The future of antibiotic growth promoters in poultry production

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Summary

Estimates by the United Nations (UN) indicate that in today’s world population there are nearly one thousand million hungry people and that the world’s population will surpass nine thousand million people by the year 2050, accordingly, the UN’s Food and Agriculture Organization (FAO) has called for doubling the amount of food the world produced in 2010 by the middle of the century (2050). FAO also emphasized that this 100% increase in the production of food will have to be done with a minimal increase in cropland area and adverse environmental impact, additionally, it estimates that at least 70% of this additional production of food will have to come from the use of technologies designed to enhance production efficiency. It is the opinion of the author that in order to meet this monumental task, the use of all, new and old technologies, must be available to food animal producers around the globe. Second only to the productivity gains achieved through genetic selection of farm animals, antibiotic feed additives (AFAs), and in particular those classed as growth promoters (AGPs) have for more than a half century been the most significant and reliable technology used to enhance food animal productivity through the prevention and control of subclinical enteric diseases that erode performance efficiency. However, misguided activist groups with an anti-animal agriculture agenda have in recent years mounted a well organized and financed political campaign at the International level against conventional animal agriculture, and the use of AGPs. Such political pressures are what led the European authorities to ban the use of all AGPs, starting with avoparcin in 1997 and ending with the banning of the remaining AGPs on January 1, 2006. The endless stream of international regulatory proposals brought forward by activist groups adversely impacting food animal producers/companies with the pretext of enhancing human health, food safety, environmental sustainability and animal welfare are, in the opinion of the author, nothing more than the means of bypassing the legally established regulatory system in order to achieve their ultimate stated goal, the conversion of the entire society to vegetarianism. By removing the tools that make animal agriculture more efficient and profitable, like the use of AGPs, the activist groups hope to remove the incentive of companies to get involved in food animal production, at least in the more developed countries. In general the communications media and many politicians around the world have seized the opportunity to gain higher ratings and more votes by sensationalized reporting and legislative proposals to restrict the use of AGPs, like “The Preservation of Antibiotics for Medical Treatment Act”, also known as PAMTA which has been introduced in the United States of America (USA) Congress every year for the past decade without success but it is heavily supported by activist groups with an anti-animal agriculture agenda. It is this type of political pressure and legislative proposals that have forced the USA Food and Drug Administration Center for Veterinary Medicine (FDA-CVM) to publish in recent years a series of “Industry Guidance Documents” in the Federal Register to address the problem of antimicrobial resistance and eventually phase-out production uses of antimicrobials medically important in human medicine. Based on the European experience the most probable outcome of these AGP bans will be a detriment of animal health, an increased cost of production and use of antimicrobials for therapy without a measurable improvement in antimicrobial resistance in human medicine.
In spite of more than 60 years of use and an endless search for a “smoking gun”, to this date, to the knowledge of the author, not a single human fatality has been directly and unequivocally linked to the use of AGPs in food animal production. Contrary to public perception, the continued use of AGPs is beneficial to both, animal and human health. There are numerous scientifically documented benefits derived directly from their use in animal feeds; such as the prevention and control of enteric diseases, enhanced food safety, improved animal welfare, a lesser carbon footprint from the production of food of animal origin that results in preservation and less contamination of the environment and a more sustainable animal agriculture, improved efficiency of production and lower cost of production resulting in lower prices and more accessibility to high quality animal protein to the most needed populations of the world as the UN and the FAO have demanded.

Introduction

The debate as to whether antibiotics should be added to animal feeds at low or subtherapeutic concentrations dates back to the beginning of their use as feed additives in food-producing animals. Since the Swann report was made public in 1969, the common practice of adding antibiotics at low levels to the feed of animals destined for human consumption has been further scrutinized for its potential to create antibiotic resistance (Swann, 1969). The Swann report suggested that AFAs from the same classes used in human medicine not be used in food animals. More recently, the World Health Organization (WHO) has also made similar suggestions but has been willing to allow continued usage when proper scientific risk assessments have been conducted. However, in its “WHO global principles for the containment of antimicrobial resistance in animals intended for food”, WHO recommends making all uses of antimicrobials in food-producing animals by prescription only, and that in the absence of public health safety evaluations, all uses of antimicrobials also used in human medicine for growth promotion should be terminated or quickly phased-out (WHO, 2000).

Numerous scientific reviews have been conducted to determine if this practice poses a significant risk to human health. Most scientific reviews (NRC, 1998; Bezoen et al., 1999; USGAO, 1999; Phillips et al., 2004; IFT Expert Report, 2006) acknowledge the fact that feeding low levels of antibiotics to food-producing animals can result in the development of antibiotic resistant bacteria and therefore a theoretical risk to humans that come in contact with the animals or consume their products, as they have acknowledged the theoretical risk to humans posed by house pets that have been treated with antibiotics. Likewise, the scientific reviews have concluded that antibiotic use in humans, rather than animals, is the driving force behind the antibiotic resistance problems encountered in human medicine and that the practice of feeding low levels of antibiotics to food-producing animals poses no immediate or imminent threat to human health, as this practice has been in existence for over 60 years.

Further proof now exists from the analysis of data collected on antibiotic consumption in humans and animals and the monitoring of antibiotic resistance in zoonotic and commensal bacteria from humans and animals. The Danish have collected, analyzed and published such data since 1997 when the ban of the most commonly used AGPs used in food-producing animals took place, those reports are known as the DANMAP reports and can be accessed by anyone by visiting their website at http://www.danmap.org. The DANMAP reports have shown that in spite of the banning of the AGPs, the consumption of antibiotics and the prevalence of antibiotic-resistant bacteria have continued to increase in both humans and food-producing animals. The only benefit from the ban of AGPs has been a substantial reduction in resistance on indicator bacteria from food-producing animals which the health authorities have publicized as a success, although this “success” has not resulted in any measurable improvement in antibiotic-resistance in human medicine. Interestingly, in the last published report (DANMAP, 2010) the researchers document a steady increase in annual cases of methycillin-resistant Staphylococcus aureus (MRSA), from 47 cases in 1997 (when AGP use for all practical purposes ended) to 1104 cases in 2010.

