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IMPORTANCE OF VETERINARY DRUG RESIDUES

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1.1 INTRODUCTION

Food animal production over the last 50–60 years has significantly increased with the implementation of modern genetics, breeding, husbandry, and nutrition. During this same time period, livestock producers have relied on the use of veterinary drugs as one of several strategies to ensure economic viability of the industry. This need for increased use of veterinary drugs, and especially antimicrobial drugs, has been linked to changes in standard livestock practices where the objective is to increase feed and space efficiency and to a need to generate greater quantities of meat, milk, and egg products in an ever increasing competitive global market. While the consumer appreciates the need to increase livestock production and generate reliable and affordable animal-derived products, this is tempered by the consumers’ requirement that the food items be “free” of drugs or chemicals introduced in the production system. The wide availability of related information via the Internet has exposed the consumer to useful facts but all too often to controversial
statements and hypotheses with very little factual support from the scientific literature regarding the prevalence of drug residues in our food, how veterinary drugs are used, and what safeguards are implemented to reduce these residues. This introductory chapter will briefly review the role of drugs in modern livestock production, quality assurance programs, adverse human health effects of drug residues, and economic impact of these residues to the livestock industry.

### 1.2 VETERINARY DRUG USE IN LIVESTOCK

Modern livestock production can be described as involving intensive animal production practices that often use veterinary drugs at subtherapeutic level in feed and water in order to improve feed efficiency for growth and production and maintain animal health. In such close animal–animal contact practices, prevention of disease is more important than treating for disease that would require therapeutic levels (higher doses) of the drug. The United States defines subtherapeutic use of an antimicrobial as a feed additive less than 200 g of drug per ton of feed.

*Subtherapeutic drug* use may take the form of (i) *antimicrobials* delivered to the animal as a feed or water additive and (ii) *hormones* delivered via ear implants or feed additives.

The antimicrobials approved in the United States and EU to be used in this legal manner often belong to the tetracycline, sulfonamide, or macrolide class of antimicrobials. Several EU countries and others banned or limited the use of these drugs as growth promoters as there are concerns that their use promotes the emergence of antimicrobial resistance. This cause-and-effect relationship is continually being debated across various jurisdictions; although epidemiological evidence continues to accumulate, definitive conclusions from rigorous research in livestock production systems has not been forthcoming. This issue will be further explored in this and other chapters of this book.

The use of hormone growth promoters in livestock has also been a controversial debate as various regulatory authorities in different jurisdictions regulate these drugs in a different manner. The U.S. FDA has approved the legal use of 17β-estradiol, testosterone, progesterone, trenbolone, and zeronol as solid ear implants and melengestrol acetate (feedlot heifers) and ractopamine (swine) as feed additives. Compared to the United States, the EU in 1988 issued a total ban of all hormonal active growth promoters in livestock production. Prior to 1988, in the Netherlands (1961) and Belgium (1962–1969), there was a total ban on anabolic agents for growth promotion purposes in slaughter animals in order to protect consumers and for the benefit of international trade (Stephany, 2010). It should be noted that the
United States challenged the EU’s ban, and in 1998, the WTO found that the EU’s ban was not supported by science and inconsistent with WTO obligations (USTR, 2009).

Therapeutic drug use in veterinary livestock involves administration of veterinary drugs according to label to treat an individual animal or herd or flock of animals by various approved routes of administration. The use of water additives is recognized in all countries as a form of therapeutic drug use and not subtherapeutic drug use or for growth promotion purposes. It has however been our experience (Mason et al., 2012) that treatment of large herds via water medication does not always result in each animal in the herd receiving therapeutic drug levels. This has often been associated with competition between animals in the herd and/or malfunctioning medicators. The approved use of the many therapeutic drugs will be outlined in the species-specific chapters of this book.

