FARAD Digest

Primer on estimating withdrawal times after extralabel drug use

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Passage of AMDUCA and its implementation by the FDA-Center for Veterinary Medicine has allowed food animal veterinarians to use drugs legally in an extralabel manner as long as an appropriately extended **withdrawal time (WDT)** is followed. Providing these extended WDT for specific drug classes has been the main focus for the FARAD Digest series in the *JAVMA*.[1] But, what is the basis of these extrapolations and how can veterinarians be reasonably assured that a WDT selected for a specific extralabel indication is appropriately extended? The purpose of this article is to address these pivotal questions and to illustrate the scientific basis involved in deriving extended WDT.

What is a WDT?

The concept of a WDT is deeply rooted in regulatory policies and definitions. It is an integral part of the approval process necessary for developing a veterinary pharmaceutical for use in food animals. In general terms, a WDT is that interval required after dosing for tissue concentrations of a drug or its metabolite to deplete to less than a specific concentration that has been established as being safe for human consumption. Thus, there are 2 components needed to determine WDT. The target tissue concentration established as safe by the appropriate regulatory authority, defined as the **tolerance (TOL)** in the United States, and the time it takes for a drug in a specific tissue to deplete to the TOL. Outside of the United States, the regulatory target often is the **maximum residue level (MRL)**, which is conceptually similar to TOL, except it is based on different food safety considerations (eg, safety factors, food consumption factors). The WDT is then defined as the time it takes for 99% of the animals to deplete the drug given at a label dosage to less than the established TOL (Fig 1; estimated with a 95% level of statistical confidence). These concepts also apply directly to estimating milk WDT.

The primary pharmacologic determinant of a WDT is the administered dose and the rate of depletion

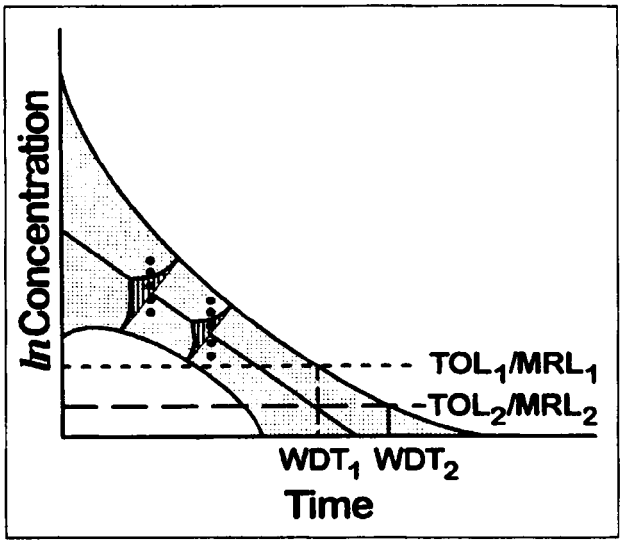

Figure 1—Relationship of drug decay in a specific tissue to the established tissue tolerance (TOL) or maximum residue level (MRL) and resulting withdrawal times (WDT). Notice that the WDT established is based on drug decay in the upper 99 percentile of the animal population (estimated with a 95% statistical confidence) and not on the mean rate of tissue depletion often reported in pharmacokinetic studies. This figure also illustrates the problem of using the WDT (eg, WDT_1) based on a target concentration (eg, TOL_1 or MRL_1) in one country to extrapolate to a drug registered in a different country whose WDT (eg, WDT_2) is based on a different regulatory end point (eg, TOL_2 or MRL_2). The TOL is applicable for a drug approved in the United States, and the MRL is applicable for a drug approved in another country.

of the drug in the tissue. Analysis (Fig 1) is repeated for all critical tissues (eg, muscle, liver, kidney), which usually have different TOL and MRL depending on food consumption factors. The tissue with the longest WDT (because of the slowest depletion or lowest TOL) determines the WDT for the drug in that species. The primary determinant of the WDT is the kinetics of drug depletion, which is represented by the mean depletion time. These are the data most often reported in the literature when a pharmacokinetic study has been conducted. In contrast, variability between animals, reflected in the width of the statistical distribution about the mean tissue depletion rate (Fig 1), determines the label WTD.

