

# Bugs, Drugs and You

Jean Szkotnicki

Canadian Animal Health Institute, 160 Research Lane, Suite 102, Guelph, ON N1G 5B2  
*Email:* jszk@cahi-icsa.ca

## ■ Introduction

Antimicrobial resistance is a subject that has been discussed since mankind first began using antimicrobial drugs to treat disease over 50 years ago. The concern is that by using antimicrobial drugs to treat for disease we actually select for resistance thereby limiting the use of the antimicrobial drugs. Microbes have the inherent ability to develop ways to survive the use of medicines that are meant to kill or weaken them. When a microbe becomes resistant to many drugs, the infection it causes can become difficult or even impossible to treat. Someone with an infection that is resistant to a certain medicine can pass the resistant infection to another person, leading to the spread of a disease resistant to treatment.

Microbes can also transfer from animal to man and may cause disease in both animals and man. Examples of such diseases include, tuberculosis, brucellosis and food borne infections like salmonellosis.

## ■ Why do we use antimicrobial drugs in animals?

One of the first reports that examined the use of antimicrobials in food animal production was the Swann Report (1969). This report defined an antibiotic as follows,

“An antibiotic is generally defined as a chemical substance produced wholly or partially by a micro-organism (usually a fungus or bacterium) which has the capacity in dilute solution to inhibit the growth of, or to destroy, bacteria and other micro-organisms.” Chemical purification techniques permit the synthetic manufacture of antibiotics so they can be sold commercially. These products are sold in the form of an injectable, a tablet/pill/bolus, and as feed additives.

In Canada and elsewhere, we use antimicrobial drugs to treat sick animals, to prevent disease in stressed animals or animals exposed to contagious disease and to enhance production. By using antimicrobial drugs in food animals we,

- Contribute to safe and wholesome food from healthy animals
- Reduce human exposure to zoonotic pathogens through direct contact with animals
- Promote the health and well-being of animals
- Reduce the cost of food production
- Help optimize the use of arable land for food production.

According to a 1999 Report of the Council for Agricultural Science and Technology (CAST) entitled, "Animal Agriculture and Global Food Supply", per capita consumption of meat, milk and eggs is expected to increase in the future. Presently, developed countries have the highest per capita consumption of food animal products, however, per capita consumption is increasing dramatically in developing countries. The CAST report concluded that, "total meat consumption in developing countries is projected to more than double by the year 2020, while, in developed countries, it is projected to increase no more and, in some cases, less than, population growth. Because most of the world's population is in developing countries, which are experiencing the most rapid growth rates, global demand for meat is projected to increase more than 60% of current consumption [1999] by 2020."

This increased demand for food animal products will result in an increased demand for animal health management tools, inclusive of antimicrobials. This demand will be in the face of 3 new forces. They are:

- Globalization of the food supply.
- A shift in food safety from chemical residues to microbial pathogens.
- Emergence of a Hazard Analysis Critical Control Points (HACCP) focus for food safety on a mandatory and voluntary basis.

## ■ Globalization

Canada's red meat industry is a world leader when it comes to globalization of the food supply. The Canadian pork industry is the largest exporter of hogs and pork products in the world and our beef industry is the 3<sup>rd</sup> largest exporter of cattle and beef products.

## ■ Food Safety Shift from Chemical Residues to Microbial Pathogens

Canada and other developed parts of the world have had food safety programs that focus on chemical residues of antimicrobial drugs, as well as other contaminants. In the case of antimicrobial drugs, the Veterinary Drugs Directorate (VDD) of Health Canada conducts the risk assessment for a drug sponsor that wants to bring a new product to the marketplace. VDD assesses each new antimicrobial drug to ensure it:

- Does not pose a safety risk to humans and animals.
- Does as the label claims.
- Is manufactured under good manufacturing conditions.

Human safety is paramount to the assessment conducted by VDD. Antimicrobial drugs are assessed for:

- Acute Toxicity
- Sub Acute Oral Toxicity
- Mutagen and Carcinogenicity
- Reproductive Effects
- Teratology
- Chronic Toxicity
- Residue Depletion.

This review process is similar to other veterinary drug regulatory agencies in the world. It has a chemical focus with maximum residue limits (MRL's) or tolerances being set for antimicrobial drugs as a risk management tool. Our Canadian Food Inspection Agency (CFIA) then tests to see if meat products have no residues beyond the MRL, thereby ensuring there are no harmful residues in meat. Results of this compliance program are glowing - food animal producers and veterinarians use antimicrobial drugs responsibly and judiciously from a residue standpoint.

The VDD and other regulatory agencies around the world are now looking beyond assessing and managing the risk of using antimicrobial drugs from the standpoint of chemical residues to include microbial safety. That is not to say that microbial safety has not been a part of the VDD process in the past. It has been a component of the review process, with Canada being one of the first agencies in the world to begin labelling most new antimicrobial drugs for animal use as prescription only. As well, reviewers have asked new drug sponsors to provide data relating to microbial safety.

