REPORT OF THE COMMITTEE ON PHARMACEUTICALS

Chair: Dr. Liz Wagstrom, Des Moines, IA
Vice Chair: Dr. Larry Hawkins, Carrollton, MO

Dr. Thomas J. Burkgren, IA; Dr. William H. Fales, MO; Dr. Paula J. Fedorka-Cray, GA; Dr. Joe S. Gloyd, DE; Dr. Richard E. Hill, IA; Dr. Patrick L. McDonough, NY; Ms. Valerie H. Patten, NY; Mr. Steven Roach, IL; Dr. A. David Scarfe, IL; Dr. Roy A. Schultz, IA; Dr. Paul L. Sundberg, IA; Dr. R. Flint Taylor, NM; Dr. Deepanker Tewari, PA; Dr. Lyle P. Vogel, IL.

The Committee met on November 9, 2005 from 8:00 a.m. – 12:00 p.m. at the Hershey Lodge and Convention Center, Hershey, PA. Approximately 30 people attended the meeting including 9 committee members.

Committee members were welcomed and each given the opportunity to introduce themselves.

Paula Fedorka-Cray updated the Committee on the animal arm of the National Antimicrobial Resistance Monitoring System (NARMS). Animal NARMS is a passive surveillance system for all food animal species, in addition to some exotic/companion animal information. Bacterial isolates come from veterinary diagnostic laboratories, sentinel farms and packing houses. Resistance testing is done on *Campylobacter, E. coli, Enterococci*, and *Salmonella*. The level of pan-susceptible isolates has remained stable over the past several years. The most common resistance among isolates is to tetracyclines, but there is wide variation between species as well as serotypes. *Salmonella* serotypes vary over time and vary by species and source. Major serotypes from animals often differ from the major serotypes found in human cases. There appears to be a decrease in the prevalence of *Salmonella Newport,* as well as the proportion of multi-drug resistance among *S. Newport* in the NARMS isolates.

NARMS *Campylobacter* data indicated that there is an inverse relationship between resistance to tetracycline and flouroquinolones. There is a higher level of resistance among *Campylobacter coli* isolates than *C. jejuni.*

Dr. Fedorka-Cray gave an update on the Collaboration for Animal Health, Food Safety and Epidemiology (CAHFSE) project. The project has been collecting data from farms since 2003, and is able to be focused on current needs for sentinel projects.

Dr. Peter Davies presented a time specific paper – The Danish Experience with Withdrawal of Growth Promoting Antibiotics – Impacts to Animal and Public Health after Five Years. He updated the audience on two Danish programs – the Danish On-Farm *Salmonella* Control program and the program removing antimicrobial growth promoters from use in agriculture. The Danish reports at the recent SafePork 2005 scientific meeting indicate that post-harvest initiatives would have been more cost effective and efficient than pre-harvest control of *Salmonella* on swine farms. Dr. Davies gave the time line of antibiotic activities in Denmark, starting with the ban of avoparcin in 1995. 1n 1998 there was a ban on growth promotants in finishing pigs, followed by a ban on growth promotant use in weaned pigs in 2000. The goal of this program was to protect public health. Data on results is available through the DanMap and VetStat reports. Aggregate use of antimicrobials in Denmark now exceeds the level from 1998 at the start of the ban, due to increases in therapeutic uses in animal. Increases in antimicrobial use exceeded the increases in the pig population during that time period. There are other factors that may be contributing to the increasing use of antimicrobials in addition to the withdrawal of growth promotants. Management changes made by producers include increasing weaning age of animals, decreasing density of diets, adding Zinc and Organic Acids to the diets, and the increase of more therapeutic antimicrobials. These management changes have not lessened the need to increase the use of therapeutic antimicrobials. Regulatory differences exist between Denmark and U.S. including the restriction of dispensing by veterinarians, and mandated veterinary visits. There has not been a

consistent trend in changes in resistance patterns in foodborne pathogens. His summary statements included:

- Anticipated decrease in total antimicrobial use in food animals not been realized
    - Cloud of animal health and welfare issues has grown darker
- Reduction in resistance of zoonotic and commensal isolates from pigs variable
- Major problems with resistance in human pathogens have increased in incidence
    - Silver lining of public health benefit hard to perceive
- These animal health and use challenges occurred despite rigorous veterinary oversight of the pig industry

The complete text of Dr. Davies paper is included in these proceedings.