The argument used against antibiotics

The activist groups opposed to the routine use of antimicrobials at low or subtherapeutic concentrations in poultry feeds frequently state that poultry companies unnecessarily feed millions of pounds of antimicrobials each year to promote growth and enhance feed efficiency in otherwise “healthy flocks” of broiler chickens and turkeys. They also claim that poultry companies use AFAs as crutches to continue raising poultry flocks in filthy
and poorly managed conditions. These groups fail to recognize that nearly one half of the total amount of antimicrobials added each year to poultry feeds belong to a class of AFAs known as "polyether ionophores" that are primarily used for the purpose of preventing coccidiosis (a protozoal parasitic disease) in broiler and turkey flocks, and have no use in human medicine (AHI, 2011). Even the most risk averse European Union (EU) regulators recognize this fact and have not banned the use of the ionophore anticoccidials for coccidiosis prevention in food-producing animals.

The activist groups have also failed to recognize that the beneficial effects of AFAs on poultry health and welfare have been scientifically documented in "healthy chickens" maintained under ideal conditions of sanitation and management (Roura et al., 1992). University of California researchers demonstrated that indicators of immunologic stress, such as elevated plasma levels of interleukin-1, elevated serum levels of copper and elevated liver concentrations of metallothionein could be induced in broiler chicks exposed to a dirty environment or given an injection of Salmonella typhimurium lipopolysacharide. In addition, the chicks with signs of immunologic stress also had lighter body weights and higher feed conversions than the chicks without signs of immunologic stress. In all experiments, the chicks that were fed low concentrations of antibiotics in the feed had significantly lower levels of indicators of immunologic stress, heavier body weights and lower feed conversions. Interestingly, "healthy chicks" kept in clean environments under optimal management conditions also showed signs of immunologic stress, and the addition of low concentrations of antibiotics to their feed significantly lowered them resulting in heavier body weights and lower feed conversions leading the researchers to conclude that, "We were able to reduce signs of an immune response taking place in 'healthy' growing chicks housed according to conventional laboratory guidelines by feeding antibiotics, suggesting that activation of the immune system sufficient to impair growth occurs across a wide range of conditions of sanitation".

Another argument frequently made against the use of AGPs is that the productivity improvements derived from their use are miniscule, in the range of 0.5 to 3%, and that such minimal benefits are not worth the risk of creating antimicrobial resistance. A recently conducted experiment to demonstrate the benefits of supplementing diets of turkey hens with virginiamycin will serve to illustrate how "miniscule improvements" can translate into huge benefits (Cervantes et al., 2011). In this experiment, even under optimal conditions of sanitation and management, the addition of 22 ppm virginiamycin to the feed of turkey hens for eleven weeks resulted in a 0.133 kg (6.519 vs. 6.652) live weight advantage and a 0.05 (1.907 vs. 1.857) advantage in feed conversion. According to the activists argument, the improvements seen here would only represent a 2.05 and a 2.62% advantage and therefore would be referred to as "miniscule" (even though the statistical analysis of the data indicated that the differences were significant at the 0.05 alpha level of probability). However, when we apply these "miniscule" differences to a commercial size operation that raises five million hens/year, the weight advantage of the virginiamycin-fed turkeys translates into an additional 666,780 kg of live weight while the feed conversion advantage translates into a savings of 1991.3 metric tons of feed, no one would argue that these differences are not "miniscule".

Finally, the activist groups fail to recognize that poultry companies strive to raise poultry flocks under the best possible management practices as healthy flocks perform better and are more profitable (NTF, 2004).

Perception vs. reality

The basis for the opposition to the use of antimicrobials at low concentrations in animal feeds for food-producing animals comes from concerns about the development of antimicrobial resistance in bacteria present in animals and its potential transfer to the public through the food chain. Although this may seem like a reasonable concern, an in-depth examination of the data on antimicrobial-resistant bacteria of significance in human medicine leads to a different conclusion.

Of the 20 most serious bacterial infections exhibiting problems with antimicrobial resistance in human medicine, 12 are in no possible way related to antimicrobial use in food-producing animals as these bacteria cannot be acquired via the food chain. Of the remaining 8, assuming that transfer of antimicrobial resistance from animals to people occurs, the calculated percent contribution to antimicrobial resistance in all cases is 1% or less, and in most cases is less than 0.5% (Bywater and Casewell, 2000). Likewise, results from the SENTRY Antimicrobial Surveillance Program, which since 1997 has analyzed worldwide data on antibiotic resistance patterns from both, human and animal...
bacterial isolates has found little significant association between human and animal patterns (Jones and Turndige, 2003). According to Ron Jones, M.D., results from the SENTRY Antimicrobial Surveillance Program “clearly show a disconnect between antimicrobial resistance patterns in humans and animals, calling into question the alleged link between resistant bacteria in animals and those in humans”. These conclusions are further supported by data collected in the USA by the National Antimicrobial Resistance Monitoring System (NARMS), which includes antimicrobial resistance data from bacteria collected from humans by the Centers for Disease Control and Prevention “CDC” and animals by the U.S. Department of Agriculture “USDA” (NARMS, 2010a,b).

The politics

European union sequence of events

Sweden was the first country to unilaterally ban the routine use of all antimicrobials added at low concentrations to animal feeds in 1986. At that time Sweden was not a member of the EU. The Swedish model was then supported by other Scandinavian countries like, Denmark and Finland. When Sweden and Finland entered the EU in 1995, special derogations from EU laws were permitted so that they could continue their ban of in-feed antimicrobials (Williams, 2001). However, as the extended derogations from EU laws were to expire at the end of 1998 and were contrary to the policy of the EU which allowed the use of in-feed antimicrobials in the rest of the member countries, the Scandinavian countries put additional lobbying efforts to persuade the EU Commission to enact the same policy throughout the remaining EU countries.