A few points must be addressed in this scenario. First, the WDT is heavily weighted by the rate of drug depletion in the target tissue, a pharmacokinetic parameter correlated but not equivalent to the drug's kinet-

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ics in plasma. The nature of the correlation is dependent on the complexity of the drug's pharmacokinetic properties. For example, for some sulfonamides, the rate of depletion in plasma and target tissues may be parallel, making extrapolations relatively straightforward. In contrast, aminoglycoside antibiotics have complex tissue kinetics, which are not reflected in the plasma drug concentration versus time profile. For some slow-release (eg, extended duration) medications, the rate of drug depletion actually is controlled by the dosage formulation used, making extrapolations across different formulations difficult. Second, many drugs are metabolized by the body, and the TOL is then determined by the concentration of the so-called marker residue, which is analyzed in the tissue and is used to track overall drug depletion. The pharmacokinetic profile of such a drug often is complex. Finally, there is a large statistical safeguard built into the regulatory system that already compensates for slight errors in dosing, between-individual differences in tissue depletion rates, and other clinical factors. Thus, small errors in dosing or adherence to WDT or alternatively mild disease states that alter drug disposition are accounted for in studies that determined WDT.

Extralabel WDT adjustment—When a veterinarian makes the clinical decision to administer an extralabel dose of drug, how much should the WDT be extended to comply with AMDUCA and ensure that animals being treated are void of violative tissue residues? The following 2 conditions of extralabel use must be considered: increasing the dose for a disease covered by the label or using a normal dose for a disease not covered on the label. Of course, some combination may be present.

The simplest scenario is when a higher dose is used for a label disease condition. In this case, pharmacokinetics is on the side of the veterinarian.[2] To understand this, one needs to be familiar with the concept of half-life, which is the time required for 50% of a drug to be eliminated from an animal or tissue. This is scientifically based on the principles of linear, first-order decay as reflected by the fact that the plot of drug depletion (Fig 1) is a straight line when plotted on a logarithm concentration versus time plot (semilog plot). When there is linear decay, the concept of half-life is operative (Table 1).

After 10 half-lives have passed, 99.9% of the drug has been eliminated (or if discussing a tissue, 99.9% of the drug has been depleted), and from a 10-g initial dose, only 0.098 g (98 mg) of drug is remaining. The typical therapeutic antibiotic produces a peak plasma concentration of 10 μg/ml. Assuming homogeneous distribution throughout the body, the peak tissue concentration would be 10 μg/g or 10 PPM. If the process (Table 1) is repeated for this tissue starting at 10 PPM, after 10 half-lives, only 0.001 PPM or 1 PPB would remain in the tissue. If this scenario reflected the label dose and the TOL was 1 PPB (assuming no metabolism), the WDT would be 10 half-lives. If the drug had a short half-life, such as 2 hours, the WDT may be only 20 hours (2 hours X 10 half-lives), which under current regulatory guidelines would be rounded up to 1 day. In contrast, if the relevant half-life was 1 day for a second drug, then the WDT would be 10 days. In this simplified presentation, we are using a working half-life that reflects the slowest depleting 1% of animals given the drug. One can now appreciate the logic required to estimate withdrawal intervals (WDI) for extralabel drug use.

Table 1—Relationship of half-life to amount of drug in an animal after dosing

No. of half-lives	Drug remaining (g)	% Drug eliminated
1	50.0	50.0
2	25.0	75.0
3	12.5	87.5
4	6.25	93.75
5	3.125	96.88
6	1.562	98.44
7	0.781	99.22
8	0.390	99.61
9	0.195	99.80
10	0.098	99.90

Let us assume that the label dose is doubled. How long should the half-life be extended? In this scenario, our starting dose would now be 200 g, and thus after only 1 more half-life, we would be back to a 100-g dose. The WDT would only be extended by a single half-life (2 hours) to 22 hours and would remain 1 day for the first drug with a half-life of 2 hours and would become 11 days for the second drug for which the half-life is 1 day. In contrast, what happens if the extralabel use involves administering the drug to a diseased animal whose pathophysiologic state results in a doubling of the tissue half-life? Now, the WDT should be 40 hours in the first case, which would require a 2-day WDI and 20 days in the second case. One can appreciate that the impact of a severe disease process on WDT is greater than an increase in dose. This is consistent with surveys conducted to determine the cause of violative residues that often identify culled animals as being problematic (Fig 2; Table 2).

The final scenario is when the drug is approved in 1 species but is used in another. This situation becomes much more complicated because of the necessity to extrapolate drug disposition parameters across species. Techniques are available to do this; however, their direct application to determining WDT has not been validated. The best rule of thumb to follow is that, in general, half-lives are shorter in a smaller species. Using the WDT established in a larger species (eg, bovine) as the WDT for a smaller species (eg, ovine) is conservative and should not result in violative residues unless the drug is metabolized differently in the 2 species. Going the other way (small to larger species) is problematic at this point.

