

# Dairy Session

Moderators: Michael Capel, Greg Johnson

## Prudent drug use for the dairy practitioner

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### Abstract

As consumers become more savvy about the food they eat, dairy farmers and their veterinarians must be progressively vigilant to make sure that public health is protected. These protections come not only from residue prevention, but also in the implementation of prudent drug practices that minimize the risk of development of antimicrobial resistance, which may be passed on to humans who consume animal-based food products. Throughout the last decade, the FDA has issued several guidance policies and implemented prohibitions in drug use in attempts to reduce the risk of development of antimicrobial resistance in humans. As dairy farms become larger, veterinarians are spending less time doing individual animal treatments and more time directing those treatments on farms. Whether animals are treated on-farm by veterinarians or by farm personnel, there are specific expectations that must be in place in order to reduce the risk of antimicrobial resistance development and drug residues in meat or milk.

**Key words:** dairy, drug use, stewardship

### Résumé

Alors que les consommateurs deviennent de plus en plus exigeants en ce qui concerne leur alimentation, les producteurs laitiers et leurs vétérinaires doivent être des plus vigilants afin de s'assurer que la santé publique soit bien protégée. Cette protection implique non seulement la prévention des résidus mais aussi la mise en place de méthodes judicieuses d'utilisation des drogues afin de minimiser le risque de développement de résistance antimicrobienne qui pourrait être passée aux humains qui consomment des produits alimentaires d'origine animale. Au cours de la dernière décennie, le *FDA* a émis plusieurs directives et mis en place des programmes de restriction dans l'utilisation des drogues afin de réduire le développement de résistance antimicrobienne chez les humains. Alors que les fermes laitières deviennent de plus en plus grosses, les vétérinaires passent moins de temps à prodiguer des soins individuels aux animaux et plus de temps à régir ces traitements à la ferme. Peu importe si les animaux sont traités à la ferme par les vétérinaires ou par le personnel de la ferme, il y a des attentes bien particulières qui doivent être rencontrées afin de réduire le risque de développement de résistance anti-

microbienne ou de minimiser la présence de résidus de drogues dans le lait ou la viande.

### Introduction

Antimicrobial residues in milk and meat from dairy cattle have long been scrutinized by the US public and governmental agencies. There are also increased concerns about the presence of elevated levels of antimicrobial resistance in both veterinary medicine and human medicine. Additionally, there is heightened fear that certain antimicrobial use practices in veterinary medicine are leading to decreased treatment efficacy in human medicine. Dairy farmers and their veterinarians must be progressively vigilant to make sure that public health is protected following consumption of products from dairy animals, and that perception of milk and dairy beef remains as high as possible.

### Antimicrobial Residues in Dairy Beef

Cull dairy cows have the highest incidence of confirmed meat residue violations at slaughter of all food animal classes, with 568 violations noted in the Red Book during FY11.<sup>11</sup> According to this document, the percentage of cull dairy cows with violative meat residues is approximately 10 times higher than in cull beef cows. This correlates to cull dairy cows accounting for approximately 90% of all of the violative residues found in beef animals harvested for meat each year. In recent years, publication of the Red Book lags substantially beyond completion of the fiscal year they summarize. However, the USDA has now started publishing Residue Quarterly Reports online (USDA FSIS-Residue Quarterly Reports).<sup>12</sup> The reports currently available for the most recent year (July 2014 – June 2015) indicate that there have been 515 dairy cull cows identified as violative, with 600 residues identified in those animals. Of the residues identified, ceftiofur, penicillin, and the sulfonamide family were the most common violative residues identified. During this time period, USDA conducted 192,746 in plant tests on all animal classes, of which 105,295 (54.6%) were conducted on cull dairy animals. As a result of these tests, there were 871 animals with confirmed violative residues, of which 59% were dairy animals. This is particularly shocking when taking into account the small percentage that cull dairy cows represent among the total animal marketings across all species.

