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FARAD Digest

Update on withdrawal intervals following extralabel use of procaine penicillin G in cattle and swine

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Extralabel drug use (ELDU) is defined as the use of an FDA-approved medication in a manner that differs from what is provided on the label of the medication.[1] Administration of the medication to a different species or at a different dose, volume, route, duration, indication, or frequency than indicated on the label is considered ELDU. Extralabel drug use also requires an extended withdrawal period to avoid violative residues, and practitioners can get advice on withdrawal intervals (WDIs) following ELDU from the Food Animal Residue Avoidance and Depletion Program (FARAD). Penicillin is one of the most commonly used medications to treat disease in food-producing animals across the globe.[1,2] However, it was approved over 40 years ago, and in the US, the current FDA-approved label dose (6,600 U/kg [3,000 U/kg]) is not consistent with current clinical practice. Globally, the dose of penicillin utilized has been changed in order to achieve the desired clinical effect. The Canadian label dose has been increased to 15,000 U/kg in swine and 21,000 U/kg in cattle. In the UK, the label dose is 8,000 to 10,000 U/kg for both swine and cattle. When an antimicrobial susceptibility test is performed, the penicillin dose used by the Clinical and Laboratory Standards Institute (CLSI) to determine susceptible breakpoints for bacterial pathogens is 22,000 U/kg IM for cattle and 33,000 U/kg IM for pigs.[3] According to FARAD submissions, as of January 2021, penicillin is 1 of the top 25 drugs for which WDIs are requested following ELDU. Those submissions were prompted by the use of an above-label dose to achieve clinical effect or administration of a greater-than-recommended volume at an injection site or by an unlabeled route. Such deviations from the approved label alter the known meat and milk WDIs for both cattle and swine. Given that above-label doses of penicillin are required to achieve clinical efficacy, a new FARAD Digest regarding the development of new WDIs for penicillin following ELDU was needed. The purpose of this digest is to describe how common ELDU of penicillin alters WDIs for both cattle and swine.

Procaine penicillin G and penicillin G benzathine

Penicillin G is a β-lactam antibiotic that inhibits bacterial cell wall synthesis by preventing the complete synthesis of peptidoglycan, a critical component of the bacterial cell wall.[4] Following exposure to penicillin G, susceptible bacteria cannot maintain the correct intracellular osmotic gradient, leading to cell lysis and death. Thus, penicillin G is classified as time dependent and bactericidal. The spectrum of activity of penicillin G includes gram-positive and anaerobic bacteria. Some gram-negative bacteria, such as *Pasteurella spp* and *Mannheimia haemolytica* are also susceptible. Resistance to penicillin G occurs through 3 main mechanisms: decreased uptake, altered target, or drug modification primarily through β-lactamase activity. Unfortunately, all bacteria of the Enterobacterales order and β-lactamase–producing staphylococci are resistant to penicillin G.

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Because penicillin is a time-dependent antimicrobial (time > minimum inhibitory concentration [MIC]), the plasma free-drug concentration (ie, unbound drug) must be maintained above the MIC for at least 40% to 50% of the dosing interval to achieve clinical efficacy.[4,5] This can directly affect how frequently the drug needs to be administered. Drug formulation also affects the frequency of drug administration. Penicillin formulations for food animals contain either procaine penicillin G (PPG) alone or in combination with penicillin G benzathine. Procaine is a sodium channel blocker added to the formulation to decrease pain on injection. Procaine penicillin G is an aqueous suspension with slow absorption from the injection site; consequently, the peak plasma drug concentration is generally not achieved until 12 to 24 hours after IM or SC administration. Prolonged absorption of PPG from the injection site results in a flip-flop pharmacokinetic effect, whereby the absorption rate, rather than the elimination rate, is the main influence on the plasma concentration profile.[6,7] The slow absorption of PPG is caused by poor aqueous solubility when the suspension is administered by the IM or SC route.

