation of antimicrobials in animals which is based on science, and support FDA's current regulations regarding their marketing, availability, and use.

- We support government programs to improve antibiotic resistance monitoring. Companies are conducting their own monitoring on labeled pathogens either as a condition of approval or through voluntary efforts. We are very interested in working cooperatively to enhance these systems.

- We support "prudent use" of antibiotics to reduce animal suffering and safeguard human and animal health. We believe that current practices as regulated by FDA, USDA and state authorities are prudent, and look forward to further dialogues about how we can better support these practices.

-We support continued implementation of HACCP systems by the USDA and the meat and poultry processors to improve the microbiological safety of meat and poultry.

- And we support the availability of antibiotics to treat and prevent disease and improve productivity in food-producing animals. As we have all agreed, outright prohibitions based on speculative information, are simply NOT an option for drugs otherwise found to be safe and effective.

While empirical evidence has been presented in the media and elsewhere to support the contention that a public health threat exists, the conclusions being drawn are scientifically suspect and we must work together to ensure that we have the best available information.

Clearly, food borne illness is a concern!

No one is questioning that Salmonella and other enteric pathogens continue to be a problem and can be transmitted to humans through improperly handled and cooked meat and poultry. Salmonella has been around for a long time, well before the advent of antibiotics. Foodborne illness will occur whether or not antibiotics are used on the farm. On the contrary, if animal diseases are not controlled with antibiotics, the problem of food-borne illness could be worse.

In fact, our food is safer today because antibiotics have kept livestock and poultry healthier when presented to market. And meat and poultry processing plants appear to be doing a good job of controlling bacterial contamination.

Supporting this contention are recent reports issued by USDA's Food Safety and Inspection Service. FSIS, since 1992 has been conducting a series of baseline studies to examine the contamination levels of carcasses after slaughter and inspection.[1] Excised samples of beef and pork were taken from carcasses hanging in the cooler after all processing and inspection procedures had been performed. For chickens, a whole carcass rinse was used. The samples were taken from meat and poultry plants around the country in a design that optimized the chances of the data being statistically representative of large and small meat and poultry processors.

The results show a low overall prevalence of Salmonella on beef and dairy carcasses – just 1-2% -- and 8% of pork carcasses. Not unexpectedly, Salmonella was recovered from about 20% of chicken broiler carcasses. Data on chicken carcasses collected in 1983, showed a prevalence of about 35%.

FSIS also quantified the actual numbers of bacterial cells in an attempt to determine the degree of contamination. In steers and heifers, less than 1 colony forming unit(cfu) per square centimeter was recovered in 100% of positive carcasses while in cows and bulls, less than 1 cfu were recovered in 90% of the positive samples. Calculating back from recoveries of the pathogen in

whole bird rinse fluids from chickens, of 260 samples positive for Salmonella, 95% were estimated with less than 1 cfu per square centimeter. In pork, 86% of the samples were also reported with less than 1 cfu per square centimeter. By anyone's standards, these must be considered exceedingly low pathogen counts. It's important to point out that this is in the face of decades antibacterial use on the farm. In fact, it begs the question -- if meat and poultry is coming out of these plants so clean, then why is food borne illness estimated to be so high?

In a recent newspaper article, Marion Burros of the New York Times conducted a market basket survey to compare "organic" poultry (presumably raised without antibiotics or other animal drugs), with conventionally produced poultry. To her surprise, she reported that there was virtually no difference in pathogenic bacterial loads between the organic and conventional products.[2] While this was not a scientific study, it highlights the fact that sanitary slaughter, and proper handling of raw products are the critical factors in preventing bacterial contamination.

While is has been suggested, it has not been shown that the in-vitro susceptibility or resistance of a bacterial pathogen has a major impact on the frequency or outcome of food borne illness. For example *E.Coli 0157 H7* which has caused outbreaks associated with the consumption of undercooked ground beef, is a virulent pathogen, but appears to be quite susceptible to most antibiotics.[3] Outbreaks of Salmonella food borne illness have appeared in the literature in some cases linked to resistant pathogens that may have come from animal sources. However, to my knowledge it has not been documented that the susceptibility of the organism was the reason the outbreaks occurred in the first place or significantly affected the final clinical outcome.

My point here is that there are multiple points in the food process from farm to fork and all play their part. The real risk of foodborne illness involves possible contamination of the product during processing, then improper refrigeration, storage and/or cross contamination, and finally inadequate cooking. Animal drugs have little if anything to do with these critical control points.

I want to now examine recent concerns that have appeared in the media and consider the scientific arguments.

While antibiotic resistance issues have been with us for a long time, more recently events both in the US and overseas have caused renewed concerns about the use of antibiotics in animals, in

particular the fluoroquinolone class of antibacterials currently approved only in poultry in the US but in a variety of species in Europe for treatment of bacterial infections.

