

## Extralabel use of penicillin in food animals

Michael A. Payne, DVM, PhD; Arthur Craigmill, PhD; Jim E. Riviere, DVM, PhD;  
Alistair I. Webb, BVSc, PhD

**P**enicillin is the antimicrobial for which consultation is most frequently sought through FARAD and is one of the most commonly detected drug residues in tissue and milk. This article reviews studies related to extralabel penicillin administration and provides recommendations to assist veterinarians in preventing violative residues in tissue and milk.

Allergic reactions to foods containing residue concentrations of penicillin are rare and are almost always dermatologic reactions.<sup>1</sup> There are, however, reports<sup>2,3</sup> of anaphylactic reactions developing after consumption of food containing penicillin residues. Pasteurization only reduces penicillin residues approximately 10% to 20%,<sup>4</sup> and penicillin can persist at concentrations that can adversely affect the growth of starter cultures for fermented dairy products.<sup>5</sup>

### Procaine Penicillin G

Procaine penicillin G is approved for parenteral use in cattle, swine, and sheep. Labeled directions indicate daily IM administration of 3,000 U/lb of body weight for 4 to 7 days. This is equivalent to approximately 6,600 U/kg (1 mL/100 lb) of body weight of a typical 300,000 U/mL formulation. Antimicrobial susceptibility data suggest that to maintain therapeutic tissue and blood concentrations, dosages higher than those indicated on the label may be required for some pathogens.<sup>6</sup>

### IM Administration in Cattle

Label withdrawal times for IM administration of approved PPG formulations in cattle range from 4 to 10 days. In a study<sup>7</sup> involving typically used clinical doses, steers received 5 daily IM treatments of approximately 3.5 and 10 times the US label dose. The cattle were then serially euthanatized at intervals ranging from 1 to 12 days after treatment. The authors calculated withdrawal recommendations on the basis of a 95% confidence interval for the 99th population percentile, to ensure that edible tissue concentrations

---

From the Food Animal Residue Avoidance Databank (FARAD), Environmental Toxicology Extension, College of Agricultural and Environmental Sciences, University of California, Davis, CA 95616 (Payne, Craigmill); FARAD, Center for Cutaneous Toxicology and Residue Pharmacology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Riviere); and FARAD, Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Webb).  
Address correspondence to Dr. Payne.

---

### ABBREVIATIONS

FARAD	Food Animal Residue Avoidance Databank
PPG	Procaine penicillin G
IU	Intrauterine

---

would be less than the tolerance concentration of 50 ppb. On the basis of these data, FARAD recommends 12- and 21-day slaughter withdrawal intervals for up to 5 daily IM doses of 24,000 and 66,000 U/kg (10,900 to 30,000 U/lb), respectively. The observation that larger injection site volumes resulted in higher injection site residues was the basis for a recommendation that injection volumes not exceed 30 mL.<sup>7</sup> Current labels for PPG in Canada and the United States limit injection volume to 15 and 10 mL/site, respectively.

When used in cattle on-label at 6,600 U/kg, IM, PPG products have a milk withdrawal time of 48 hours. In lactating dairy cattle administered 5 daily treatments IM at more than 4 times the label dose, milk residues are detected up to 96 hours.<sup>8</sup> Injection volumes of PPG in that study never exceeded 20 mL/site. FARAD recommends a milk withdrawal time of 5 days for IM doses up to 28,000 U/kg (12,727 U/lb) to ensure that milk residues are less than the FDA's unofficial safe concentration of 5 ppb.

Clearance of penicillin in calves is rapid at birth and increases only slightly during the next 1 to 5 weeks.<sup>9,10</sup> The rapid clearance is consistent with the 7-day slaughter withdrawal time for the only PPG product labeled for nonruminating calves (6,600 U/kg IM, for up to 4 days). For calves older than 2 months treated at extralabel doses, the adult recommendations and caveats are appropriate.

