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CgFARAD™ NEWSLETTER

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CGFARAD™ AND FOOD SAFETY RELATED RESEARCH

Dr. Ron Johnson, Co-director, CgFARAD™

Dexamethasone sodium phosphate injectable is approved for use in beef cattle and lactating dairy cattle in Canada, however it does not have an established withdrawal time or maximum residue level currently. Dexamethasone sodium phosphate is indicated in cattle for treatment of bovine ketosis and as an anti-inflammatory agent. The pharmacological effects of glucocorticoids, like dexamethasone, is concerning regarding potential adverse effects for public consumers of beef and milk. Dr. Ron Johnson (Principal Investigator, Biomedical Sciences, OVC) and Dr. David Renaud (Co-PI, Population Medicine, OVC) are conducting a dexamethasone depletion study in beef cattle and lactating dairy cattle that has been funded by OMAFRA-UGuelph (Alliance), the Dairy Farmers of Ontario and the Beef Farmers of Ontario. The beef cattle study is underway at the Ponsonby General Animal Facility at the University of Guelph. The lactating dairy cattle study is scheduled to start in late march/early April, 2021 at the Elora Research Station-Dairy Facility. Results of these two studies will assist veterinarians with rational withdrawal time estimated that can ensure human food safety.

Our lab is continuing the grant work evaluating the risks of violative drug residues in poultry from extra label drug use combinations administered in feeds. The project is being funded by the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) Food Safety Research Program and CgFARAD™ stakeholders. We have successfully completed the proposed work in turkey hepatocytes that was successfully defended by Samantha Lyster in her MSc thesis defence in August of 2020. Due to COVID-19 disruptions the second MSs thesis student, Philip Russel, was delayed for almost a full semester, but is now well into his research, which will focus on broiler chicken hepatocytes as a tool to evaluate drug-drug interactions *in vitro*.

This will assist the CgFARAD™ pharmacology service with identifying combinations of drugs being requested for use in poultry feed that are at risk of violative residues from drug-drug interactions. Two MSc graduate students are working on this project.

REGULATION OF VETERINARY DRUGS

Dr. Trisha Dowling, Co-director, CgFARAD™

To protect consumers from adverse health effects, federal programs are charged with the regulation of chemicals and drugs and the detection of chemical and drug residues in foods of animal origin. The United States Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) and the Health Canada's Veterinary Drugs Directorate (VDD) approve veterinary drugs and establish the acceptable concentrations of drug residues in

animal-origin food products. The United States Department of Agriculture's Food Safety and Inspection Service (FSIS) and the Canadian Food Inspection Agency (CFIA) monitor meat, poultry, eggs and honey for residues of drugs and chemicals. Monitoring of antimicrobial residues in milk and dairy products is mainly carried out on a state or provincial basis at the processor level. Before any drug can be approved in the United States or Canada for use in a food producing animal, an extensive toxicologic evaluation of the drug and its metabolites is undertaken. This ensures that any drug residues in animal-derived foods do not harm the consumer.

Based on the results of toxicity tests, regulatory agencies establish an acceptable daily intake (ADI). The ADI represents a level of daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer. The ADI is used to determine the maximum concentration of a marker residue in edible tissues, honey, milk, or eggs that is legally permitted or recognized as acceptable. In the US, these acceptable concentrations are termed tolerances while in Canada and the European Union they are termed maximum residue limits (MRLs). The MRL is calculated such that daily intake of food with residues at the MRL will result in a total daily consumption of residues in quantities at or below the ADI. ADIs are based on the total residue of a chemical present in food (parent compound and all metabolites) whereas MRLs are based on a single, measurable marker residue, which may be the parent compound or any of its metabolites. In establishing MRLs, consumption estimates for the various foods are taken into account so that foods consumed infrequently or in small amounts are allowed greater MRL values than those foods likely to be consumed daily or which represent a major component of the diet. Because of differences in consumption factors, MRLs and label withdrawal times may differ between countries, even though ADIs are equivalent.

Drug manufacturers administer the proposed label drug dose to a number of animals and perform sequential euthanasia to measure tissue drug concentrations. The label withdrawal time (WDT) is determined by identifying the time that is required for marker residue concentrations in the target tissue (eg, muscle, liver, kidney) to fall below the MRL (tolerance) level with a confidence level of 95%. Therefore, small errors in dosing or mild disease states are accounted for in determining the WDT.