The passage of the Animal Medicinal Drug Use Clarification Act (AMDUCA) 1994 in the United States allows food animal veterinarians to administer drugs in an extralabel manner within certain guidelines as outlined in the following text. Veterinarians often have to resort to using these drugs in an extralabel manner for a number of reasons. New generics of old drugs are approved based on bioequivalence to pioneer formulation, which allows the same dosage and milk discard/meat withdrawal times. The problem with this approach is that new bacteria being treated have much higher MICs than bacteria and microorganism many years ago, and thus, higher dose must now be used. Veterinarians often consult with FARAD to find out new withdrawal times, and this is described in more detail in Chapter 14. The scientific issue is that most antimicrobials used in dairy practice today are old drugs (or generic copies of old drugs) that are now not effective unless given at higher doses, necessitating extended milk discard times. Risk of exposure to low-level residues of most other drugs out there is “theoretical,” but low label dosages of antimicrobials, used to insure adequate withdrawal times, will promote resistance, which is the major public health issue. There are more modern approaches that would allow dosage adjustments with new withdrawal times, but we are stuck in the science of the 1970s. Legal precedence and business issues tend to hand tie the FDA (in approving all generics just like the first one that was approved even if science has advanced in 30 years). Production use of antibiotics as growth promoters may very well be banned, and therapeutic use at higher doses by licensed vets maintained.

Phytoceuticals are increasingly being used on organic farms with varying degrees of success. These drugs are not regulated by the FDA-CVM as they are often described as “generally recognized as safe” (GRAS). There are however several guidance documents and requirements that organic livestock farms are required to follow and are discussed elsewhere in this book.
1.3 QUALITY ASSURANCE PROGRAMS

Consumers are very aware of drug and chemical use in the livestock industry, and oftentimes, there is general misinformation about how these drugs are used in the industry. The infrequent catastrophic drug residue violations are often a direct result of careless farm management. *The subsequent economic cost to the livestock industry is not ignored by the many stakeholders involved in livestock production and distribution and sales of meat, milk, fish, and egg products*. This will be discussed in more detail in a later section of this chapter.

In lieu of these scenarios, the livestock industry has been aggressively policing itself to make sure that producers are educated and trained to prevent drug residue violations on their farms. Many if not most livestock producers follow and adhere to their respective quality assurance programs for their commodity group that attempt to minimize drug residue violations and promote judicious use of veterinary drugs. A summary of the steps producers are encouraged to follow whether it is the beef, dairy, pig, goat, or poultry industry is as follows:

1. Improve husbandry practices by maintaining appropriate husbandry, hygiene, examinations, and vaccinations.
2. Consult with a veterinarian prior to use of drugs or medicated feed or water as therapeutic alternatives may be more appropriate.
3. Use drug according to veterinary label and only resort to using veterinary drugs as a last resort. This is especially important for antimicrobial drug use.
4. Antimicrobial drug use is inappropriate for viral infections without bacterial complication.
5. Optimize antimicrobial drug regimen using current pharmacological information and principles.
6. Mitigate veterinary drug spillage into the environment.
7. Keep good records of drug use on each farm.
8. Extralabel drug use in the United States must follow the FDA regulations: prescriptions, including extralabel use of medications must meet the AMDUCA amendments to the Food, Drug, and Cosmetic Act and its regulations. This includes having a valid veterinary–client relationship.

The passage of the AMDUCA in the United States in 1994 allows food animal veterinarians in the United States to administer drugs in an extralabel manner within certain guidelines. Several chapters in this book will focus on
PK principles that can be used to extrapolate across and within species, across routes of administration, and across doses. To date, legislation similar to AMDUCA does not exist in other major livestock-producing countries.

1.4 ADVERSE HUMAN HEALTH EFFECTS OF DRUG RESIDUES

Inappropriate use of several of veterinary and human drugs in livestock production can result in significant residue levels in meat, dairy, and poultry products that can cause adverse health effects in consumers. Although approximately 80% of all food animals are given drugs during their lifetime, residue violations are often less than 1% thanks to rigorous surveillance and testing in major livestock-producing countries and increasing so in smaller developing states. However, many consumers in developed and developing states rely on livestock products as their major source of protein. The average American consumes 200 pounds of meat and fish, 67 pounds of poultry, 30 pounds of eggs, and 600 pounds of dairy products annually. In spite of the low level of drug residue contamination, this high level of consumption of livestock products increases the possibility that any one violative incident can result in adverse health effects affecting more than one individual or community following acute or chronic exposure.

