

## **REPORT OF THE COMMITTEE ON PHARMACEUTICALS**

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The Committee met on October 16, 2006 at the Minneapolis Hilton Hotel, Minneapolis, Minnesota from 1:00 – 5:30 p.m. Twenty-two members and guests attended the meeting. Committee members were welcomed and each given the opportunity to introduce themselves.

Dr. Richard Carnevale, Animal Health Institute gave an update on the activities of Codex Alimentarius. The Codex Alimentarius is a food standard setting organization of the United Nations. It is charged with setting a wide variety of food safety and commodity standards which are used by member countries in their import and export requirements. Codex sets standards for veterinary drugs, pesticides, food additives and contaminants that may be in food of animal or plant origin. In recent years Codex has been examining the issue of antimicrobial resistant food borne pathogens that may be present in food and how that may affect food safety and human health. I plan to give some background on Codex and how they got involved in the antimicrobial resistance issue, update the audience on the latest decision to establish a Codex Task Force to review the evidence and develop recommendations for member countries on evaluating and managing the risks of antimicrobial resistance in their food production systems, and provide some industry perspective on how the advice this Task Force delivers may affect the worldwide use of antimicrobial agents in livestock production.

Dr. Lyle Vogel, American Veterinary Medical Association (AVMA) gave an update on the World Organization for Animal Health (OIE) activities followed by an overview of the Institute of Food Technologists (IFT) report on the use of antimicrobials in food production. OIE has previously published four guidelines regarding antimicrobial resistance. The topics are antimicrobial resistance surveillance, measuring the quantities of antimicrobials used in animals, responsible use of antimicrobials, and risk analysis of use in animals. Now the OIE is developing a categorized list of antimicrobials of veterinary importance to complement the responsible use and risk analysis guidelines. The list will also be used in meetings with the World Health Organization (WHO) to discuss the appropriate balance to be achieved between animal health needs and public health considerations while considering risk management strategies. The list will also inform the recently established Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance as it develops guidance on the assessment of the public health risks of antimicrobial resistance and while it develops risk management advice. An OIE Ad hoc Group on Antimicrobial Resistance has drafted a list that divides classes of antimicrobials into three categories - critically important, highly important, and important. The categorized list will be distributed to OIE member countries for review and comment and will be considered for approval at the OIE Annual General Session in May 2007.

Dr. Vogel continued his presentation with an overview of: Antimicrobial Resistance: Implications for the Food System - An Institute of Food Technologists (IFT) Expert Report. An IFT panel has produced a report that elucidates the state of the science regarding the public health impact of antimicrobial resistance associated with the use of antimicrobials in the food chain. The report also evaluates antimicrobial resistance control strategies. The report is available at [www.ift.org/ExpertReport](http://www.ift.org/ExpertReport). In this report, antimicrobials generally refers to disinfectants, sanitizers, and other products used in food processing and antibiotics refers to the drugs used in animals and humans. The report states that antimicrobials are important tools that are integral to our complex food system. However, the use of antimicrobials, especially antibiotics, can create selective pressure leading to the emergence of resistant organisms. Bacterial resistance mechanisms are quite diverse, as are the modes of action of antimicrobials. Therefore, one size fits all solutions are not feasible. Antimicrobial resistant foodborne pathogens are a subset of foodborne pathogens and, consequently, interventions that effectively reduce the prevalence of foodborne pathogens also reduce the prevalence of antimicrobial resistant foodborne pathogens. Risk management strategies are in place all along the food chain (multiple hurdle strategies), but can be improved. Ongoing surveillance of antimicrobial resistance reveals that resistance trends are not consistently in one direction; some are decreasing while others increase. The decreases, particularly in the last 6-7 years, combined with decreasing trends of foodborne diseases in humans have decreased the burden of human illness with some antimicrobial resistant organisms (e.g., multi-resistant of *Salmonella* spp., penta-resistant *Salmonella Typhimurium*, and ciprofloxacin-resistant *Campylobacter* spp.).

Dr. Elizabeth Wagstrom, National Pork Board (NPB) presented an overview of the implications of, and actions taken to comply with, the Japanese adoption of the Codex minimum residual levels (MRL) for veterinary drugs. Japan represents a market for over \$1 billion of United States (US) pork or 45 percent of the value of U.S. pork exports. Japan is the largest market for U.S. pork, in volume and value. Japan purchases approximately 753 million pounds of U.S. pork muscle. The new food safety standards will apply to all food products including pork, fresh and frozen, offal and processed meats. The new Japanese standards are based on Codex Alimentarius, a series of international standards established by the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) to ensure food safety. U.S. standards were developed by the Food and Drug Administration (FDA) to ensure food safety. Codex and U.S. residue standards may differ for certain products and residue testing protocols. Compliance with U.S. product withdrawals will satisfy most, but not all, of the new Maximum Residue Limits (MRL) set by Japan. If Japan detects a violative residue at the current testing level of 3-5% of containers, they will increase the testing level to 50%. If a second violative residue is detected, testing would increase to 100% and become the expense of the exporter. If a third violation is detected, imports will be suspended. The NPB, Meat Export Federation (MEF), and the American Association of Swine Veterinarians (AASV) have gathered information from pharmaceutical manufacturers regarding their recommendations for withdrawal times that would result in compliance with the Japanese MRLs. This information is posted at the NPB's web site. AASV is recommending that if a product is not listed on the web site that product should not be used in finishing hogs or in the breeding herd.