Residue Monitoring Programs

The Canadian Food Inspection Agency (CFIA) and US Department of Agriculture's Food Safety and Inspection Service (FSIS), test for chemical contaminants in meat, poultry, milk and egg products. They screen for chemical residues from approved and unapproved veterinary drugs, pesticides, and environmental compounds. Residue detection programs are designed to:

1. provide a structured process for identifying and evaluating residues of concern in food animal products;
2. analyze chemical compounds of concern;
3. collect, analyze and report results; and,
4. identify the need for regulatory follow-up subsequent to the detection of violative concentrations of residues.

When a violation is detected, the FSIS or the CFIA condemns the carcass or adulterated product. If the product has been distributed into commerce, it is subject to a voluntary recall. The federal agencies take appropriate action when a violation is detected. These actions include follow-up inspections, further directed sampling according to a surveillance plan, or even seizure and recall of products when the human health risk is considered

unacceptable. Follow-up actions vary according to the magnitude of the health risk; regulatory emphasis is on preventing repeat violations and preventing distribution of contaminated products into the public food supply. As a deterrent, the FSIS posts a Residue Repeat Violator List on its web site. The list identifies producers with more than one residue violation in the last 12 months. The list is useful to processors and producers who are working to avoid violative residues.

With increasing public concern over the risks of chemical contamination, there has been greater focus on strengthening the identification, ranking, and testing for chemical hazards in meat, poultry, and egg products. The US and Canada now use multi-analytic methods that analyze more compounds per sample while using fewer samples (>350 compounds can be screened for in a single sample). The new multi-residue methods (MRM) approach:

1. screens for a variety of analytes, not just antimicrobials;
2. has been validated at concentrations appropriate to tolerances;
3. uses mass spectrometry to forensically distinguish individual analytes, even if multiple drugs are present in the same sample;
4. mitigates unknown microbial inhibition responses; and
5. reduces the time and personnel needed to obtain results.

With this system, the probability of detecting a residue violation is 99% if the violation rate is equal to or greater than 1% in the population of animals being sampled.

When inspection program personnel detect evidence of disease or drug use in an animal carcass, they hold and test samples from those carcasses. An animal may be suspect because of historical information on a production class, or appearance on ante- and post-mortem inspections. Typical suspect animals include culled dairy cows, bob veal calves (calves <3 weeks of age and weighing <68 kg), any animal with visible evidence of an injection site, any animal showing evidence of an infectious disease, or animals of a given production class for which a high incidence of residue violations has been detected through the monitoring program.

Animal and egg products imported to the United States or Canada have passed inspection in their country of origin; therefore, import sampling is re-inspection. The level of re-inspection by the FSIS or CFIA depends on the exporting country's performance history. Import sampling is designed to verify the equivalence of chemical residue programs in countries exporting meat, poultry, honey, and egg products to the United States or Canada.

Banned Drugs in Canada and the U.S.

When producing food for human consumption, it is important to know the final destination of those products. While drug labels and withdrawal times are appropriate for animals and their products that remain in Canada, it is important to recognize the importance of Canadian exports to other countries. The US is Canada's biggest export market so it is important to understand the differences in federal drug regulations between the two countries when it comes to drugs banned for use in food animals.

The sections of the Canadian Food and Drugs Act that pertain to the banned drugs state:

B.01.048. (1) No person shall sell

(a) any animal intended for consumption as food if any product containing any drug listed in subsection (2) has been administered to the animal;
(b) any meat, meat by-products, eggs or milk intended for consumption as food and derived from an animal if any product containing any drug listed in subsection (2) has been administered to that animal; or
(c) any meat, meat by-products, eggs or milk that contains any residue of any drug listed in subsection (2).

(2) The drugs referred to in subsection (1) are
(a) chloramphenicol and its salts and derivatives;
(b) a 5-nitrofuran compound;
(c) clenbuterol and its salts and derivatives;
(d) a 5-nitroimidazole compound; and
(e) diethylstilbestrol and other stilbene compounds.

C.01.610. No person shall sell any substance having oestrogenic activity for administration to poultry that may be consumed as food.

C.01.610.1 No person shall sell a drug for administration to animals that produce food or that are intended for consumption as food if that drug contains
(a) chloramphenicol or its salts or derivatives;
(b) a 5-nitrofuran compound (e.g. furazolidone and nitrofurazone);
(c) clenbuterol or its salts or derivatives;
(d) a 5-nitroimidazole compound (e.g. metronidazole); or
(e) diethylstilbestrol or other stilbene compounds.

