How do violative residues happen in swine?

Knowing how violative residues happen in swine involves understanding the following subject areas.

1. **Pharmacokinetics.** How drugs move through the body.

2. **Withdrawal times.** How are they determined? How could management practices or disease alter withdrawal times?

### 1. Pharmacokinetics: How drugs move in the body

The term used for describing how drugs leave the body is elimination half-life ($T_{1/2}$). This term describes the time it takes for the concentration of a drug in serum or tissue to decrease by 50%. The $T_{1/2}$ observed in serum changes in relation to 3 factors.

- Rate of **absorption** from the site of administration
- **Distribution** of the drug from the blood out into tissue
- Rate of **elimination** from the blood

In the drug approval process, estimates of tissue $T_{1/2}$ are used to calculate slaughter withdrawal times. However, the serum $T_{1/2}$ may also serve as an indicator of elimination from tissues because the serum and tissue concentrations are related. This relationship may vary considerably for different drugs, so it is very important to know the facts before estimating tissue withdrawal times based on serum elimination characteristics. This is one reason why a veterinarian is required to be involved any time a drug is used in a manner different from label directions.

This discussion focuses on administration routes of oral (PO), intramuscular (IM), and subcutaneous (under the skin, abbreviated SC or SQ).

**Absorption** - If a drug is given in the vein, then it is instantly 100% available to the body, and the rate of elimination from the body will be determined by the balance between distribution and elimination. However, in swine the most common routes of administration are IM and PO. A drug given by these routes must first be absorbed into the blood before the processes of distribution and elimination can begin.
Penicillin G and oxytetracycline are examples of drugs where different formulations for injection result in different elimination $T_{1/2}$ characteristics. Long-acting oxytetracycline formulations maintain longer blood concentrations by being more slowly released from the site of injection than conventional formulations. For penicillin G, the apparent serum $T_{1/2}$ is shortest for procaine penicillin G and longest for "long-acting" penicillin G. For both oxytetracycline and penicillin G, the absorption of drug from the injection site is slower for the long-acting formulations, resulting in a longer period of available replacement for drug that is eliminated from the bloodstream.

**Distribution** is the process of a drug moving from the blood into tissues such as muscle and fat. When a drug has been distributed out to the tissues from the bloodstream, it is not exposed to the organ(s) of elimination, and therefore is going to stay in the body. Once equilibrium is reached between the bloodstream and tissues, drug will diffuse back from the tissues as the bloodstream concentration drops due to elimination from the body. If a very small proportion of the drug is present in the bloodstream as compared to the tissues, the serum $T_{1/2}$ will tend to be longer due to only a small fraction of the drug being exposed to the organ(s) of elimination.

**Elimination** of a drug from the body occurs when the drug is exposed to the organ(s) responsible for elimination. This will usually be the liver and/or kidney for drugs used in swine production. A constant percent of the drug exposed to the elimination organ(s) is eliminated per unit time for most drugs used in swine. Therefore, the amount of drug eliminated from the body is dependent on the speed of the elimination process and how quickly the drug is exposed to the organ(s) of elimination over time.

**Relationship between absorption, distribution, and elimination.**

This figure illustrates how a drug that is slowly released from the injection site, or that is sequestered out in the tissues, will be more slowly eliminated from the body. This is because the organ(s) of elimination only clear the drug from the bloodstream.
2. Withdrawal times

Withdrawal times are determined for edible, target tissues by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) during the drug approval process. These target tissues are most commonly the liver or kidney. As the primary organs of elimination, they will typically display a residue for the longest time. During withdrawal studies, the target organ is determined and animals are sampled at various times after drug administration is stopped. Statistical procedures are used to determine when almost every animal given the drug would be below the drug tolerance concentration in the target organ. A muscle tolerance has also been established for some drugs. For those drugs for which only a kidney or liver tolerances has been established, if a violative residue is found in the target organ, the whole carcass would need to be discarded. On the other hand, for the drugs for which a muscle tolerance has been established, even if a violative residue is found in the kidney or liver, if a violative residue is not found in the muscle, the carcass would not need to be discarded. The disposition of such carcasses can not be determined until testing of liver, kidney, and muscle is complete.

It is important to realize that withdrawal times are based on the target organ falling below a tolerance, rather than to an absence of detectable drug residue. A tolerance concentration for a drug is determined by using an acceptable daily intake of the drug for an average sized person and an estimated annual consumption of the target organ. The acceptable daily intake is calculated using toxicology study data combined with safety factors.

Violative residues (above the tolerance concentration) may be caused by the following factors.

*Failure to observe an appropriate withdrawal time*

- Records and age-based treatment protocols are essentials for violative residue avoidance.

*Regimen changes for an approved drug*

- **Increasing the dose** is a common cause of residue violations. An increased amount of drug in the body takes longer to eliminate.
- **Increasing the volume of drug per injection site** may slow the release of drug from the site, thereby slowing exposure of the drug to the elimination processes.
- **Administering the drug more frequently than specified on the label** will cause the drug to accumulate to higher levels in the body because more drug is still present from the previous doses when each new dose is given. This has the same effect as increasing the dose.
- **Increasing the duration of drug administration** may also increase the amount of drug in the body, the same as increasing the dose.
- **Use of a drug for an indication other than indicated on the label** may prolong the time needed for drug elimination. Different diseases and different ages of animals may alter drug absorption, distribution, or elimination characteristics.
Extralabel use of a drug without an appropriate withdrawal time

- Use of a drug other than as specified on the label is legal only within the confines of a valid Veterinary-Client-Patient Relationship (VCPR).
- Drugs without an established withdrawal time in a species do not have a tissue tolerance concentration established for that species. Therefore, any amount of the drug detected would be violative.
- If adequate scientific evidence does not exist to establish an appropriate withdrawal time, then the animals receiving the drug may not be used for food. The veterinarian in the Veterinary Client Patient Relationship (VCPR) is responsible for determining the withdrawal time and assuring that the requirements of the Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations are met. (Refer to Good Production Practice #4 in the Pork Quality Assurance Handbook for a definition of a valid VCPR)
- Relying on serum or plasma T1/2 estimates to establish an extralabel withdrawal time may underestimate the time the drug is present in edible tissue. Some tissues may “bind” or hold the drug longer than serum disappearance curves would indicate.

Alteration of elimination processes

- The studies for establishing withdrawal times are conducted in healthy animals of the age for the conditions on the label. Due to the statistical procedures used to construct withdrawal times, there is usually enough leeway to account for minor disease alterations encountered in label applications.
- Very young and very old animals may have slower elimination processes.
- Animals with severe dehydration, impaired blood circulation, or diseases that directly affect the liver or kidney may have prolonged tissue concentrations of drugs.

Summary

The time required for elimination of a drug from the body is dependent on the processes of absorption, distribution, and elimination. Changes in any of these processes may affect how long the drug stays in the body. Slaughter withdrawal times are determined during drug approval based on statistical evaluation of concentrations in target organs of healthy animals. Extralabel use of a drug in food animals is legal only within the context of a valid veterinary-client-patient relationship (VCPR). The veterinarian is responsible for determining an extended slaughter withdrawal time when extralabel drug use is necessary. Producers and veterinarians must plan ahead and adhere to quality assurance practices to avoid violative residues in pork products.