As political pressure from the Scandinavian countries mounted to affect a change in EU policy, an independent analysis was conducted by the University of Gent in Belgium to determine the feasibility of applying the Swedish model to the rest of the EU (Viaene, 1997). The conclusions from this analysis were not favorable as it pointed out the significant loss in production efficiency and increased costs associated with the ban of AGPs. The analysis also pointed out the high economic cost associated with the Swedish ban of in-feed antimicrobials manifested by increased use of feed, lowered production efficiency and higher use of antimicrobials for treatment while not detecting a measurable improvement in antimicrobial resistance in people. The ban had created also an adverse impact of animal production on the environment by increasing the demand for animal feeds and water, and the production of animal waste products. Also, the inclusion of alternative feed additives, like zinc oxide, that were used in an attempt to prevent enteric diseases, had resulted in the contamination of the land with increased concentrations of zinc, a heavy metal. The report also indicated that the EU was facing increased competition in export markets and concluded that with open world markets the European producers should have access to all the tools available to improve production efficiency, including the AGPS. It is important to note that all AGPs that were being questioned by Sweden had already past a stringent EU regulatory review in regards to their efficacy and safety for animals, people and the environment.

Since there was disagreement between the Swedish and the Belgian analyses of the Swedish model, the EU Commission asked the Scientific Committee on Animal Nutrition (SCAN) to review all the available information and make a recommendation. The SCAN was established in 1976 as an advisory scientific committee to the EU Commission in matters pertaining to the use of feed additives in food-producing animals. The SCAN is composed of a group of expert scientists from various EU member countries appointed to the committee for their recognized scientific excellence. The SCAN recommended not extending the ban on AGPs to the rest of the EU without conclusive data and risk assessments.

The E.U. bans on antibiotic feed additives

Avoparcin

The first AGP to undergo review by the SCAN was avoparcin, and although the expert scientists of the SCAN did not recommend its ban (SCAN, 1996); the EU Commission banned its use as an AGP for food-producing animals in 1997. Concerns about the potential spread of vancomycin-resistant enterococci (VRE) from food animals to people through the food chain were cited as the reason for the ban and the precautionary principle was invoked to implement it. Avoparcin belongs to the glycopeptide class, and so does vancomycin, an antibiotic considered critically important in human medicine. Although VRE will develop in food animals fed avoparcin and the same VRE have been detected in raw meat of animals fed avoparcin, the preponderance of evidence suggests that its transmission to people does not occur to a
degree that could impact human health adversely. For example, the prevalence of VRE infections in people in the EU before the ban was much lower than in the USA, in spite of the fact that avoparcin had been fed extensively for many years to food-producing animals in the EU. In contrast, the prevalence of VRE infections in hospitalized patients in the USA is much greater than in the EU, in spite of the fact that avoparcin has never been fed to food animals in the USA and that its use in any other form in food-producing animals is prohibited by law (Phillips, 1999; Acar et al., 2000; Phillips, 2004; IFT Expert Report, 2006). The only conclusion that can be reached is that vancomycin use in humans, rather than avoparcin use in food-producing animals, is responsible for the development of VRE infections of significance in human health.

Interestingly, in the last published DANMAP report (2010) the researchers found that when selective media rather than conventional media was used to isolate E. faecium from broiler chickens, up to 47% of the isolates exhibited resistance to vancomycin, this was so in spite of the fact that the animal analogue (avoparcin) had been banned from use as an AGP in animal agriculture more than 15 years earlier. The researchers stated that the reasons for the long persistence of vancomycin-resistant E. faecium in Danish broilers 15 years after the van of avoparcin are unknown. Interestingly as well, in the same published report the researchers document a steady increase in annual cases of methicillin-resistant Staphylococcus aureus (MRSA), from 47 cases in 1997 (when AGP use for all practical purposes ended) to 1104 cases in 2010.

**Virginiamycin**

The second AGP to undergo review by the SCAN was virginiamycin, like in the case of avoparcin, the SCAN did not recommend its ban (SCAN, 1998). Nevertheless, the same rationale applied to the avoparcin ban was used by the EU Commission to justify the ban of virginiamycin in 1999, invoking the precautionary principle and citing concerns about the potential spread of streptogramin-resistant Enterococcus faecium (SREF) from food-producing animals to people via the food chain. In addition to virginiamycin, the EU Commission at the same time also banned the use of bacitracin, tylosin and spiramycin (European Commission, 1998). Quinupristin-dalfopristin (Q-D) is an antibiotic used to treat hospital-acquired infections in humans caused by vancomycin-resistant Enterococcus faecium (VREF). Q-D belongs to the streptogramin class of antibiotics, and so does virginiamycin. Although SREF will develop in food animals fed virginiamycin and the same SREF have been detected in raw meat of animals fed virginiamycin, the preponderance of evidence suggests that its transmission to people does not occur to a degree that could impact human health adversely (Phillips, 1999; Acar et al., 2000; McDonald et al., 2001; Kieke et al., 2006). A very extensive sensitivity survey conducted in American and Canadian medical clinics before Q-D use began in North America found that out of more than 1,000 clinical isolates of E. faecium tested, 99.8% were sensitive to the new human antibiotic (Jones et al., 1998). Therefore, this study showed that after nearly 3 decades of continuous use of virginiamycin in food-producing animals in the USA and Canada, there was virtually no evidence of SREF in the human population. Evidence is also mounting that confirms that E. faecium have host specificity that prevent E. faecium of chicken origin to colonize people and vice versa (Wiliems et al., 2000), and that enterococci responsible for hospital-acquired infections are genetically different to those isolated from food-producing animals (Wiliems et al., 2001; 2005).