It becomes pretty obvious why the USDA and FDA are paying so much attention to the dairy industry. In general, inspector-generated sampling is completed at a higher rate in cull dairy cattle than in cull beef cattle for a couple of reasons. Inspector-generated sampling targets *individual suspect animals* and suspect *populations of animals*.

1. The rate of inspector-generated sampling is determined by the incidence of previous residue-positive sampling. Since cull dairy cows have a 10-fold increase in positive samples vs cull beef cows, there are more samples collected from cull dairy cows as a percentage of the total animals that are marketed.
2. Residue testing is also triggered by the presence of a carcass defect. Observations of animals that are marketed with mastitis, metritis, pneumonia, peritonitis, surgical incisions, or active injection-site lesions may generate a suspect test for antimicrobial residues.

This rate of sampling is based on professional judgment of the plant veterinarian and public health criteria.<sup>11</sup>

Another contributor to increased violative residues in dairy cattle is that they are treated with antimicrobials at a much higher rate than beef cull cows or beef feedlot cattle, thus presenting more risk for mistakes to occur. This cannot be used as an excuse for the startling high incidence of antimicrobial residues in cull dairy beef. We must continue to work with dairy producers to assure that all products are used in compliance with the labels, including stated withdrawal times. In addition, when products are utilized in an extra-label manner, proper withdrawal times must be established and maintained to prevent adulteration of the food supply.

### Preventing Antimicrobial Residues in Milk

The US Pasteurized Milk Ordinance (PMO) states that every load of milk that is shipped in the United States must be tested for the presence of  $\beta$ -lactam antibiotics.<sup>8</sup> This practice has reduced antibacterial residues from  $\beta$ -lactam antibiotics in milk to less than 0.1% per year from 13% in 1962.<sup>2</sup> Figure 1 shows the annual pounds of milk that is dumped and the percentage of all samples that were found to be positive. For fiscal year 2015, the percentage of violative samples was 0.012%, which was the lowest in history.<sup>3</sup>

When the causes for these remaining residues are investigated, the majority were caused by mistakes in management. Examples include failing to mark treated cows or treated cows being mixed with non-treated cows. Therefore, it would seem prudent to develop testing strategies that focus on testing the bulk-tank or tanker-truck milk leaving the farm in addition to individual treated cows, as testing individual cows will often not catch the mistakes that occur.

### FDA Guidance on Antimicrobial Resistance and Residue Prevention

Since 2003, the FDA has issued 3 guidance policies that are intended to direct drug use on US livestock farms. The first was Guidance for Industry (GFI) 152 entitled *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*.<sup>4</sup> This document was published to outline the risk assessment approach the FDA will undertake to determine if new antimicro-

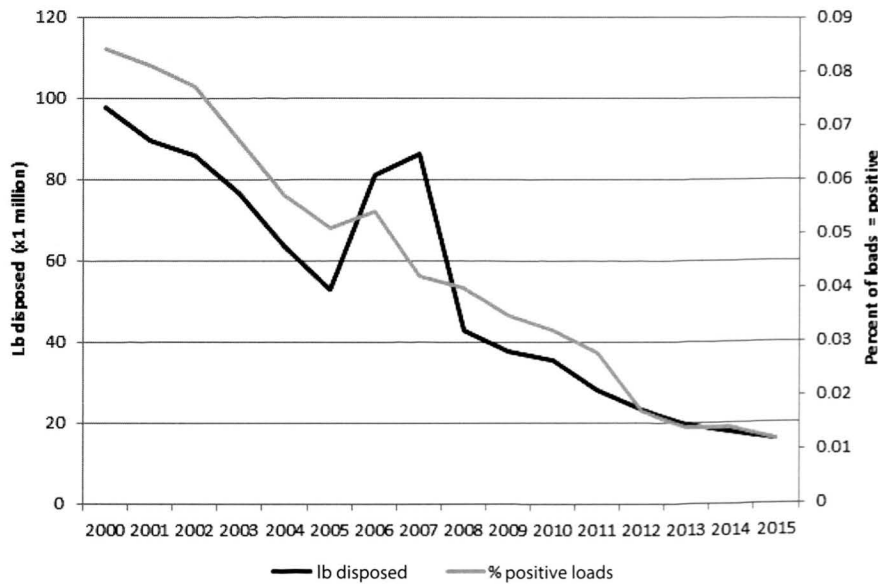


Figure 1. Milk disposition due to drug residues in the US (Fiscal 2000-2015). National Milk Drug Residue Database FY 2000-2015.