A very good example of the aforementioned case was associated with clenbuterol residues. In one 6-month period in 1993, more than 1200 hospitalizations and 3 deaths in France and Spain were reported to have resulted from eating beef livers contaminated with clenbuterol. One study documented in Portugal four cases of acute food poisoning, involving a total of 50 people, due to the ingestion of lamb and bovine meat containing residues of clenbuterol (Barbosa et al., 2005). An outbreak with hospitalization was described in Italy in 1997 involving 15 people within 0.5–3.0 h after the consumption of veal and not livers (Brambilla et al., 2000). No deaths were reported but clinical signs and symptoms disappeared within 3–5 days. More recently, 286 villagers in Changsha, capital of Hunan province in China, were hospitalized and suspected to have been made sick from consuming clenbuterol-tainted pork (UPI, 2011). Symptoms of clenbuterol intoxication can be described as predominantly gross tremors of the extremities, tachycardia, nausea, headaches, and dizziness. This drug is a beta-agonist, acts as a bronchodilator, and can have anabolic effects such as increase lean body mass and weight gain. It is not approved for use in humans or in food animals by the U.S. FDA, and extralabel use in food animals is strongly prohibited. However, there is approval for use in horses with recurrent airway obstruction (heaves), and there are no studies to support meat withdrawal times for this drug given to horses intended for food.
1.5 WITHDRAWAL TIME DETERMINATIONS

Several chapters in this book will describe in brief several of the methods used by the U.S. FDA (2006) and the European Medicinal Agency (EMA, 1996, 2000) to derive regulatory withdrawal times that ensures the consumer is protected from exposure to drug concentration that will cause adverse health effects. The guidance documents for these calculations from each of these regulatory authorities are always changing with new revisions, and they may vary slightly, but there are some common features that the reader should appreciate.

For example, in assigning a milk withdrawal time, the U.S. FDA uses an algorithm that calculates the upper 99th percentile of the population and 95th percent confidence limit. As with the tissue withdrawal period, this assures that when the drug product is used according to its approved label, there is only a 5% chance that one animal in 100 will have milk residues above the milk tolerance concentration. In the EU, the recommended method is also a statistical method based on a linear regression model in which the upper 95% tolerance limit of the 95% percentile of the residue depletion curve is used to determine the withdrawal period. As per the U.S. FDA, the minimum number of animals in a milk residue study is 20, based on the statistical requirements for the calculation of the withdrawal time. In the EU, milk withdrawal periods are established for individual animals and not for tank milk as per the U.S. FDA-CVM. The reader is encouraged to consult with updated guidance documents in the respective jurisdictions with regard to recommended regulatory methods to calculate the meat and milk withdrawal times. There are several chapters in this book that describe alternative and more flexible pharmacometric methods that utilizes the current advances in mathematical modeling and well-accepted software that considers a larger population of animals and other variables such as production and disease status that are often overlooked in the current regulatory methods in many jurisdictions. These novel methods are not currently accepted by regulatory agencies in the establishment of meat and milk withdrawal periods for veterinary drugs. However, several of them such as physiologically based pharmacokinetic (PBPK) modeling have been adapted with success by the U.S. EPA in their guidance for conducting a human health risk assessment of environmental contaminants.

1.6 ANTIMICROBIAL RESISTANCE

The U.S. FDA in 2010 provided guidance on the judicious use of antimicrobial drugs in livestock and recognized that failure of antimicrobial therapies in humans can be related to human and animal use of antimicrobials among
other factors. The FDA believes that “the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. In contrast, FDA considers uses that are associated with the treatment, control, or prevention of specific diseases, including administration through feed and water, to be uses that are necessary for assuring the health of food-producing animals.” This topic is discussed in more detail in subsequent chapters of this book that describe the prudent drug use of antimicrobials in ruminant and pig production systems.

1.7 ECONOMIC IMPACT OF DRUG RESIDUES

There is a significant economic impact associated with drug residues in meat, milk, or egg products. Besides loss in sales of product, public perception can have the greatest impact on consumers already weary about drug and chemical use in food production systems in developing and developing countries. Oftentimes, the consumer is exposed to misinformation from media sources whose understanding are limited with regard to how these drugs are used on livestock farms and the many stages between the farm and table where residue violations are prevented. The remainder of this book will highlight many of the established practices that are effective in the mitigation of drug residues and scenarios where residue violations are likely to occur and warrant future research and attention by regulatory authorities.

REFERENCES