Let's look first at DT 104, which you've heard about in the media and at this meeting. Several papers published by the Central Public Health Laboratory in London since 1993 reported on the increasing prevalence of isolates of a *Salmonella typhimurium* Determinant Type 104 (StDT104) strain. They also reported the emergence of what they have concluded is a trend -- of increasing " resistance" to ciprofloxacin, a fluoroquinolone drug for humans.[4] A link has been suggested by the authors that the increasing " resistance" was likely due to the fact that in 1994 enrofloxacin, a fluoroquinolone, was approved for use in the United Kingdom in food-producing animals.

The situation with this new strain of Salmonella is worth attention in attempting to document its epidemiology in order to control its spread. But the conclusions that this pathogen represents an extreme threat to public health -- and that fluoroquinolone use in animals is responsible for reducing the usefulness of ciprofloxacin in humans -- are not warranted by the available data.

The percentage of isolates of StDT 104 of all Salmonella serotypes isolated from the London laboratory in 1996 was only about 13%. While there were significant increases in this isolate from 1991 until 1995, recent evidence indicates a leveling off in 1996 and even a 20% decrease extrapolated from eight months of preliminary 1997 data.[5] In the US, a 1996 report from the CDC, FDA, USDA National Antimicrobial Monitoring System indicates that of 1,272 total Salmonella isolates subjected to susceptibility testing, only 95 or 1% of all isolates showed a multi-drug resistant pattern similar to that seen with StDT104.[3] My point here is that a variety of factors may have caused the rise of DT104 in Britain, and the situation now appears to have abated.

More importantly is the criteria that is being used to conclude there is a resistance problem with this strain. The London laboratory reports resistance to ciprofloxacin as anything above a Minimal Inhibitory Concentration (MIC) of 0.125 ug/ml. However, both the British Society for Antimicrobial Chemotherapy (BSAC) and the US National Committee for Laboratory Standards (NCCLS) have set a clinical breakpoint for ciprofloxacin at 4.0 ug/ml. The vast majority of the isolates reported as resistant to ciprofloxacin were between 0.25 ug/ml and 1ug/ml. So in reality, and under these international standards – which the US relies on – these DT104 isolates are

actually quite susceptible to antibiotic treatment, according to the clinically derived standard for resistance.

Another issue at the crux of the controversy is the timing of approval of enrofloxacin in the UK, since this event is being used as the cause for the increasing "resistance". While it is true that the drug was officially licensed by the government in late 1993, the product was not launched by the company and available for farm use until 1995. [6] Up until that time there had been very limited availability of the drug mainly for ongoing investigational studies. The increased prevalence of StDT104 resistant isolates was first seen between 1994 and 1995, before the product was even available to most veterinarians. So the implication that widespread use in animals was responsible for the increasing trend in resistance would not appear to be substantiated.

To further add to these doubts about the origin of the claimed resistance, data from laboratories in Scotland don't support the findings in England. In Scotland the testing of about 350 human and veterinary salmonella isolates indicated no resistance at levels of 0.125ug/ml in animal isolates, while 17% of the human isolates showed " resistance" at 0.25ug/ml.[7]

Finally, the data from the London laboratory appears to have been selectively analyzed. *Salmonella enteriditis* (SE) is clearly the most prevalent serotype of all Salmonella isolates recovered and probably accounts for much of the Salmonella food borne illness in the UK. Of 30,000 annual samples, between 60-65% are SE. No increase in SE resistance has been reported for ciprofloxacin . It is significant that *Salmonella enteriditis*, the most common form of salmonella, remains uniformly susceptible to a variety of antibiotics. [4]

After DT104, an often-heard charge is that salmonella is becoming increasingly resistant to antibiotics because of animal use.

Allegations have been made that animal and human resistance patterns are the same, which some people say constitutes "direct evidence" that resistance in people is coming from animals. There is no question that a common source of Salmonella is animal derived products, but, there is evidence that person-to-person transmission also occurs. While there are a number of such reports in the literature which I will not reference here, a 1988 paper estimated that a significant number of Salmonella infections could be caused healthy human carriers.[8] Another paper in 1987

concluded that food-borne illness resulting from contamination by human carriers must be considered along with animal sources.[9]

A report was recently released from the CDC/FDA/USDA National Antimicrobial Monitoring System summarizing data from the 1996 human susceptibility testing of human Salmonella and Campylobacter isolates.[3] The data comprised about 1,500 random samples taken from 14 State Health Departments in the US. While the sample size is small, the report indicates that the eligible human population from which the samples were drawn was about 74 million people.

Several observations can be made from this data. No clinical ciprofloxacin resistance of any identified serotypes is reported. For all Salmonella serotypes, the 15 tested drugs showed between 75-100% clinical susceptibility. There were 95 S. typhimurium isolates which do show higher frequencies of resistance to several drugs. These isolates are compatible with the StDt104 strain, but represent a very small portion of all samples. However, a third of the isolates were *Salmonella enteriditis* which showed overall greater sensitivity to the tested antibiotics. Similar to experiences in the UK, SE is more likely to be associated with food borne illness than other serotypes. For all serotypes, 10 of the 14 antibiotics were between 90-100% clinically susceptible.