Dr. Richard Coulter, Phibro Animal Health Corporation (PAHC) presented an update on the situation regarding import of pork into Canada from pigs that may have been fed the antimicrobial compound Carbadox.

### Summary of current situation regarding US pig meat for export to Canada and the Canadian Veterinary Drug Directorate (VDD) position (as at October 10, 2006)

#### Background

- Carbadox was involved in a misuse event non-adherence to Western Diversionary Program (WDP) in 2001. Subsequently Health Canada (HC) placed a stop sale on all Carbenoxolone (CBX) products in Canada.
- In 2004 the drug registrants voluntarily withdrew the registrations and Drug Identification Numbers (DIN) in Canada as HC appeared immovable.
- In 2005 Canada indicated they were revising their import MRL for carbadox and pig meat from the US. Rather than the 5 parts per billion (ppb) meat 30ppb liver limits using the terminal metabolite quinoxaline-2-carboxylic acid (QCA) as the marker, Canada chose to move to "Nil Detectable" represented as a 50ppt of Desoxycarbadox (DCBX) being the limit of detection for the intermediate metabolite. The limit of detection (LOD) would apply to all tissues.
- In late 2005 the VDD initiated the early stages of a regulatory process which could have resulted in all US pig meat from pigs treated with carbadox being unacceptable for sale in Canada regardless of the residue status of that meat (ie even if the residue is zero). The VDD were very aggressively pressing for changes to the Canadian Food and Drug Regulations to bring these CBX specific changes into law in Canada. These changes would require pre-approval by the Parliamentary Cabinet, public debate and comment through the Government Gazette process, then promulgation through regulatory amendment. The VDD was initially planning the Gazette 1 release early last summer (May/June)
- The US swine industry, US Government and Canadian Swine and other Meat Industries all opposed the VDD proposals as did PAHC.
- To date Canada has never detected a positive residue relating to CBX in US pig product, whether the test used was the US regulatory GC-EC QCA test or the Canadian HPLC-MS/MS DCBX test. The last positive CBX related residue detected in Canada was associated with the 2001 mis-use situation.

#### Current Status

- As of October 06, 2006 the VDD's stated position is that they are satisfied the existing regulatory framework meets their needs without amendment and their preferred position is not to move for any modification of the existing regulations.
- The VDD being satisfied will now step back from the process to allow the Canadian Food Inspection Agency (CFIA) to review border testing arrangements for imported product. The CFIA briefly indicated they would adopt some form of risk based statistical testing program. This would appear consistent with normal trade practices.
- The Canadian Pork Council have maintained all along that Canadian border testing should be as stringent as other comparable trading partners, but should

not be more so. In this regard the proposed Canadian testing will have a numerical threshold of approximately 1/30th of the next most sensitive partner Japan, however, the target metabolite is different, and the 50ppt LOD is not predicted to be trade disruptive, even if not particularly founded on strong scientific logic.

- The CFIA will continue discussions with the US Food Safety and Inspection Service (FSIS) on the general US food assurance testing program already in place. It is likely that the CFIA will seek increased testing or even DCBX targeted testing in the US. The FSIS is likely to oppose these proposals as they are driven by VDD specific ideology rather than accepted Sanitary Phyto Sanitary (SPS) trade principles. The National Pork Producers Council (NPPC) has to date strongly encouraged the FSIS to remain committed to established principles and the FSIS have not shown any indication of departing from this course. PAHC completely concurs with the NPPC position.

In summary, the outlook is very good and US producers should be confident that by adhering to the US legal requirements for the use of Mecadox (dosage and WDP) they will continue to be compliant with all trading partner needs including Canada.

While this looks to be a very straightforward and logical outcome, there were certainly rough patches. I believe the quality of this outcome was the result of the work of dozens of people but a significant portion of the credit is due to the cooperative efforts of:

- Martin Rice and the team from the CPC
- Nick Giordano and the NPPC
- Ellen Terpstra and the United States Trade Representative (USTR) group in Washington
- in particular, Ag Attache Lisa Anderson and Minister Counselor Gary Groves from the US Embassy in Ottawa.
- Former Ambassador Clayton Yeutter and Ron Doering Esq also worked tirelessly to inform and engage people on their respective sides of the border.

Dr. Randall Singer, University of Minnesota presented information about risk and benefit analysis of the use of antimicrobials in animal production. Antibiotic use is likely the major selection pressure influencing changes in antibiotic resistance. Because many antibiotics are used in animal agriculture, there is considerable opportunity for the spread of resistant bacteria and antibiotics into the environment from animal operations. For example, the discharge of wastewater from animal agricultural facilities has been associated with increased levels of resistant bacteria as well as antibiotics. Once in the environment these antibiotics can act as a selection pressure, further influencing the acquisition of resistance genes. When manure is applied to fields, the resistant bacteria and antibiotics in the manure can now affect crops that are eaten raw by humans. There are many possible routes through which antibiotic use in animals can pose a risk to humans.