In the United States, the Animal Medicinal Use Clarification Act codifies which drugs are banned for extralabel use in food animals because of both residue hazards and concerns over antimicrobial resistance and includes drugs not on the Canadian list:

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol
- Dimetridazole, ipronidazole and other nitroimidazoles (eg, metronidazole)
- Furazolidone and nitrofurazone
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfathoxypyridazine) (ELDU of sulfonamides in milking sheep and goats is discouraged but not prohibited)
- Fluoroquinolones
- Glycopeptides (eg, vancomycin)
- Gentian Violet
- Phenylbutazone in female dairy cattle 20 months of age or older
- Cephalosporins (except cephapirin in cattle) ELDU is permitted for EL therapeutic uses but label dosage regimen must be followed
- Human antiviral drugs in poultry

For lactating dairy cows, the significant prohibitions under AMDUCA are the use of sulfonamides and phenylbutazone. The US has not had the injectable trimethoprim/sulfadoxine formulations (eg, Trivetrin, Borgal) for sale for over 30 years. Currently in the US, sulfadimethoxine (Albon Injection 40%, generics) is the only marketed sulfonamide with approved formulations for lactating dairy cattle. Therefore, under AMDUCA, any lactating dairy cow treated with trimethoprim/sulfadoxine must not enter the US for slaughter and the CgFARAD™ cannot give withdrawal guidance.

When it comes to approved nonsteroidal anti-inflammatory drugs (NSAIDs) approved for use in food animals, Canada has more approved products than the US. Therefore, there is little reason to use phenylbutazone in lactating dairy cattle and there are no MRLs for it in any species. The US does not have ketoprofen (Anafen) or meloxicam (Metacam, Meloxicam Oral Suspension) as approved drugs for food animals, so treated animals must follow extended withdrawal periods if going for slaughter in the US. However, the CgFARAD™ does have data in some species to help determine these extended withdrawals.

The AMDUCA regulations are also significant for Canadian exports of any food animal species for the fluoroquinolone and cephalosporin antimicrobials. The fluoroquinolones, such as enrofloxacin (Baytril – Canada and the US), danofloxacin (A180 – Canada, Advocin – the US) and marbofloxacin (Forcyl – Canada only), can be used in an extralabel manner in Canada and the CgFARAD™ will give withdrawal guidance where residues depletion information is available. But any species of food animal treated in Canada in any manner inconsistent with US labeling, must not be exported to the US. So if a fluoroquinolone is used to treat a lactating dairy cow for coliform mastitis, that animal cannot be sent to the US for slaughter.

The US AMDUCA regulations regarding cephalosporins are slightly less strict than for fluoroquinolones, but they primarily target the extralabel use of ceftiofur. So ceftiofur formulations may be used for a nonapproved disease but only at the label dosing regimen. For example, ceftiofur sodium (Excenel in Canada, Naxcel in the US) is labeled for the treatment of bovine respiratory disease but could be used for the treatment of a septic calf as long as the label dose, route and frequency of administration were followed.

While unrelated to AMDCUA regulations, the CgFARAD™ is a aware of another drug issue that impacts exports to the US. In the US, procaine penicillin G is approved for intramuscular injection in swine at 6,600 units/kg once daily for up to 4 days with a 7 day withdrawal time. The comparable products in Canada are labeled for intramuscular administration at 15,000 units/kg for up to 5 days with an 8 day withdrawal time based upon Canadian MRLs for swine tissues and residue depletion studies carried out by the Canadian Food Inspection Agency. However, when the USDA instituted the very sensitive MRM methods, a high rate of penicillin residues violations occurred in swine. This was because the US has never established tolerances for penicillin residues in any swine tissues and the MRM methods were capable of detecting extremely low concentrations. So with a “zero” tolerance, the US label withdrawal time was insufficient. The situation was worse for swine treated in Canada with the higher approved dose and the 8 day withdrawal time. A USDA study eventually recommended at least a 51 day withdrawal period when procaine penicillin G is used in swine destined for slaughter in the US. Because of this issue, the CgFARAD™ recommends avoiding procaine penicillin G in swine that could eventually be exported to the US. This has led to veterinarians consulting the CgFARAD™ for withdrawal guidance for the use of ampicillin trihydrate (Polyflex – Canada and the US). The Polyflex formulation of ampicillin trihydrate is

approved in Canada for cattle and swine but only for cattle in the US. A previously marketed formulation of ampicillin trihydrate (Princillin Injection) was approved in the US for swine with a dose of 6.6 mg/kg to be administered intramuscularly once or twice daily for up to 3 days with a withdrawal time of 15 days. So there are US tolerances for ampicillin in swine tissues and they are exactly the same as the Canadian MRLs. Ampicillin trihydrate is approved for use in swine in Canada at 6 mg/kg once daily for up to 7 days of treatment with a 4 day withdrawal time. Therefore, treating swine in Canada with the on label dosing regimen for Polyflex and following the old US withdrawal period of 15 days should be sufficiently conservative to prevent detectable residues in exported swine.

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