The tetracyclines most commonly used in animals are chlortetracycline, tetracycline, oxytetracycline, doxycycline, and minocycline, with oxytetracycline being the most broadly used. Despite its popularity in the United States, this antibiotic is not officially approved for use in all domestic species or in all possible clinical situations. Thus, extralabel use of oxytetracycline in food animals is common, and appropriate withdrawal times may not correspond with the ones established for label use.

Pharmacodynamic and Pharmacokinetic Properties

Oxytetracycline can be administered IV or IM, but the oral route is often preferred for treating populations of food animals. Absorption of oxytetracycline from muscular tissue and the gastrointestinal tract is generally good. Metabolism of oxytetracycline is negligible (Table 1). Approximately 60% of the dose is eliminated in urine via glomerular filtration, and the other 40% is eliminated in feces. Enterohepatic circulation has been described for practically every species treated, with up to 20 times the plasma concentration of oxytetracycline in the bile. This process tends to prolong drug residues in tissues.

Certain diseases may affect the disposition of oxytetracycline. In pneumonic pigs treated orally with oxytetracycline, a great interindividual variation in the plasma concentration was found. The ultimate consequence of these differences may be increased variability in tissue residue depletion and, consequently, the need to increase withdrawal times to avoid violative residues.

Extralabel Use of Oxytetracycline

When using oxytetracycline in an extralabel manner, all requirements of the recently enacted AMDUCA legislation must be followed. According to this legislation, extralabel use of oxytetracycline, or any other drug, in animal feed is forbidden.

Extralabel use of injectable oxytetracycline products in cattle—Label withdrawal times range between 15 and 22 days for short-acting, and 28 days for long-acting, formulations at dosages of 6.6 to 11.0 mg/kg of body weight/d (3 to 5 mg/lb/d) administered IV or IM. The tolerance for oxytetracycline in edible tissues of cattle is 0.1 µg/g of tissue (100 ppb). Recently, the FDA/Center for Veterinary Medicine established a "safe level" of 30 ppb of oxytetracycline in milk. This "safe level" does not represent an official tolerance level, but rather is a guide to assess whether a potential public health hazard may arise. At the present time, no injectable products have been approved for use in lactating dairy cows.

In a recent study, a short-acting preparation of oxytetracycline was administered once by 1 of 3 routes: IV, IM, or IU (intrauterine). When oxytetracycline was administered as a single dose, 16.5 mg/kg (7.5 mg/lb), IV, or 11 mg/kg (5 mg/lb), IM, milk from most cows was cleared of oxytetracycline (< 30 ppb) by 120 hours after administration and 156 hours were required for all animals to have residue concentrations < 30 ppb. According to this information and label withdrawal times in foreign countries, parenteral administration (IV, IM) of a short-acting preparation of oxytetracycline at 10 to 20 mg/kg (4.5 to 9.0 mg/lb) would require a minimum 144-hour milk-discard interval. Testing of milk from treated cows is also recommended, because the variability in residue depletion is high, especially when clinical conditions are involved.

In another study in which a long-acting preparation of oxytetracycline (25 mg/kg [11.4 mg/lb], q 24 h) was administered IM twice to postparturient cows with retained fetal membranes, milk residue levels of 400 ppb were detected for > 144 hours. A study of 10 cows that received a single dose (20 mg/kg [9 mg/lb]), IM of a long-acting preparation of oxytetracycline reported a withdrawal interval of 156 hours. According to this

Table 1—Pharmacokinetic variables of oxytetracycline in horses, swine, and cattle

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)*</th>
<th>Route</th>
<th>Vd (L/kg)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses</td>
<td>10.0</td>
<td>IV</td>
<td>0.7</td>
<td>13</td>
</tr>
<tr>
<td>Pigs</td>
<td>10.0</td>
<td>IV</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>Cows (adult)</td>
<td>5.0</td>
<td>PO</td>
<td>1.9</td>
<td>14</td>
</tr>
<tr>
<td>Calves (5 wk)</td>
<td>2.5</td>
<td>IV</td>
<td>1.1</td>
<td>9</td>
</tr>
<tr>
<td>Calves (12 wk)</td>
<td>7.5</td>
<td>IV</td>
<td>2.5</td>
<td>14</td>
</tr>
<tr>
<td>Calves (14 wk)</td>
<td>6.9</td>
<td>IV</td>
<td>1.5</td>
<td>9</td>
</tr>
</tbody>
</table>

*To convert dose to mg/lb, divide by 22.
Vd = volume of distribution.
information, the FARAD recommends a milk withdrawal interval of 168 hours after parenteral administration of a long-acting preparation of oxytetracycline at 20 mg/kg. A milk withdrawal interval of 192 hours could be conservatively extrapolated for use of oxytetracycline at 20 to 30 mg/kg (9.0 to 13.5 mg/lb).

A minimum meat withdrawal time of 35 days should be observed when short-acting formulations of oxytetracycline are administered by injection (IV, IM) at dosages > 20 mg/kg (9 mg/lb). This recommendation is based on results of a study in which volatile concentrations of oxytetracycline persisted in the kidneys and muscle at the injection site for > 19 days after the final dose of a short-acting preparation of oxytetracycline (20 mg/kg) that was administered for 3 consecutive days. The label withdrawal time of 15 to 22 days for dosages of 6.6 to 11.0 mg/kg (3 to 5 mg/lb), every 24 hours, should be increased to 28 to 30 days in animals treated at shortened dosing intervals (as happens when cows are treated for pneumonia). Detectable residue levels of oxytetracycline were found at the injection site for 35 days after administration of 5 mg of oxytetracycline/kg (2.3 mg/lb), IM (combined with another antibiotic), every 12 hours, for 6 days. For long-acting formulations, results of some studies in which single doses (20 to 40 mg/kg [9 to 18 mg/lb]) were administered IM to cattle suggest an extended meat withdrawal time of 30 days. However, different formulations would be expected to result in various tissue depletion profiles.