Of note is that the highest levels of resistance are to drugs commonly used for years in humans, not unique to animals. But, there are three drugs used almost exclusively in animals which bear attention. Apramycin, ceftiofur, and gentamicin show very little resistance in human isolates. For the first two, it shows that antibacterials can be used in animal populations for many years without a significance transfer of resistant Salmonella to humans. With gentamicin, resistance has been reported in animal isolates, but it doesn't seem to be showing up in human Salmonella isolates.[10] Of final interest is the observation that 14% of typhimurium and 13% of heidelberg isolates showed clinical resistance to kanamycin, a drug not known to be used in food-animal medicine.

Now let's consider Campylobacter resistance.

Reports have also surfaced that Campylobacter, a common isolate in poultry has shown high levels of resistance to the fluoroquinolones both in the US and overseas. In an article that first

appeared in the New York Times and duplicated in numerous papers around the country, unpublished data was reported as implicating the poultry use of fluoroquinolones as causing resistance in this pathogen.[11] The Minnesota Department of Health collected samples of chickens and turkeys testing them for the presence of Campylobacter and subjecting the isolates to sensitivity testing. The reported results showed a high frequency of recovery of Campylobacter spp. from birds with between 20 -89% of the isolates reportedly resistant to ciprofloxacin.

This information has never been published. It is not known what susceptibility breakpoint was employed, what methods of isolation and characterization of Campylobacter species was employed and whether the results are statistically significant. Furthermore, the samples sizes were quite small – only 50 retail chickens and 60 turkey cecal samples[6]. Most importantly, no comparison to previous results prior to the availability of fluoroquinolones for animal use were noted in the article. This makes it difficult to understand the hypothesis that fluoroquinolone use in poultry has altered the inherent resistance patterns to this drug class.

According to data collected by the same Minnesota Department of Health human *C. jejuni* isolates have shown decreased susceptibilities to nalidixic acid and ciprofloxacin since 1992. This is three years prior to the approval of the fluoroquinolones sarafloxacin and enrofloxacin in poultry.[12] The point here is that Campylobacter resistance in people was noted before fluoroquinolones were ever used in animals.

Furthermore, Campylobacter has never been considered to be highly susceptible to the fluoroquinolones, and other drugs such as Erythromycin, are recommended in treating these infections.[13] Campylobacter also produces mild self-limiting infections and don't require treatment very often. Data reported from Holland indicates that resistance to this pathogen was first noticed in that country in 1987 and tied to the use of the drug in animals.[14]The problem with this conclusion is that the a fluroquinolone was only first available for use in 1987 in animals while norfloxaxin had been approved for human use since 1985. In Spain high levels of resistance were reported for human Campylobacter isolates against the fluoroquinolones and again being blamed on animal use.[15] However, no testing of animal isolates was done to confirm that the source of resistance may have been animals. It is important to note that there is little to no protection from generic competition in Spain and antibiotics are more freely available in both

animals and humans. The situation in Spain is not reflective of either the rest of Europe or the US. It does though support the idea of adequate controls.

In conclusion ...

I want to stress that AHI appreciates the issue of resistance—it clearly is a problem, but how much of it is really due to animal drugs and what is the medical impact? I have attempted to raise questions on the scientific conclusions being drawn by some in order to show that the problem is complex and that the risks of using animal drugs must be put in context with the real risk factors associated with food borne illness—failures in food hygiene.

The World Health Organization will be holding a consultation in June of 1998 on the medical impact of the fluoroquinolones in animals. This meeting was postponed from February largely at the behest of both the FDA and European Medicinal Evaluation Agency (EMEA), who felt that the program allowed too little time to develop comprehensive scientific papers. We look forward to those discussions.

Finally, food safety is important—it is a high priority with the current administration.

- We shouldn't scare the public with unsubstantiated concerns without a sound scientific basis.
- We shouldn't divert our attention from the real causes and solutions to the problems of food borne illness.
- Everyone agrees that antibacterials are necessary to keep animals and people healthy—animal drugs work to improve the food supply not to damage it.

This is a top priority for AHI. The concerns being raised today are not new—they have been exhaustively studied for more than 30 years, and there is still no direct link established that shows that animal drugs increases the risk of contracting food borne illness, nor significantly decreases the effectiveness of antibiotics in people.

With that said, however, we are eager to work with all interested groups on this issue. Like FDA, CDC, AAVPT and others, we support a strong regulatory process based on science to ensure that

antibiotics are used appropriately. We share an understanding of the value that antibacterials have for keeping food safe and people healthy.

To continue to ensure consumer confidence in the food supply and the prudent use of these products, the AHI and its member companies support the U.S. science-based regulatory process. As Dr. Angulo and other speakers clearly noted, these products provide a distinct benefit for animal health. I look forward to everyone working together to safeguard their effectiveness in animals and people.

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