As concerns about antibiotic resistant bacteria infecting humans continue to grow, a major way in which to reduce the overall level of resistance is to reduce the use of antibiotics, especially those that are important in human medicine. For this reason, an antibiotic like florfenicol would appear to be an attractive option because it is not used in human medicine, and therefore, one might expect florfenicol use to pose little

risk to human health. Unfortunately, a theme that will continue to become more and more common as we delve into bacterial genetics is the presence of multiple resistance genes that are linked within the bacterial cell. The use of antibiotics that appear to have no relevance in human medicine may still be selecting for resistances to antibiotics that are important in human medicine.

Antibiotics used in animal agriculture might also have benefits to human health. Reductions in the incidence of food animal illnesses may reduce bacterial contamination on meat, thereby reducing human illness. Antibiotic use in agricultural animals may benefit human health by reducing the incidence of animal illness, but this use can also select for antibiotic resistant bacteria which can threaten human treatment options. A recent mathematical model predicts that the use of macrolides as feed additives in chickens may increase the incidence of human macrolide-resistant *Campylobacter* infections but may also reduce total human illness days per year caused by *Campylobacter*. The model suggests that very minor perturbations in microbial loads on meat products can have relatively large negative impacts on human health, and consequently, small improvements in food animal health result in significant reductions in human illness. This prediction warrants further evaluation through specific empirical studies.

Because the complete cessation of all antibiotics in animal production is not a viable option, the key is to continually monitor changes in antibiotic resistance over time, especially as the use of new compounds increases. Only through a rigorous monitoring program can we evaluate the potential impacts of the use of an antibiotic on resistances to other antibiotics and thus comprehend the animal and human health risks. In addition, such a monitoring program would help ensure that the most efficacious antibiotic is being used for each specific health problem. Coupled with a monitoring program is the need for continuous development of non-antibiotic strategies for improving animal health.

Dr. David White, Center for Veterinary Medicine (CVM) from the Food and Drug Administration's CVM gave an update on CVM activities as well as an update on the National Antimicrobial Resistance Monitoring System (NARMS). He reported that CVM is improving performance under the Animal Drug User Fee Act (ADUFA), and are collecting user fees and minimizing time for actions on submissions. He reported that FDA is re-analyzing the economic and environmental impacts of the proposed changes to the bovine spongiform encephalopathy (BSE) feed regulations, and expect to issue a final rule as soon as possible. He also updated the group on new test development to detect meat and bone meal in animal feeds. FDA's Animal Feed Safety System held an open meeting in September to review their approach to risk modeling for animal feeds. FDA has published a proposed rule for development of an index of legally marketed unapproved new animal drugs under the minor use minor species program. Dr. White presented a list of new approvals and supplemental approvals issued by FDA in the last year. He updated the group on the Guidance 152 activities, and reported on the findings of the September Veterinary Medical Advisory Council (VMAC) review of a fourth generation cephalosporin.

Dr. White then gave an update of the NARMS results. Notable results included an observation that resistance varied widely between different serotypes of *Salmonella*. In addition, different commodities exhibited resistance to different antimicrobials. He

gave the example that isolates from turkey were more resistant to gentamicin, while isolates from chicken were more resistant to ceftiofur. Other NARMS activities reported on include:

- Outside expert review in 2005 that looked at key elements, established goals
- Science Board review during FY 07 will focus on sampling, epidemiological and microbiological research, harmonization of data reporting, and coordination with international surveillance
- Improved retail meat sampling and isolate testing methods
- Working to strengthen data reporting and harmonization has resulted in the first executive summary now in preparation and looking at antimicrobial susceptibility trends among bacteria under surveillance by source and year.

Dr. Dave Dargatz, Center for Epidemiology and Animal Health (CEAH), Veterinary Services (VS) gave an update on the Collaboration for Animal Health, Food Safety, and Epidemiology (CAHFSE). This project was a collaboration between Animal and Plant Health Inspection Service (APHIS), Agriculture Research Services (ARS), and Food Safety and Inspection Service (FSIS) with cooperation for the pork industry. Over a 2 ½ year period approximately 50 farms were sampled quarterly to address both animal health and food safety objectives. Data was collected to describe the epidemiology of ileitis caused by *Lawsonia* in pigs. Information on porcine reproductive respiratory syndrome (PRRS) prevalence was also collected. Food safety objectives included characterizing *Salmonella*, *Campylobacter*, *Enterococcus*, and generic *E. coli* on farms for antimicrobial susceptibility. These results, along with management information from the farms will allow for hypothesis generation and potential identification of risk factors. The CAHFSE project is currently inactive, and will be revised and activated in 2007 if budget allows.

The response to the 2005 Resolution requesting \$2.5 million in FY 07 for the Collaboration on Animal Health, Food Safety and Epidemiology (CAHFSE) was reviewed with the Committee