### Oral Exposure to Veal Calves

Calves can be exposed to antimicrobials in utero or postpartum. FARAD recommendations for withdrawal periods for veal calves fed colostrum from cows treated during the nonlactating period can be found in a previous FARAD Digest.<sup>11</sup> It is a common practice to feed calves milk from treated cows (ie, hospital or waste milk). On the basis of the observed 3-hour half-life of penicillin in liver, the tissue with the highest residue concentration, FARAD recommends a 2-day slaughter withdrawal interval for calves consuming 3 mg of PPG/kg (1.36 mg/lb) of body weight in milk, equivalent to approximately 14,000 ppb.<sup>12</sup> The study

also revealed that the length of time calves were fed contaminated milk did not change the withdrawal interval. By use of this and other FARAD data, several states use a program in which waste milk may be fed to calves with a 45-day slaughter withdrawal if a milk sample, diluted 100 times, yields negative results with an FDA-approved assay.<sup>a</sup>

### **IM Administration in Swine**

Procaine penicillin G products are approved in the United States for swine at the same dose as cattle (approx 6,600 U/kg), with label slaughter withdrawals ranging from 6 to 7 days. In a study<sup>13</sup> of typical extralabel doses,<sup>13</sup> market pigs were administered 5 daily IM injections of either 15,000 or 66,000 U/kg (6,818 or 30,000 U/lb; approx 2 or 10 times the label dose). On the basis of the resultant serial slaughter and tissue-testing data, the Canadian government calculated slaughter withdrawal times of 8 and 15 days for the 2 doses, respectively. Because injection technique was critical to ensure that injections were made into rather than between muscle bodies, the authors recommended the use of 18-gauge, 4-cm needles inserted horizontally, caudal to the ear, at the margin of haired and hairless skin, with injection volumes that did not exceed 11 mL/site. FARAD concurs with these withdrawal recommendations.

### **SC Administration**

Some practitioners prefer to inject large volumes of PPG SC to achieve more efficient administration and decrease injection pain and muscle blemishes. Blood concentrations after IM and SC administration of PPG are similar, particularly when injection volumes do not exceed 20 mL/site.<sup>8,14</sup> Larger injection volumes appear to limit maximum attainable blood concentrations and increase the risk of drug entrapment at the site of injection. Subcutaneous PPG administration has resulted in erratic, higher, and more prolonged residues in milk, organs, and injection sites, leading to recommendation against the practice.<sup>7</sup> Similarly, in a case report,<sup>15</sup> milk residues persisted for 18 days in a cow treated with 20,000 U of PPG/kg (9,090 U of PPG/lb), SC, twice per day for 4 days. Practitioners using the SC route of administration for PPG are advised to use injection site volumes of 20 mL and to test the urine or milk of cows prior to culling or being returned to a milking string.

### **Procaine and Benzathine Penicillin Mixtures**

The less soluble benzathine salt of penicillin G is combined with PPG to produce products with slower absorption after injection. Commercial products containing mixtures of benzathine and procaine are labeled for treatment at approximately 4,400 U/kg (2,000 U/lb), SC, with slaughter withdrawal times of 30 days. No such mixtures are approved for use in lactating dairy cattle. Used off-label, such preparations may result in prolonged periods of detectable drug in blood and tissue. FARAD recommends testing milk and urine after extralabel administration because adequate data upon which to base withdrawal recommendations do not exist.

### **Intrauterine Administration**

Penicillin is not labeled for IU administration in food animals. Penicillin can be absorbed from the uterus into systemic circulation and excreted in milk and urine. Most cows treated IU with up to 2 million units of PPG will have detectable milk residues for < 24 hours, but milk residues detected up to 80 hours have been reported.<sup>16-18</sup> Unfortunately, data regarding tissue depletion after IU administration of PPG do not exist. In a limited number of cattle, after IU administration, PPG was not detectable in serum at 10 hours or in urine at 24 hours,<sup>17,19</sup> suggesting that modestly extending the label withdrawal interval to 12 days would prevent violative tissue residues. For doses larger than 2 million units administered IU, testing milk and urine prior to marketing is recommended.

### **Subconjunctival Administration**

Although results of clinical trials have not supported the efficacy of subconjunctival PPG administration for infectious bovine keratoconjunctivitis,<sup>20</sup> FARAD still receives withdrawal requests related to that practice. Examination of milk residues after bulbar subconjunctival injection of 300,000 units of PPG suggests use of a milk withdrawal interval of 22 to 36 hours.<sup>21</sup> Data regarding tissue depletion after subconjunctival administration are not available, but on the basis of the short duration of milk residues and the low dose on a body weight basis, FARAD suggests extending the label slaughter withdrawal to 12 days.