A study conducted in the USA and published in The New England Journal of Medicine which was specifically designed to prove the transfer of SREF from chickens to people, failed to do so (McDonald et al., 2001). Between July 1998 and June 1999, the researchers cultured 407 raw chickens obtained from 26 grocery stores in 4 states, and isolated SREF from 58.2% of them. Resistance was defined as a minimum inhibitory concentration (MIC) of at least 4 ppm. The authors attributed the high level of resistance to the use of virginiamycin. During the same period the authors also cultured 334 stool samples from outpatients at various medical clinics in the same 4 states. In contrast to the significant level of resistance found in the raw chickens, only 2 stool samples, or 0.6% of the total yielded SREF. It is worth noting that both samples had an MIC of 4 ppm reported by the authors as a “low level” resistance.

These results agree with the findings of a more recent study also conducted in the USA specifically designed to show the transfer of SREF from chickens to people and interpreted by the authors as casting doubt on the use of virginiamycin in food-producing animals (Kieke et al., 2006). This study compared the prevalence of SREF between 567 hospital patients, 100 healthy vegetarians, 160 retail samples from conventionally grown chickens and 26 retail samples from antibiotic-free grown chickens. Enterococcus faecium were isolated from 105 patients (105/567 = 18.5%), 65 vegetarians (65/100 = 65%), 77
conventional (77/160 = 48.1%) and 23 (23/26 = 88.5%) antibiotic-free retail samples. As in the study previously discussed, the researchers found no SREF in any of the human samples whereas they found SREF in 56% of the retail samples from conventionally-grown chickens, indicating no detected transmission of SREF from chickens to people. Moreover, E. faecium were isolated from a significantly higher proportion of vegetarians than of self-reported chicken eaters (65 vs. 18.5%) and from a significantly higher proportion of antibiotic-free grown chickens than conventionally grown chickens (88.5 vs. 48.1%). Not satisfied with the results, the researchers resorted to quantifying what they called the “inducible resistance” of the E. faecium isolates from all groups by first growing the isolates in a conventional medium and then transferring a sample during the log phase of growth to a BHI broth that already contained 0.25 mcg/ml of virginiamycin where the cultures were allowed to grow for 24 hours. After that period, the bacterial density was readjusted in a fresh BHI broth that already contained 8 mcg/ml of Q-D where the cultures were allowed to grow for an additional 24 hours. The level of inducible Q-D resistance was expressed as relative growth, by comparing the optical density of the culture pre-exposed to virginiamycin and subsequently challenged with Q-D with that of the same culture without virginiamycin pre-exposure before the challenge with Q-D. Through this series of steps, the authors constructed an outcome measure that, in their judgment, suggested higher “inducible resistance” among isolates from conventionally-grown chickens. Even the authors of the study recognized and acknowledged some serious caveats in the design and interpretation of their study. For example, comparing hospital patients to healthy vegetarians is not a valid comparison, nor does it represent the largest segment of the population (healthy meat eaters). That crucial group was noticeably omitted. The researchers also acknowledged that, “Although the multivariable analysis adjusted for many factors, confounding may have occurred, and other factors associated with vegetarian status may have contributed to the observed associations”. More fundamentally, the study used statistical associations for a highly contrived index of inducible resistance to reach a conclusion that implicated chicken as a possible resistance risk, even though the data clearly showed that there was no SREF in any human patient and that the risk of having E. faecium isolated was smaller among chicken eaters than healthy vegetarians, and also smaller among conventionally grown chickens than antibiotic-free grown chickens.

The science

Virginiamycin risk assessments

Three risk analyses have been conducted for virginiamycin. A quantitative risk analysis showed that the risk of the continued use of virginiamycin as an AFA in food-producing animals, assuming that transmission of resistance from foods derived from animals to people occurs (an unproven assumption in this case), is negligible and rapidly decreasing by the increased use of newer antibiotics as alternatives to Q-D (Cox and Popken, 2004). The FDA-CVM also completed its own risk assessment and also concluded that the risk from the continued use of virginiamycin in food-producing animals is very small (USFDA-CVM, 2004).

Since regulators always tend to focus on the risk of continuing a practice and seldom examine the risk of discontinuing that same practice, an additional quantitative risk analysis examined both, the risk and benefit, derived from the continued use of virginiamycin as an AFA in food-producing animals (Cox, Jr., 2005). The analysis was based on a new quantitative technique known as Rapid Risk Rating Technique (RRRT) that estimates and multiplies exposure based on existent data, dose-response and consequence factors as suggested by the WHO to estimate the impacts on human health from withdrawing virginiamycin (WHO, 2003). The increased human health risks associated with a ban of virginiamycin from more pathogens reaching consumers were predicted to far outweigh the benefits from reduced streptogramin-resistant vancomycin-resistant Enterococcus faecium (SRVREF) infections in human patients. More specifically, an estimated increase of 6,660 cases of campylobacteriosis per year vs. an estimated increase of 0.27 cases of SRVREF per year.

Due to all of this and the thorough examination of many other published research reports, a panel of experts concluded that, “there is little or no evidence that resistant enterococci from animals are a risk to human health”, and that “a ban of growth promoting antibiotics was not justified on this basis, and will have no impact on the prevalence of VRE in human infections” (Phillips et al., 2004). Similar conclusions have been reached by other scientific reviews like the HAN report from the Netherlands that concluded that, “Documented in-vivo cases showing spread of antimicrobial resistant Gram positive bacteria from livestock to humans are in essence non-existent” and that, “the continued use of AGPs presents no imminent hazard to public health” (Bezoen et al., 1999).
More politics

The final bans
The use for growth promotion in food-producing animals of the remaining AFAs (avilamycin, bambermycin, monensin and salinomycin) was banned in the EU effective January 1, 2006. The EU once more invoked the precautionary principle to implement the ban as none of these antimicrobials even had human analogues.