**Extralabel intramammary use of oxytetracycline in cattle**—Results of a study conducted in healthy cows revealed that a single IU dose of 2 g of oxytetracycline in 500 ml of saline solution/cow yielded milk residues < 30 ppb by 6 days after treatment (in 1/6 cows). The residue levels in the milk of the other 5 cows were less than the FDA safe level of 30 ppb by 96 hours. According to these data and label withdrawal times for oxytetracycline formulations approved in foreign countries, the FARAD recommends a milk discard time of 168 hours for doses up to 2 g. If the dose is increased to 4 to 6 g, the milk discard time should be extended to 192 hours. These milk withdrawal intervals apply only to oxytetracycline administered as an aqueous solution. As always, FARAD recommends testing milk, because individual variation is excessive. On the basis of label withdrawal times in foreign countries, FARAD recommends meat withdrawal intervals of 18 days for a single 1- to 2-g dose, 28 days for a single 3-g dose, and 35 days for a single 4- to 6-g dose.

**Extralabel intramammary use of oxytetracycline in cattle**—The only oxytetracycline formulation approved for intramammary treatment for mastitis is no longer marketed. Studies have shown that following intramammary infusion into 1 quarter, oxytetracycline residues are in milk from untreated quarters. After administration at the label dose (1 to 3 infusions, 12 or 24 hours apart) of the approved preparation that contained 426 mg of oxytetracycline, the label milk discard and meat withdrawal times were 96 hours. Intramammary extralabel use of a different parenteral oxytetracycline formulation at the same dose would require a minimum 96-hour milk-discard interval, followed by milk residue testing. If the dose is doubled, milk should be withheld for a minimum of 120 hours, followed by residue testing. The effects of different formulations have not been studied; thus, this milk discard estimate may not apply to all formulations. Because drugs are readily absorbed from mastitic glands, an extended meat withdrawal interval of 19 days should be observed.

**Extralabel oral use of oxytetracycline in cattle (in water only)**—According to label information for this use of oxytetracycline in other countries and the available literature, a withdrawal time of 14 days for meat and 7 days for milk should be allowed after administration of oxytetracycline hydrochloride in water at a dosage of 20 to 40 g/kg (9 to 18 g/lb), every 12 hours, for 3 to 4 days in adult animals. In preruminant calves, a meat withdrawal time of 21 days after administration at the rate of 30 mg/kg/d (13.5 mg/lb/d) for 4 days should be appropriate.

**Topical application of oxytetracycline products in cattle**—Topical application of oxytetracycline solution (25 mg/ml) in footbaths or sprays to treat hairy foot warts requires no withdrawal time. To avoid milk residues, it is recommended that someone other than the milker do the treating.

**Extralabel use of oxytetracycline products in small ruminants**—Pharmacokinetic studies of oxytetracycline done through the USDA's Minor Use Animal Drug Program indicate that sheep and goats eliminate oxytetracycline faster than cattle after IV and IM administration. Similarly, an interspecies analysis of all FARAD pharmacokinetic data selected oxytetracycline as a "well-behaved" drug amenable to interspecies extrapolation. Therefore, withdrawal times for cows after parenteral administration should be adequate for sheep and goats. For single doses of injectable oxytetracycline (6.6 to 11.0 mg/kg [3 to 5 mg/lb]), FARAD recommends testing milk following a discard period of at least 96 hours. Following multiple doses or high doses, a milk discard time of 144 hours should be observed, followed by residue testing.

Results of a European study revealed that oxytetracycline was detected in milk (sensitivity, 450 ppb) for up to 110 hours in sheep treated once with 420 mg in the right udder half. In the same study, infusion of oxytetracycline into the right udder half resulted in diffusion into milk of the left half for 14 hours. In another study conducted in 8 goats given an oxytetracycline mastitis formulation containing 426 mg of oxytetracycline hydrochloride on 3 occasions 24 hours apart, the drug became undetectable at 108 hours (sensitivity of the method, 0.25 ng/ml or 250 ppb). According to this information, intramammary use of oxytetracycline in small ruminants would require extending the milk discard time to 144 hours.
Voluntary withdrawal period for exported swine—
For swine, it is noteworthy that the National Pork Producers Council recently (August 1996) called for a voluntary 14-day withdrawal period for the use of tetracycline products in feed or water by those producers supplying packers for international markets. This call is exclusively destined to avoid nontariff trade barriers to the sale of US pork products to countries with different levels of tolerance for tetracycline products and is not associated with any food safety issues in the United States or with domestic withdrawal times.

Conclusion
As can be appreciated from this discussion, estimation of extralabel withdrawal times is sometimes inexact because of lack of supportive data. Often, we have used extrapolation strategies based on published drug pharmacokinetic data that have proven to be appropriate in the past. Whenever possible, the veterinarian should attempt to test the animal for the presence of drug on the farm or before slaughter. The FARAD compendium (in its hardcopy version or at the Web sites) should be consulted for selection of approved drugs for these indications and for current tolerances and available field tests for the detection of oxytetracycline residues.

References