Causes of drug residues in meat and milk

Drug residues in meat and milk are caused by a variety of contributing factors. Any kind of extra-label usage of a veterinary drug may result in a residue being found in either milk or meat from a treated animal. Examples of this might include changing the dosage or route of administration from stated label instructions, or giving a drug to a lactating animal that is intended only for use in non-lactating animals.\(^1\) When a drug is used extra-label, failure to adjust the approved withdrawal time and follow through with it can result in a residue violation. Some of the top drugs for residues in both meat and milk are: penicillin, sulfa drugs, and flunixin.

Each of these drugs made it to the top of residue list for different reasons, and will be discussed in order to highlight some of the ways in which education can further reduce the incidence of residue violations.

Penicillin stands out far above any other drugs as a major source for violations in meat and milk. Because it is easily accessible to producers without the need for a prescription and is commonly used in an extra-label manner, maintaining adequate withdrawal times can be a problem for some producers. According to the Animal Medicinal Drug Use Clarification Act (AMDUCA), extra-label usage is only permitted when directed by a veterinarian, and only when a valid Veterinarian/Client/Patient Relationship (VCPR) has been established.\(^2\) This is especially important in the case of penicillin, because while the label dosage is 6,600 U/kg IM, it is commonly recommended by veterinarians to administer three to five times the label dose and/or administer SQ, necessitating an increased withdrawal period.\(^3\)

For example, if a dose was given to a dairy cow at 24,000 U/kg IM, the recommended milk withdrawal would increase from 2 days to 5 days and the meat withdrawal for that animal would increase from 10 days to 14 days.\(^4\) Changing the route of administration to SQ is also off-label and drastically alters the amount of time the drug remains in the body. As long as the injection site volume is 20mL or less, levels of the drug attained in the blood are comparable, but elimination from the injection site and from organs and milk can be highly erratic. For this reason, it is recommended that milk and urine be tested before culling or adding her milk back to the bulk tank.\(^5\)
Being responsible for about half as many violations as penicillin, sulfa drugs like sulfadimethoxine (SDM) and sulfamethazine (SMZ) tend to make their way into the food supply because of confusing surrounding the uses for the various versions of the drug that are available.\textsuperscript{6} Because of concerns related to carcinogenic potential in humans, any use of SMZ is explicitly prohibited in lactating dairy animals over 20 months of age and use of any sulfonamide in cattle in an extra-label fashion is prohibited.\textsuperscript{7} As a class of drugs that is available for purchase without veterinary oversight, it isn’t hard to imagine that a dairy producer might accidentally purchase SMZ boluses labeled for beef cattle instead of the SDM boluses which are labeled for lactating dairy animals. Or perhaps because SDM is labeled for treating shipping fever complex, it is administered to beef animals at a holding facility in between transport from farm of origin to slaughter and the seven day meat withhold is inadvertently overlooked.\textsuperscript{8} In addition, SMZ has high oral bioavailability and a long half-life, making it even more likely to be discovered during residue testing.

The concept of half-lives is the basis for estimating withdrawal times for extra-label usage. Under labeled conditions, the withdrawal time is usually between five and ten half-lives (when 96.88\% and 99.9\% of a drug has been eliminated, respectively) depending on the maximum tolerance of a drug that is allowed by the Food and Drug Administration (FDA). If a veterinarian recommends doubling the labeled dose, the withdrawal time is simply increased by 10-20\% to accommodate an additional half-life worth of drug. When the estimation gets complicated is when a drug is being used to treat a disease process that it is not labeled for. Different disease processes can have the effect of lengthening the half-life of a drug unpredictably. When a half-life is increased, the effective withdrawal time can be drastically longer than the label indicates, leading to a residue violation if the animal is culled before clearing the drug.\textsuperscript{9} For this reason, the FDA directs that carcasses which appear to have evidence of a disease process be targeted for residue testing.

Flunixin meglumine is the third most common drug found in meat and milk and is a prime example of how route of administration can alter withdrawal time. The labeled dosage is no more than 2.2 mg/kg per twenty-four hours with a withdrawal of 36 hours for milk and 4 days for meat when administered IV. When given IM, withdrawal time increases to 72 hours for milk
and 30 days for meat. Research suggests this may be because the IV formulation contains propylene glycol, which is irritating to muscle tissue. The damage to muscle tissue at the injections site is thought to impair absorption and clearance of the drug from the tissue, increasing the half-life significantly but not predictably.\(^\text{10}\) The most likely reason for IM injection is that producers fail to read the label before administration or are unaware of how pharmacokinetics are altered by route of administration and choose to give the injection IM vs IV simply based on convenience.\(^\text{11}\)

Another reason that flunixin is such a common source for residues is rampant non-judicious use. In one survey of food animal veterinarians, NSAIDs were second only to antimicrobials in terms of drug usage in dairy cows. This is consistent with the fact that cull dairy cows are the most likely class of animals in which a tissue residue violation is detected at slaughter. This could be due to concurrent use of IM flunixin when treating a sick cow with an antimicrobial, but failing to adhere to the extended withdrawal period for flunixin before shipping to slaughter. Another possibility is that because flunixin is highly efficacious and easy to use, some producers may be using the drug to mask symptoms so that cull dairy cows will pass ante-mortem inspection and fetch them a higher price than if the animal appeared sick and was not allowed to be sold for human consumption.\(^\text{12}\)

Keeping drug residues out of the human food supply is a constant challenge because of the many players involved. Based on the examples presented, it is easy to appreciate the complexity of establishing appropriate withdrawal recommendations. In addition to being directed by law, this is why it is important for producers to work closely with their veterinarian to ensure that they are creating a valuable product for their bottom line and a safe product for consumers. Education of veterinarians and producers about proper drug usage has had and continues to have the biggest impact on reducing residues. In the case of bulk tank samples, the U.S. has been successful in reducing the number of residue violations by about 80% since 1995.\(^\text{13}\) With continued efforts toward education and awareness, it is likely that we can reduce the number of violations even further.
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