Consequences & the E.U.’s double standard
A double standard exists in regard to antimicrobial use in food-producing animals in the EU, as poultry, swine and cattle are in most cases not raised without antimicrobials but rather raised without AGPs. In all probability, the oldest and most complete records of antimicrobial consumption and uses in human and veterinary medicine, as well as prevalence of antimicrobial-resistant bacteria in humans and animals, is the Danish database known as DANMAP (1997-2010). Therefore, data from DANMAP’s reports will be used to document the results and conclusions from the Danish ban on AGPs.

As mentioned before, the lack of prophylactic use of AFAs has resulted in higher prevalence of enteric disease outbreaks in food-producing animals, which in turn has resulted in more frequent use of antimicrobials for treatment of sick animals, unfortunately the antimicrobials used for treatment of sick animals are from those classes that are much more commonly prescribed in human medicine than the ones used in the feed before the bans. As pointed out by various groups of experts (Casewell et al., 2003; Phillips et al., 2004; IFT Expert Report, 2006), and as evidenced from the continuous yearly increases in the amount of antimicrobials prescribed for food animals in Denmark, from 57,300 kilograms the year after the bans to 125,500 kilograms in 2010 (DANMAP, 1998-2010). These records document an increase in antimicrobial consumption greater than 100% entirely due to increases in the prescription of antimicrobials for treatment of sick animals (Graph #1). In contrast, the size of the food animal population and the total production of meat in Denmark has not drastically changed (Graph #2). If we divide the total number of kilograms of meat produced each year after the ban of AGPs by the total number of milligrams of pure antimicrobial consumed, it can be established that there has been an increase greater than 100% in the amount of antimicrobials used per kilogram of meat produced (Graph #3). Thus, it is becoming increasingly clear, that the use of AGPs was accompanied by other, previously unrecognized, health promotional and prophylactic benefits.

The focus on food animals
Even if one assumes that antimicrobial resistance transfers from animals to people, the potential contribution of food animals to the overall antimicrobial resistance problem would be minimal to nil (Bywater and Casewell, 2000). On the other hand, a two-year retrospective study on antibiotic...
resistance in a community, conducted by researchers from Wales and published in the British Medical Journal (Magee et al., 1999) clearly documents the positive correlation between antibiotic prescribing practices in a community and the development of antibiotic resistance in the people from the same community. The number of prescriptions written on a yearly basis per 1000 patients produced practically a mirror image when compared to the average resistance rates in bacteria isolated from surgical samples from the community hospital. In all cases, the higher the number of prescriptions written for a given antibiotic, the higher the average resistance rate in the bacteria tested in surgical samples from the hospital of the same community.

Therefore, it is difficult to understand the reasoning for which for the most part the antimicrobial resistance debate has remained restricted to antimicrobial use in food-producing animals. Clearly, from all the scientific reviews of the subject and even with the acknowledgement of the WHO, antibiotic prescription by medical doctors in human practice is the driving force behind the antibiotic resistance problem. Also, of the 2 distinct animal populations, food animals and companion animals, and as pointed out by others (Barber, 2001; Simjee, 2002; Cervantes, 2003, 2004; Barber et al., 2003), companion animals are a much more likely source of antibiotic resistance transfer to humans than food-producing animals.

Dogs, cats and other companion animals get treated with the same classes of antibiotics commonly prescribed in human medicine with little to no supervision by any regulatory agency, in much the same way as those prescribed by medical doctors in the USA, and on any given period, humans and companion animals consume on average 10 times more antibiotics per unit of body weight than food-producing animals (Barber, 2001). In addition, companion animals often share living quarters with their owners increasing the likelihood of bacterial transfer, so it is difficult to comprehend why some scientists, regulators, politicians and organizations like the WHO are most concerned with antibiotic use in food-producing animals. One has to wonder if there are other factors, such as the fear of taking on the known emotional bond between people and their pets, that are causing the debate to remain primarily restricted to antibiotic use in food-producing animals.

**Results of the E.U. bans**

**Antimicrobial resistance**

As anticipated, the AGP bans implemented by the E.U. have resulted in lower levels of antimicrobial resistance for the corresponding antimicrobial in indicator bacteria isolated from raw meats. This is not surprising as with few exceptions, the use of an antimicrobial, whether in humans or animals, will result in the development of antimicrobial resistance. Interestingly, in the last published DANMAP report (2010) the researchers found that when selective enrichment media rather than conventional media was used to isolate E. faecium from broiler chickens, up to 47% of the isolates exhibited resistance to vancomycin, this was so in spite of the fact that the animal analogue (avoparcin) had been banned from use as an AGP in animal agriculture more than 15 years earlier. The researchers stated that the reasons for the long persistence of vancomycin-resistant E. faecium in Danish broilers 15 years after the van of avoparcin are unknown. Interestingly as well, in the same published report the researchers document a steady increase in annual cases of methicillin-resistant Staphylococcus aureus (MRSA), from 47 cases in 1997 (when AGP use for all practical purposes ended) to 1104 cases in 2010.

The DANMAP data has shown that the improvements seen in indicator bacteria isolated from raw meats have not translated into lower levels of antibiotic resistance in human medicine (Casewell et al., 2003; DANMAP, 2007; Goosens et al., 2003; Phillips, 2004; Phillips, 2007). The last published DANMAP report (2010) points out that the consumption of antibiotics and the antibiotic resistance problems have continued to increase in both, humans and animals. So after more than a decade of implementing the AGP bans it is becoming increasing clear that the bans have not achieved the ultimate objective, a measurable reduction in antibiotic resistance problems in human medicine.