### **Treatment of Sheep and Goats**

Although many PPG products for cattle and swine are also approved for sheep, none are approved for goats. When used IM at the label dose of approximately 6,600 U/kg, all PPG products for sheep have an 8- or 9-day slaughter withdrawal time. Unlike the situation in cattle and swine, data regarding tissue depletion after extralabel PPG administration in small ruminants do not exist. Limited plasma data regarding IV administration of penicillin to sheep and goats suggest that penicillin serum half-lives in those species are similar to or shorter than that of cattle.<sup>22,23</sup> However, after IM administration of only 10,000 to 12,000 U of PPG/kg (4,545 to 5,454 U of PPG/lb), measurable residues in goat milk samples persisted through 72 hours.<sup>24</sup> Sheep milk residues were detectable until 8 days after IM administration of up to 20,000 U/kg.<sup>25</sup> The limited and conflicting data in sheep and goats do not allow FARAD to make recommendations for extralabel withdrawal intervals with confidence. Practitioners choosing to treat off-label with PPG should consider testing milk or urine prior to marketing.

### **Testing for Penicillin**

At any given time after administration, penicillin concentrations in urine will be higher than those in tissues or serum,<sup>12</sup> making urine the sample of choice for preslaughter testing for penicillin. Several authors, in studies that used large numbers of untreated cattle, have found false-positive results of the live animal swab test of 20% to 69%, which indicates the assay's lack of usefulness.<sup>b</sup> One commercially available cow-urine

screening immunoassay, however, has undergone a large masked field trial in cooperation with USDA.<sup>26</sup> In that trial involving 759 slaughter cows, all 6 violative  $\beta$ -lactam tissue residues identified via regulatory assay were predicted by positive urine test results. By use of the regulatory plant screening assay as the gold standard, the observed false-positive rate of the urine assay was 6.3%. The immunoassay requires no incubator or reader and will detect residues of several  $\beta$ -lactam antimicrobials, including penicillin, amoxicillin, ampicillin, cloxacillin, and hetacillin. The test cannot, however, be used to detect cephalosporin antimicrobials.

The FDA approves milk tanker screening assays for meeting certain performance standards.<sup>27</sup> Approved and unapproved tests have been used on-farm to test milk from bulk tanks and individual cows, which often results in higher rates of false-positive results, particularly when applied to the milk of mastitic or postpartum cows. Practitioners will consider economic losses associated with false-positive results when tailoring a testing program to a farm.<sup>28</sup> Producers with high-risk operations, especially those already under regulatory scrutiny, may choose to accept increased costs resulting from implementation of a testing program. Results of studies<sup>29,30</sup> using spiked and incurred residues suggest that some commercial  $\beta$ -lactam assays are adequate for use in sheep and goat milk. As with cows' milk, some false positives can be anticipated.

- 
- a. Roh M, FDA, Pacific Region, Oakland, Calif: Personal communication, 2006.
- b. Payne MA. *Detection of antibiotic residues in the tissues of cull dairy cattle: performance of regulatory assays using ceftiofur as a model*. Doctoral dissertation, Department of Molecular Sciences, School of Veterinary Medicine, University of California, Davis, Calif, 1997.
- 