bials submitted for FDA approval have impact on the development of antimicrobial resistance in non-target bacterial species, and the risk of human health issues related to transmission of food-borne pathogens to humans. Within the document, the FDA states “that food-borne human exposure to antimicrobial resistant bacteria is complex and often involves the contributions from other sources of exposure” but feel that assessing the food-borne pathway of resistance development is the most significant pathway for resistance development in humans. As a result of this process, the FDA has classified antimicrobial classes as critically important, highly important, or important to human medicine. It is not surprising that many drugs or drug classes that are listed as critically or highly important to human medicine are valuable drugs in veterinary medicine.

In 2012, the FDA released GFI 209 *The Judicious Use of Medically Important Antimicrobial Drugs in Food Producing Animals*.<sup>5</sup> This document was developed to provide practitioners guidance on proper use of drugs that are currently approved in order to minimize the development of antimicrobial resistance. Within the document, the FDA lists the following two principles regarding judicious use of drugs in food-producing animals:

**“Principle 1:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.

**Principle 2:** The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.”

It is my opinion that there is much work to be done by the dairy veterinary community to uphold these principles, especially number 2.

The final guidance policy was GFI 213, *New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*, which provided drug sponsors with a roadmap for complying with the GFI 209. This has led to feed efficiency and growth promotion claims being removed from feed-grade antimicrobials considered to be medically important. Additionally, over-the-counter labels have now been removed, leading to the need for veterinary prescription of these products for their remaining therapeutic purposes.<sup>5</sup>

Citing concerns stated within these guidance policies, essentially that antimicrobial use in food-producing animals combined with husbandry practices that likely lead to exposure of resistant bacteria to humans, the FDA has issued prohibitions and/or restrictions on the use of certain antimicrobials. The first is a prohibition on extra-label use cephalosporin products, excluding cephalixin, in major food-producing species.<sup>6</sup> The second is the Veterinary Feed Directive, released in its final form in June 2015.<sup>9</sup> The justification for these prohibitions was increased presence of multi-drug-resistant organisms in US and Canadian survey programs, the risk of these organisms being

transmitted to humans through consumption of contaminated food, and a fear that consumption of these bacteria may reduce efficacy of first-line drugs for human medical practitioners. In the document announcing the prohibition on cephalosporins, the FDA cited high levels of ceftiofur residues found in cull dairy cattle and the high quantitative levels of those violative residues. The FDA cites several factors that lead to the misuse of ceftiofur products. These include: “(1) poor or nonexistent animal treatment records for adequately monitoring treated animals; (2) inadequate animal identification systems for monitoring treated animals; (3) animal owners’ lack of knowledge regarding withdrawal times associated with the animal drug product; (4) the animal drug product was administered by a route not included in the approved labeling; (5) the animal drug product was administered at a dose higher than stated in the approved labeling; and (6) the animal drug product was administered to a type of animal (e.g., veal calves) not listed in the approved labeling.”<sup>6</sup>

### Developing Protocols and Maintaining Records

Data from the 2007 USDA National Animal Health Monitoring System (NAHMS) survey of the US dairy industry showed that 18.2% of all cows were treated for mastitis during the previous 12 months. In addition, 23% of all of the animals that were sold from the surveyed farms left due to mastitis or udder problems.<sup>10</sup> This estimate does not include cows that died from mastitis, thus underestimating the percentage of cows that leave dairies from mastitis as compared to other conditions like reproductive failure, which would likely result in few dead cows.