In spite of these facts and probably driven by political pressure, public perception, pressure from activist organizations with an anti-animal agriculture agenda and global pressure by human medical organizations like the WHO, the United States FDA-CVM has recently published 3 proposals in the Federal Register that would overtime phase-out production uses in food-producing animals of in-feed antimicrobials medically important in human medicine and require veterinary oversight for all uses of antimicrobials. These latest proposals by the USA’s FDA-CVM are known as Guidance for Industry
Consequences of the bans

Animal health and productivity
A report by researchers from the National Veterinary Institute of Oslo, Norway (Lovland and Kaldhusdal, 2001) documented severely impaired production performance in broiler flocks with high incidence of Clostridium perfringens-associated hepatitis (CPAH). The authors analyzed production performance data collected from a large processing plant in Norway, with the objective of comparing production performance data from broiler flocks with high levels of CPAH to flocks with low levels of CPAH. The study was conducted for two and a half years following the ban of avoparcin. This study showed that flocks with high levels of CPAH had 25 to 43% lower profitability than those with low levels. The authors cited impaired feed conversion and reduced weight at slaughter as the major causes for the losses. Researchers from the same Institute had reported earlier that the main effects of experimentally-induced subclinical necrotic enteritis were precisely increased feed conversion and retarded growth rate (Kaldhusdal and Hofshagen, 1992). So it has become increasingly evident following the EU bans that the AGPs, like avoparcin and virginiamycin, were preventing clinical and subclinical necrotic enteritis in poultry, even when used at inclusion rates labeled for “growth promotion”, this is in agreement with the observations made by others (Phillips et al., 2004; Cervantes, 2005, 2011a,b,c; IFT Expert Report, 2006).

In another report, the authors examined data 3 years after the bans were implemented and concluded that the only measurable benefit in humans was a reduction in acquired resistance in enterococci isolated from human fecal carriers, however, the authors stated that despite the growth promoter ban and the reduction of carriage of resistant enterococci in animals and humans, there had been no reduction in the prevalence of resistant enterococcal infections in humans (Casewell et al., 2003). The authors also stated that the AGPs had an important prophylactic activity previously unrecognized and that their withdrawal was now associated with a deterioration in animal health, evidenced by an increased incidence of diarrhea, weight loss and mortality in post-weaning pigs, and necrotic enteritis in broiler chickens. The authors closed by recommending that “the theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences”.

Results of bans on human health
An unintended consequence of the EU ban on the prophylactic use of AGPs in food-producing animals may have an even greater adverse effect on public health. Researchers reported that following the EU bans, the incidence of Clostridium perfringens-associated disease in poultry and its detection in poultry meat has increased substantially and is emerging as a real threat to public health (Immerseel et al., 2004.) According to the report, with the ban of the remaining 3 AGPs (avilamycin, monensin and salinomycin) with activity against C. perfringens, the public threat of C. perfringens-induced food poisoning is expected to increase even more.

A more recent report by a panel of internationally renowned experts in the field of antimicrobial resistance (IFT Expert Report, 2006) concluded that, “there is evidence that there are significant human health benefits from subtherapeutic antimicrobial use to prevent subclinical disease in food animals and reduce levels of Salmonella and Campylobacter contamination of poultry carcasses”.

It has also been reported that concentrations of various AFAs and ionophore anticoccidials similar to those normally used in poultry rations had an inhibitory effect on the transfer of a multiresistance-conferring plasmid in E. coli in an in-vitro test system (Mathers et al., 2004). The authors concluded that based on the results of these tests, AFAs and ionophore anticoccidials may actually inhibit resistance transfer mechanisms within poultry and livestock.

These observations appear to have been confirmed by a series of recently reported quantitative risk assessments aimed at determining the risk and benefits to human health from the continued use of antimicrobials in food animals, in which several surprising conclusions were reached (Cox Jr. et al., 2007). One was that the use of antimicrobials that benefit animal health may also benefit human health. Another one was
that the AGP bans carried out by the EU had the unintentional consequence of increased illness rates in humans (and hence increased antimicrobial use and resistance rates). Their new models based on quantitative risk assessments provide a better tool to government regulators and industry stakeholders to make better decisions for the benefit of human and animal health.

A word about the pew comission

The Pew Commission was formed in 2006 in the USA with the purpose of evaluating and making recommendations on current practices used on intensive production of food-producing animals. Although heavily dominated by activists opposed to intensive food animal production, the Commission included experts from all stakeholder segments to give the appearance of impartiality. In the spring of 2008, Pew Commission released its highly publicized report entitled “Putting Meat on the Table: Industrial Farm Production in America”, as anticipated the report was basically an endorsement of the PAMTA legislation proposal that seeks to ban the use of eight AFAs currently approved by FDA classed as growth promoters (Pew Commission, 2008). Also as anticipated, the Commission report received wide news coverage and praise by the media and activist groups opposed to intensive food animal production.

In November, 2009, after careful review and analysis of the Pew Commission’s report, the American Veterinary Medical Association (AVMA) released its own response to Pew’s Commission report (AVMA, 2009). In its report AVMA opposes the ban of antimicrobials for uses such as disease prevention, growth promotion and feed efficiency as recommended by the Pew Commission without scientific risk assessments pointing out that not all antimicrobials or their uses are equal in their probability of developing resistance or creating a risk to human health. AVMA also pointed out that the European Union’s own SCAN had agreed that there was insufficient data to support such bans and that possible theoretical human health concerns rather than probable and scientifically based benefits to human and animal health were used to justify the bans.

Additionally, AVMA listed a series of concerns about the Pew Commission such as the selective inclusion or deletion of expert opinions, significant shortfalls and lack in comprehensive idea development in many of the Commission’s recommendations, and the biased against large food animal production facilities simply because of their size.

More science

The benefits from using antibiotics

Frequently overlooked on this debate are the substantial benefits derived from the use of AFAs in food-producing animals. The benefits are significant and of importance for animal and human health, and the environment.