## References

- Sundlof SF Drug and chemical residues in livestock. *Vet Clin North Am Food Anim Pract* 1989;5:411-449.
- Lindemayr H, Knobler R, Kraft D, et al. Challenge of penicillin-allergic volunteers with penicillin-contaminated meat. *Allergy* 1981;36:471-478.
- Wicker K, Reisman RE, Arbesman CE. Allergic reaction to penicillin in milk. *JAMA* 1969;208:143-145.
- Moats WA. Inactivation of antibiotics by heating in foods and other substrates—a review. *J Food Prot* 1988;51:491-497.
- Suhren G. Influence of residues of antimicrobials in milk on commercially applied starter cultures—model trials. *Kieler-Milchwirtschaftliche-Forschungsberichte* 1996;48:131-149.
- Prescott JF Beta-lactam antibiotics: penam penicillins. In: Prescott JF, Baggot JD, Walker RD, eds. *Antimicrobial therapy in veterinary medicine*. 3rd ed. Ames, Iowa: Iowa State University Press, 2000;105-133.
- Korsrud GO, Boison JO, Papich MG, et al. Depletion of intramuscularly and subcutaneously injected procaine penicillin G from tissues and plasma of yearling beef steers. *Can J Vet Res* 1993; 57:223-230.
- Dubreuil P, Daigneault J, Couture Y, et al. Penicillin concentrations in serum, milk, and urine following intramuscular and subcutaneous administration of increasing doses of procaine penicillin G in lactating dairy cows. *Can J Vet Res* 2001;65:173-180.
- Short CR, White MB, Varma KJ, et al. Clearance of penicillin G in the newborn calf. *J Vet Pharmacol Ther* 1984;7:45-48.
- Musser JM, Anderson KL. Bioavailability and disposition of sodium and procaine penicillin G (benzylpenicillin) administered orally with milk to calves. *J Vet Pharmacol Ther* 2001;24: 161-169.
- Rangel-Lugo M, Payne MA, Webb AI, et al. Prevention of antibiotic residues in veal calves fed colostrum. *J Am Vet Med Assoc* 1998;213:40-42.
- Musser JB, Anderson KL, Boison JO. Tissue disposition and depletion of penicillin G after oral administration with milk in unweaned dairy calves. *J Am Vet Med Assoc* 2001;219:346-350.
- Korsrud GO, Salisbury CD, Rhodes CS, et al. Depletion of penicillin G residues in tissues, plasma and injection sites of market pigs injected intramuscularly with procaine penicillin G. *Food Addit Contam* 1998;15:421-426.
- Papich MG, Korsrud GO, Boison JO, et al. A study of the disposition of procaine penicillin G in feedlot steers following intramuscular and subcutaneous injection. *J Vet Pharmacol Ther* 1993; 16:317-327.
- Krainock RJ. Prolonged milk residue in two cows after subcutaneous injections of penicillin at an extra-label dose. *J Am Vet Med Assoc* 1991;198:862-863.
- Bishop JR, Bodine AB, O'Dell GD, et al. Retention data for antibiotics commonly used for bovine infections. *J Dairy Sci* 1984; 67:437-440.
- Miller HV, Kimsey PB, Kendrick JW, et al. Endometritis of dairy cattle: diagnosis, treatment and fertility. *Bovine Pract* 1980; 15:13-23.
- Haaland MA, Manspeaker JE, Moreland TW. Antibiotic residues in milk after intrauterine infusion. *Vet Med Small Anim Clin* 1984;79:382-386.
- Righter HF, Mercer DH, Kline DA, et al. Absorption of antibacterial agents by the bovine involuting uterus. *Can Vet J* 1975; 16:10-15.
- Allen LJ, George LW, Willits NH. Effect of penicillin or penicillin and dexamethasone in cattle with infectious bovine keratoconjunctivitis. *J Am Vet Med Assoc* 1995;206:1200-1203.
- Liljebjelke KA, Warnick LD, Witt MF. Antibiotic residues in milk following bulbar subconjunctival injection of procaine penicillin G in dairy cows. *J Am Vet Med Assoc* 2000;217:369-371.
- Bengtsson B, Jacobsson SO, Luthman J, et al. Pharmacokinetics of penicillin-G in ewes and cows in late pregnancy and in early lactation. *J Vet Pharmacol Ther* 1997;20:258-261.
- Schadewinkel-Scherkl AM. Passage of benzylpenicillin through the blood-milk barrier—studies on active transport, in *Proceedings*. Eur Assoc Vet Pharmacol Toxicol 5th Cong 1991; 129-130.
- Zeng SS, Escobar EN, Brown-Crowder I. Evaluation of screening tests for detection of antibiotic residues in goat milk. *Small Rumin Res* 1996;21:155-160.
- Molina A, Molina MP, Althaus RL, et al. Residue persistence in sheep milk following antibiotic therapy. *Vet J* 2003;165:84-89.
- Geisberg M. Meatsafe beta-lactam antibiotic residue test: a new tool for residue management, in *Proceedings*. 136th Annu Meet Am Vet Med Assoc 1999;518-519.
- FDA Center for Food Safety and Nutrition Web site. Beta lactam test methods for use under appendix N. Available at: [www.cfsan.fda.gov/~ear/m-a-85.html](http://www.cfsan.fda.gov/~ear/m-a-85.html). Accessed Jun 7, 2006.
- Slenning BD, Gardner IA. Economic evaluation of risks to producers who use milk residue testing programs. *J Am Vet Med Assoc* 1997;211:419-427.
- Althaus RL, Torres A, Montero A, et al. Detection limits of antimicrobials in ewe milk by delvotest photometric measurements. *J Dairy Sci* 2003;86:457-463.
- Zeng SS, Hart S, Escobar EN, et al. Validation of antibiotic residue tests for dairy goats. *J Food Prot* 1998;61:344-349.