In the US, Doanes Market Research places yearly intramammary tube sales at approximately \$24 million (US), with approximately \$15 million spent on dry cow products (including Orbeseal) and the balance being lactating products.<sup>1</sup> Extrapolating from the NAHMS Dairy 2007 data, mastitis treatments are the most common reason for the use of antimicrobial agents on US dairy farms, with 85.4% of all cows that are affected with mastitis receiving antimicrobial therapy.<sup>10</sup> According to Doane’s research referenced above, the largest majority of antibacterials used for the treatment of mastitis in the United States are from the penicillin and cephalosporin classes, which is not surprising considering that most intramammary tubes marketed in the United States are from the  $\beta$ -lactam family.<sup>1</sup>

With that being said, mastitis therapy seems to be one of the logical choices to begin development of treatment protocols. The FDA expectations are that all drug therapies on farms will be administered by a veterinarian or will be directed by a veterinarian based on a written, farm-specific protocol. Whether these treatment protocols are based on culture results or on generalized knowledge of the dairy, the area of protocol development and treatment record keeping is underdeveloped on most dairies. The treatment protocol should force the dairy employee to concentrate on making the correct diagnosis and to assess the cow to determine severity of the condition.

The difficulty from the dairy veterinarian's perspective is trying to craft treatment protocols that farm employees can comprehend and apply, but not hang too much risk on yourself in taking ownership of the treatment program. Treatment protocols should be developed based on medically relevant treatment practices and the technical ability of the farm's personnel. Currently, expectations from the regulatory personnel are high and many dairy farmers are still reluctant to follow the guidelines put forward. Following personal conversations with FDA personnel, the expectations are that written protocols are a living document that is regularly reviewed and updated by the veterinarian of record and farm management.

### Drug Labels

While there is a lot of gray area with new regulations coming forward all the time, i.e., the cephalosporin restrictions, there are a couple of requirements that the dairy industry has been dealing with for a long time due to the requirements of the PMO. According to the PMO, all prescription drugs need to be labeled according to the regulation. Specifically, drug labels must contain the manufacturer's or distributor's name and address for over-the-counter drugs or that of the veterinary practitioner for prescription drugs. If the drugs are dispensed by a pharmacy under the order of a veterinarian, the label must include the name of the prescribing veterinarian and the name and address of the dispensing pharmacy. Drug labels must also contain directions for use, designated withdrawal times for meat and milk, any cautionary statements, and the active ingredients. On farm, drugs that are for lactating cows must be stored separately from those intended for non-lactating animals, with shelves for both groups appropriately labeled. During regular PMO-governed farm inspections, the drug inventory on the farm is often checked for correct labeling and storage.<sup>8</sup> Recently, some farms have been asked to maintain an ongoing drug inventory that can be reconciled with the farm's treatment records.

### The Treatment Record

According to the FDA, the treatment record can be either paper or electronic. No matter the form, treatment records must be kept for 2 years after the animal leaves the dairy farm. In order to be a complete record, it must contain:

- The ID of animal. This also mandates that all animals on the farm be uniquely identified.
- Date of therapy.
- The condition being treated.
- The product used.
- The dosage used.
- Route and location of administration.
- The earliest date animals are cleared of violative residues for milk and meat.
- For paper records, the identification of the person administering the treatment.<sup>8</sup>

Veterinarians should also consult their state's practice act, as

there may be additional requirements put forth by individual states for protocols, labels, and record keeping.

### Conclusions

Violative residues in meat of cull dairy cattle occur at a much higher rate than for cull beef cattle. Many of these problems occur because people try to dump their problems into the cull market instead of alternative solutions such as humane euthanasia. As the industry gathers more information about treatment procedures and as the consumer becomes savvier about the source and safety of their food, increased scrutiny will develop for our clients. Development of treatment protocols and residue prevention protocols allow the herd veterinarian to undertake conversations about prudent drug use on farms, to help their clients develop realistic expectations following treatment, and to develop monitoring programs to track the success (or lack thereof) of herd treatment programs.

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