Listed below are scientifically documented benefits from the inclusion of low concentrations of antimicrobials in animal feeds:

Prevention of subclinical diseases, such as necrotic enteritis in poultry. This is the main reason AFAs are used at subtherapeutic levels in animal feeds, because they are used to prevent subclinical disease. Subclinical necrotic enteritis of poultry has been shown to have a significant adverse impact on flock performance and condemnations at the processing plant (Khaldhusdal and Hofshagen, 1992; Lovland and Khaldhusal, 2001). Previous research has demonstrated that the effectiveness of an AFA to improve performance parameters such as growth rate and feed conversion is directly correlated with its ability to control Clostridium perfringens, the causative agent of clinical and subclinical necrotic enteritis of chickens and turkeys (Stutz and Lawton, 1984). All but one of the AFAs used in poultry production in the USA classed as “growth promoters” have FDA-approved claims for the prevention or control of necrotic enteritis (Feed Additive Compendium, 2012).

Reduction of human pathogens, by improving flock uniformity, enhancing intestinal strength, minimizing gastrointestinal ruptures during evisceration and processing, and by reducing shedding of human pathogens such as Salmonella spp. and Campylobacter spp. the use of antimicrobial feed additives in animal feeds ultimately enhances the safety of the final product for the consumer (Russell, 2003; Cox et al., 2003; Hurd, 2005). Chickens raised for the organic market without antimicrobials have been shown to have a prevalence of Campylobacter spp. almost three times greater than that of conventionally-grown chickens (Heuer et al., 2001). A manuscript
published recently showed that pigs raised without antimicrobials had a higher prevalence of Salmonella spp., and Toxoplasma gondii, and even tested positive for Trichinella spiralis, a parasite considered eradicated from conventional U.S. swine operations (Gebreyes et al., 2008).

**Improved animal welfare**, because AFAs have been scientifically shown to reduce immunologic stress even in “healthy chickens” kept under optimal sanitary, environmental and management conditions, their use contributes to enhance the welfare of food-producing animals (Roura et al., 1992).

**Improved production efficiency**, this benefit is the result of better enteric health and prevention of nutrient degradation by the intestinal microflora. Typically, growth rate and feed conversion are improved which has led to class these additives as “growth promoters”. Given what we have learned since this old term was coined many years ago, and the consequences from banning their use in the EU (Casewell et al., 2003; Phillips et al., 2004, IFT Expert Report, 2006; Phillips, 2007), where the prevalence of enteric diseases and the use of therapeutic antimicrobials in food animals have increased significantly since the bans, a more appropriate name would have been “health promoters” (Cervantes, 2006a,b,c,d,e; 2011a,b,c).

**Preservation and less contamination of the environment**, due to the improvements attained in growth rate and feed conversion, the same meat output can be maintained with a reduced number of animals and farms, and a reduced number of tons of feed and animal waste resulting in more acres of the environment being preserved in its natural state. A recent scientific presentation estimated that a 0.04 improvement in feed conversion attributed to the use of AFAs in a commercial turkey production operation would eliminate the need for an additional 5,525 tons of feed that without them would have had to have been produced and delivered, and as a consequence, an additional amount of excreta corresponding to this increase in feed tonnage would have been produced and disposed of into the environment without any additional gain in meat production (Tilley and Gonder, 2007). Assuming that turkeys drink two units of water for each unit of feed, an additional 11,050 tons of water would have also been used up with the increase in feed tonnage taking more natural resources from the environment without any benefit.

Likewise, the improved nutrient digestibility achieved by the use of AFAs results in less nitrogen and phosphorous being passed onto the droppings and into the environment resulting in less pollution of the environment.

**Lower prices for the consumer**, since with the use of AFAs production efficiency is improved, the savings from the cost of production can be passed on to the consumers who can continue to enjoy an abundant supply of nutritious and safe meats at an affordable price. The UN and FAO have recommended that food of animal origin be made more accessible to the people of the world with least resources, AFAs can help achieve this goal and that is the main reason the use of AFAs in third world countries has not decreased and is not likely to decrease in the foreseeable future.

**Are there any viable alternatives?**

As of this writing, and as acknowledged by others (Bedford and Fothergill, 2003; Dibner and Richards, 2005; Niewold, 2007), there are no comparable alternatives to the AFAs in food-producing animals. Numerous compounds have been tried but none have the ability to combat or prevent bacterial infections, reduce immunologic stress and the inflammatory response like the antimicrobials can. In an effort to explain why the highly reproducible effects seen with the AFAs cannot be reproduced with other alternatives aimed at modifying the microflora of the gastrointestinal tract, Niewold (2007) hypothesized that the real mode of action of the AFAs is not primarily due to their antibacterial action at the gastrointestinal level but rather to their suppressing effect on the production and excretion of catabolic mediators produced by intestinal inflammatory cells. His hypothesis agrees with the findings reported earlier by other researchers that showed that feeding low levels of antimicrobials to “healthy” broiler chicks had a positive effect on indicators of immunologic stress and on the inflammatory reaction (Roura et al., 1992).

**Conclusions**

The world faces the daunting task of having to double the production of food attained in 2010 by the year 2050 in order to satisfy the demands of its growing population which by that time is expected to top 9,000 million people. This demand to double the amount of food produced in 2010 by 2050 will
have to be met with essentially the same area of cropland used today and with as low adverse impact as possible on the environment. It is estimated that at least 70% of the 100% increase in the production of food will have to come from improvements in production efficiency. In order to meet this monumental challenge, new and old technologies, must be available to food animal producers around the globe, including the use of the AFAs classed as growth promoters, since after the productivity improvements achieved through genetic selection of farm animals, AFAs have proven to be the most significant and reliable method of enhancing animal productivity through the prevention of subclinical enteric diseases that erode production efficiency.