Dr. John Hallberg, Pfizer Animal Health, presented information on the Safety Assurances in the Approval of Pharmaceuticals. He discussed the regulatory process for New Animal Drug Applications, including the Code of Federal Regulations and Guidance Documents. Drugs are approved when there is a reasonable expectation of no harm, following efficacy data. Safety needs to be demonstrated in the target animal, human food safety, environmental, and the product. Need to do toxicological studies to determine an Allowable Daily Intake for human consumption with no adverse health effects. Is used to determine withdrawal times, including the measurement of effects on gut flora. Numerous studies are preformed to determine safe residue levels and residue decline. Dr. Hallberg outlined the qualitative risk assessment (Guidance 152) process. A fact sheet was provided and is included at the end of this report. The target animal studies are through GLP and field efficacy studies. Environmental assessments are conducted when required by the agency. Chemistry and Manufacturing control studies are conducted to show product safety. The process can take numerous years (average 6-8 years) and costs can exceed $30 million.

Eric Dubbin gave a presentation on a number of topics concerning the Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM). In 2005 the first drug was approved through the Minor Use/Major Species (MUMS) process (Aquaflor – catfish antimicrobial). So far over 50 requests for designation have been submitted. Tylan Soluble was approved for use in Honey Bees through the NRSP-7 process using publicly available data. New approvals in the past year included Spectramast for lactating and dry Dairy Cows, Monensin in Dairy Cows, Draxxin for beef cattle and swine, Rebalance for EPM treatment in horses. Dubbin also updated the Committee on the progress made under the Animal Drug User Fee Act (ADUFA).FDA has met all the statutory time frames under ADUFA for FY 2004. They are on track to meet for FY 2005 as well. Time frames will become shorter over the five year implementation of ADUFA. FDA and industry are looking at steps to expedite getting drugs to market.

Larry Hawkins gave a presentation contrasting the regulatory requirements of compounding and FDA approved manufacturers. There appears to be some confusion among veterinarians between what is a compounded drug and an FDA approved product. He gave an overview of physical plant and record keeping requirements for an approved manufacturer. The requirements are more stringent for manufactured drugs and feed manufacturing than for compounding facilities.

The Committee approved a Resolution requesting $2.5 million in fiscal year 2007 for the Collaboration on Animal Health, Food Safety and Epidemiology. The Resolution was forwarded to the Committee on Nominations and Resolutions.

FACT SHEET

FDA's Use of a Risk Assessment Process for Food Animal Antimicrobials to Protect Human Health

Background: Historically, the Food and Drug Administration's (FDA) review of drugs intended for use in food-producing animals focused on efficacy in treating the intended disease, safety to the target animal and safety of any residues that may be present in food. Extensive testing is conducted to ensure these three safety criteria are met. In 2003, FDA finalized an additional safety measure that "for the first time outlines a comprehensive, evidence-based approach to preventing antimicrobial resistance that may result from the use of antimicrobial drugs in animals" (*FDA News*, October 23, 2003). This new regulatory process, "Guidance for Industry #152" (Guidance 152), establishes a rigorous, three-pronged qualitative risk assessment to estimate a product's microbial safety.

The Process: Guidance 152 has three components, summarized below and diagrammed on the attached page:

- *Release assessment* – determines the probability that resistant bacteria will be present in animals as a result of the drug's use.
- *Exposure assessment* – gauges the likelihood that humans would ingest the resistant bacteria.
- *Consequence assessment* – assesses the chances that human exposure to the resistant bacteria would result in adverse human health consequences.

FDA Action: The FDA makes a determination of overall risk to humans based on conclusions of the three assessments. If the assessments show that risks would be significant, FDA may either deny the application for marketing authorization or approve the application but under specific conditions designed to ensure the antimicrobial would not pose a human health risk. For example, FDA may require any of the following:

- Availability by prescription only,
- No extra-label use,
- No "prevention" use,
- No whole herd/flock use,
- Limits on duration of use,
- Limits on method of administration, and/or
- Additional review by an FDA Veterinary Medicine Advisory Committee composed of experts from both human and animal medicine.

Applying the Risk Assessment: FDA can apply Guidance 152 to any new approvals of antibiotics or new label extensions or indications. In addition, FDA has indicated that it is evaluating drugs currently on the market under Guidance 152 for their potential to cause a human health concern because of antimicrobial resistant bacteria.

For more information go to: www.fda.gov/cvm/guidance/fguide152.pdf

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