What is the take-home lesson for a veterinarian faced with establishing a WDT for extralabel use? We can assume that the label WDT represents approximately 5 to 10 tissue half-lives, and if a dose is doubled, then the WDT should only be increased by an additional 10 to 20%. If the diagnosis suggests a severe disease condition not on the drug label, which in the veterinarian's clinical judgment might prolong drug depletion, then the WDT should be lengthened.

One approach to estimating extralabel WDT is to use the WDT established in a foreign registered prod-

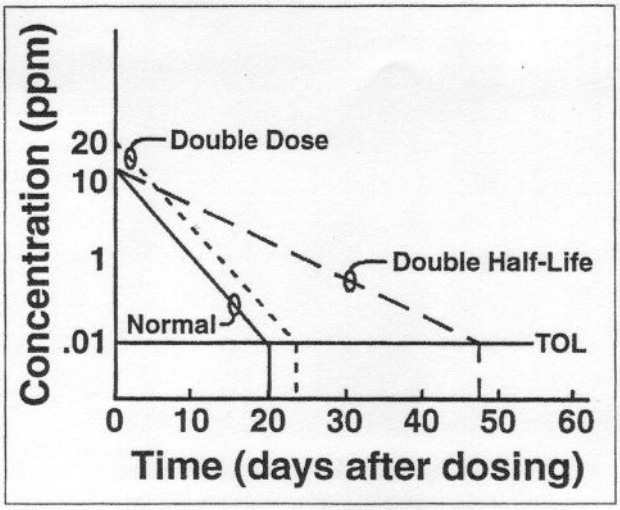

Figure 2—Relationship between time required to deplete drug to a specific target concentration (eg, TOL) when the dose is doubled versus when the underlying tissue half-life is doubled, compared with normal depletion, which is reflected in the label WDT.

Table 2—Effect of changing half-life versus dose on estimated withdrawal times (WDT)

Dose	Half-lives	No. of half-lives until withdrawal	Estimated WDT
100 g	2 h	10	20 h (1 d)
100 g	1 d	10	10 d
200 g	2 h	11	22 h (1 d)
200 g	1 d	11	11 d
100 g	4 h	10	40 h (2 d)
100 g	2 d	10	20 d

uct (same drug) that has the higher dose or clinical condition reflecting the intended extralabel use. This is problematic because the foreign WDT, even for the same pharmaceutical formulation, is based on an MRL rather than a US-FDA TOL. These end points usually are different. This can be seen when the US WDT_1 is based on TOL_1, whereas the foreign WDT_2 is based on MRL_2. It is incorrect to identify a foreign product with a higher dose that matches the anticipated extralabel dose and then just use the foreign WDT as the extralabel WDI.

The FARAD Approach

The discussion given is, by necessity, a simplification because a precise estimate of WDT requires knowledge of how the WDT was established in the label preparation (eg, dose, dose formulation, TOL, disease state, age). The FARAD refers to an estimated WDT as the WDI to avoid confusion with the legally established label WDT. When one extrapolates a WDI using data from a different US product registration, the principles given are appropriate because the label WDT is based on a US TOL or safe concentration. The adjustment is then based on dose, formulation, and disease states. If the source of the data is a foreign approval, we must transform these data by normalizing the MRL to a US-FDA TOL. The FARAD is developing a novel approach to accomplish this task by normalizing to a provisionally acceptable residue, a unit similar in concept to a safe concentration that corrects for US versus foreign food safety philosophies. We acknowledge that foreign data might be the best source of information from the perspective of food safety, analytical validity, and statistical rigor, because it reflects the upper limits of a confidence interval in a population of animals.

Whatever the source of the regulatory data, FARAD is developing algorithms to normalize depletion data across products, using the concept of an **effective residue half-life (ERH)** for the drug in a specific tissue. The ERH is based on the pharmacokinetics of the drug in the animal and tissue coupled with the statistical variance model inherent to US regulatory establishment of a WDT. This then allows doses to be extrapolated across similar pharmaceutic formulations on the basis of the administered extralabel dose.

All data relevant for these calculations are incorporated in the FARAD data files and will be linked by software (patent pending) to generate the extrapolated WDT. Appropriate field assays are identified to allow veterinarians to confirm these estimates in the animals treated. In cooperation with veterinarians who use FARAD in the future, FARAD would like to validate estimated WDI by analyzing tissue samples taken from animals following extralabel use. This WDI validation would be accomplished using population pharmacokinetic statistical approaches. Veterinarians would benefit from this approach because the WDI for extralabel use would then be case validated and would constitute a proactive approach to guarantee food safety to the general public.

References

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