There are numerous scientifically documented benefits such as the prevention of subclinical diseases, reduction of human pathogens, improved animal welfare, enhanced production efficiency, preservation and less contamination of the environment, lower costs of production and lower meat prices for the consumer that are directly derived from the inclusion of antimicrobial feed additives at low concentrations in animal feeds (Roura et al., 1992; Phillips et al., 2004; IFT Expert Report, 2006; Cervantes, 2011c).

AFAs have been included at low or subtherapeutic levels in feeds consumed by animals destined for human consumption for over 60 years. In spite of an endless search for a “smoking gun”, not a single human fatality has been conclusively and unequivocally linked to the use of AFAs in animal feeds. Numerous scientific reviews on the subject have acknowledged the fact that antibiotic-resistant bacteria can develop in animals fed low levels of antimicrobials, and that those bacteria may reach the public through the food chain posing a theoretical risk to human health (Swann, 1969; NRC, 1998; Bezoen et al., 1999; USGAO, 1999). However, there is little to no evidence to support the claim that the use of AFAs in animal feeds has contributed to the problem of antimicrobial resistance in human medicine since their use has been in existence for many years without any measurable adverse effects on human health (Phillips, 1999; Phillips et al., 2004; IFT Expert Report, 2006). The scientific reviews also acknowledge the fact that antibiotic use by humans is the driving force behind the antibiotic resistance problems encountered in human medicine, as they have also acknowledged the fact that house pets treated with antibiotics may pose an even greater risk of transfer of antibiotic-resistant bacteria to people due to the intimate association between people and their pets.

The EU Commission banned the use of all AFAs classed as growth promoters against the advice of its own Scientific Committee on Animal Nutrition (SCAN, 1996; SCAN, 1998). Almost immediately after the ban a surge of enteric disease problems in food-producing animals arose. The surge in enteric diseases of food animals was followed by a surge in antimicrobial use in food animals for treatment. The antimicrobials used to treat food animals belong to the same classes of antimicrobials most frequently used in human medicine, this might have actually had a more adverse effect on the creation of antimicrobial resistance in people than the use of the AFAs (Cervantes, 2006d,e; Phillips, 2007). The surge in use of antimicrobials for treatment in food-producing animals has clearly proven that the prior use of AFAs had a health promotional and disease prevention effect even when used at concentrations labeled for “growth promotion”.

Although the AGP bans implemented by the EU achieved the objective of reducing the prevalence of resistance in indicator bacteria in raw food products of animal origin, this has not resulted in an improvement on the problems related to antibiotic resistance in human medicine (Casewell et al., 2003; Bedford and Fothergill, 2003; Bafundo, 2004; Phillips et al., 2004; IFT Expert Report, 2006; Phillips, 2007). Data from the Danish database known as DANMAP on human and veterinary consumption of antimicrobials and antimicrobial-resistant bacteria have shown a continued increase in the amount of antimicrobials prescribed for treatment in food-producing animals every year since the first ban. Along with this increase there has been an increased rate of illnesses and consumption of antimicrobials in both, food animals and humans while simultaneously there has been an increase in the detection of antimicrobial resistant bacteria in both, food animals and humans in most EU member countries, and more recently and as reported in the most recent DANMAP report, a significant increase in cases of MRSA since the implementation of the AGP bans. This is in agreement with the most recent reviews that have concluded that along with the increased use of therapeutic antimicrobials in food animals, there has also been an increased rate of illnesses and antibiotic usage in people from the EU, with almost universal increases in the prevalence of antibiotic-resistant bacteria. Clearly, the ban of AGPs enacted by the EU did not achieve the ultimate desired effect as therapeutic antibiotic usage and antibiotic-resistant bacteria have continued to increase in humans (Phillips, 2007).

The yearly prevalence of infections by food-
borne pathogens of animal origin like Salmonella, Campylobacter and C. perfringens continues to be higher in the EU when compared to the USA. Therefore, it is becoming increasingly clear that the AGP bans have not resulted in a safer food supply.

Antimicrobial-resistance is an extremely complex problem that is not fully understood and does not lend itself to simplistic solutions like the banning of the antibiotic feed additives (Bywater, 2005). Research continues to produce surprising findings, for example, University of Georgia researchers reported that chicks raised under pristine laboratory conditions and never exposed to antimicrobials had a significant prevalence of antimicrobial-resistant bacteria (Smith et al., 2007). Likewise, in a recently published manuscript (Bhullar et al., 2012), American and Canadian researchers investigating the genes associated with antibiotic resistance discovered that environmental organisms may very well serve as reservoirs of antibiotic resistance genes as determined by culture and sensitivity testing of the microbiome of Lechugilla Cave, in the State of New Mexico, in a region of the cave that has been isolated from civilization for over 4 million years. The researchers reported that the bacteria isolated from the cave’s microbiome were highly resistant to antibiotics, and pointed out that some of these bacteria were resistant to as many as 14 different commercially available antibiotics. These findings are significant and contribute to our understanding of the prevalence of resistance, even in microbiomes completely isolated from human or animal use of antibiotics. The researchers concluded that their study supported a growing body of evidence that antibiotic resistance in bacteria is natural, ancient and hard wired in the microbial pangenome.

Responding to strong and relentless political pressure from activist organizations with an anti-animal agriculture agenda, public perception by misinformed consumer-advocate groups, global pressure by organizations like the WHO and the threat of legislative action like the PAMTA bill, the USA’s FDA-CVM has recently published 3 guides in the Federal Register that would overtime phase-out production uses in food-producing animals of non-feed antimicrobials medically important in human medicine and in the future require veterinary oversight for all uses of antimicrobials.

Given the consequences of politically-driven policies such the ones enacted in Europe and its increasingly apparent adverse consequences on animal health and productivity, and indirectly on human health and antibiotic resistance, the rest of the world, and the USA in particular, should learn from the European experience and proceed with caution letting scientific regulatory bodies make decisions based on solid science and quantitative risk assessments, rather than imposing bans that could produce unintended consequences.

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