Drug sponsors are supportive of the risk assessment process done by VDD. However, I want to point out that product safety begins with the developer of the antimicrobial drug. This includes microbial safety, as well as, chemical. Companies want to ensure that a new product has a long life; where it retains its effectiveness in the animals it is labelled for. Further, no company would want to compromise human therapies. In fact many animal health companies have a human division and they would not want to compromise human therapies they market. It is simple business sense. Companies have a research and development investment of around \$250 million overall for a new food animal drug and a time investment of 12 – 15 years. So, while companies are supportive of the drug review process there is an expectation that regulatory agencies make timely decisions.

In 1997, Health Canada held a consensus conference on antimicrobial resistance due to the growing concern regarding antimicrobial resistance and its potential to threaten human health. The meeting focused on the role of antimicrobial drug use had in human medicine due to the occurrence of resistance. It was recognized that human drug use impacted resistance much more than animal use but that the impact of human or animal use on resistance was not easily quantified. At this meeting there was limited discussion regarding animal drug use and its role in resistance. The need for better surveillance to monitor bacterial loads in healthy individuals, in those that had been treated and in food was discussed along with the need for education of medical doctors regarding prudent use.

Then in 1998 a workshop was held and issues relating to the role that animal use of antimicrobial drugs played in the development of resistant bacteria were discussed. An outcome of the meeting was establishment of an expert advisory committee that was to provide policy advice to Health Canada on antimicrobial drug use in food animals as it related to resistance. The Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health met over a 2 1/2 year period completing a Report entitled, "Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health" that was published on the Health Canada website in September, 2002 (Health Canada, 2002). The document contains 38 recommendations, which focus on the need for integrated surveillance programs, education, regulatory and policy changes involving antimicrobial drug use and mitigating strategies based on HACCP principles. The Canadian Animal Health Institute (CAHI) commended the Advisory Committee for its work in preparing the comprehensive Report. In preparing its perspective to the Report the CAHI said an integrated approach was needed to manage resistance (CAHI, 2002). CAHI thought the following key areas from the Report needed to be acted on:

***The need for a coordinated, ongoing, national surveillance system for antimicrobial resistance in the major pathogens affecting food animals.***

Canada needs to know what resistant bacteria in food animals are prevalent so that it can develop mitigating strategies that minimize the impact they might have on human health. We need to know what we are dealing with.

***The need for regulation of antimicrobials to consider the human health impacts of resistance.***

Regulations must be clear, transparent and harmonized with other developed countries recognizing that bacteria know no borders. Further, the policy-making process should not stop decision-making within the review process.

***The need to assess federal, provincial jurisdiction regarding the sale and use of antimicrobials in animals, identify compliance gaps and develop new measures leading to prudent and safe use.***

The status quo cannot be assumed. New measures are needed to address non-approved drug use issues in animals.

The Veterinary Drugs Directorate (VDD) of Health Canada is to respond to the Report in December 2002. A further elaboration on the VDD's response to the Report will be provided during the Workshop sessions.

■ **Hazard Analysis Critical Control Points (HACCP)**

A recommendation in the Advisory Committee Report identified the need for the food animal industries to develop on farm food safety programs (OFFSPs) that address antimicrobial issues. Indeed animal agriculture in Canada is a leader in this regard. Commodity organizations have developed quality assurance programs based on the HACCP principles. These programs are voluntary and all have proper drug use as a critical component. The programs are in varying stages of development by commodity organizations with audit controls being integral to the integrity of these programs.

The Animal Nutrition Association of Canada (ANAC) has also developed a HACCP-based program that has audit controls for its members, commercial feed manufacturers. Many of its members are becoming HACCP certified in an effort to build on existing standards that help to ensure animal and food safety.

The producer quality assurance programs and ANAC's HACCP-based program are both voluntary at this time. The Canadian Food Inspection Agency (CFIA)

is in the process of establishing mandatory HACCP-based regulation for the manufacture of medicated feed on farm and in commercial mills. This regulation is to be based on process controls such as, medicating ingredient inventory, equipment clean out, scale and meter calibration, and mixer validation. A key component of the regulation will be licensure whereby, a mill/individual must be licensed to be able to mix a medicated feed and a medicating ingredient can only be sold to the holder of a license. It needs to be pointed out that a driving force behind this new regulation is government's concern for managing microbial safety.

The veterinary profession is also embracing the concept of process controls to better manage drug use. This is happening globally and domestically. The Canadian Veterinary Medical Association (CVMA) guidelines say:

- Veterinarians should concentrate their efforts on assisting clients with the design of management, immunization, housing and nutritional programs that reduce the incidence of disease and decrease antimicrobial drug use.
- Veterinarians should dispense and prescribe antimicrobial drugs only within the confines of a valid veterinarian-client-patient relationship.
- Veterinarians should properly select and use antimicrobial drugs.

These programs are being encoded into specie specific guidelines.

As mentioned, an integrated approach is needed to effectively manage resistance issues – there is no one magic bullet. Inclusive to the approaches mentioned above is assessment of other mitigating factors such as food irradiation and education regarding proper food handling. While it is recognized by health professionals that food animal production is a small contributor to antimicrobial resistance that results in human health treatment failures, there is no question that globally and within Canada actions are being taken by governments, producer organizations, veterinarians and others to address this concern.

## ■ References

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