The primary difference between PPG and penicillin G benzathine is the more highly insoluble nature of penicillin G benzathine. It is absorbed from the injection site at a much slower rate than PPG, resulting in low and prolonged systemic concentrations of penicillin. Penicillin G benzathine is never administered alone; all veterinary formulations are formulated as a 50:50 mixture of PPG and penicillin G benzathine. The slow absorption rate of penicillin G benzathine increases the risk for violative drug residues in food-producing species. Because of this increased risk of violative drug residues and subtherapeutic drug concentrations, the use of penicillin G benzathine is not recommended.

Current label directions for use of PPG in cattle and swine

The label of each drug approved by the FDA for use in food-producing animals includes a withdrawal time (WDT), which is the period during which products (eg, meat and milk) from treated animals cannot be used for human consumption following use of the drug in accordance with its label.[8] A WDI is a scientifically estimated withholding period following ELDU.[8] The FARAD-recommended WDI is always longer than the WDT because of the potential for individual variation not included in estimations, as well as to comply with the extended WDI following ELDU required by AMDUCA.

Currently, there are 8 and 4 PPG products approved by the FDA for parenteral administration in cattle and swine, respectively.[9] In cattle, PPG is labeled for the treatment of pneumonia caused by *Pasteurella multocida*. Depending on the PPG product used, the WDT for meat can range from 4 to 14 days, whereas the WDT for milk is more consistent at 48 hours. The variation in the WDTs for meat are likely the result of differences in the formulations or injection site reactions induced by the various PPG products.[8] In swine, PPG is labeled for treatment of *Erysipelothrix rhusiopathiae*, and WDTs for meat range from 6 to 7 days depending on the product used.

Why are the current PPG label doses ineffective?

For most FDA-approved PPG products, the current label dose is 6,600 U/kg of body weight and drug concentration is 300,000 U/mL. That formulation was designed, like many injectable antimicrobials for food-producing animals, to deliver a convenient dose of 1 mL/45 kg (100 lbs) of body weight. However, such a low dose of PPG is seldom administered because it rarely results in clinically effective plasma drug concentrations. In fact, based on results of Monte Carlo simulations (MCS), label doses have a < 10% probability of achieving the target plasma drug concentration (plasma target drug concentration attainment) against susceptible respiratory pathogens.[10,11] The scientific literature[12–14] indicates that PPG doses ranging from 25,000 to 65,000 U/kg (approx 4 to 10 times the current label dose) are necessary for effective treatment of bovine respiratory disease. Because the activity of PPG is time dependent, the unbound concentration (free fraction) should be maintained above the MIC for at least 40% to 50% of the dosing interval.[15,16] The current clinical breakpoints for respiratory pathogens in cattle determined by the CLSI are ≤ 0.25, 0.5, and ≥ 1 µg/mL for susceptible, intermediate, and resistant interpretive categories, respectively. In cattle, administration of PPG at a dose of 66,000 U/kg may be sufficient to achieve therapeutic concentrations in the target tissue for some bacteria in the intermediate interpretive category.[12,14,16]

Given previous evidence that increasing the dose of PPG improved treatment efficacy, MCS were performed to define susceptible bacteria for laboratory antimicrobial susceptibility testing.[17] The simulations assumed IM administration of PPG once daily at doses sufficient for plasma target drug concentration attainment for 50% of the dosing interval (a PPG dose of 22,000 U/kg was assessed for cattle and 4 doses [15,000, 22,000, 33,000, and 66,000 U/kg] were assessed for swine). Results of the MCS indicated that administration of 22,000 U of PPG/kg IM once daily to cattle will yield a 94% probability of achieving an MIC concentration sufficient to achieve therapeutic drug concentrations against susceptible bacterial pathogens in target tissues **(Figure 1)**. The MCS results for swine indicated that once daily IM administration of PPG at doses of 33,000 and 66,000 U/kg will have a 91% and 100% probability, respectively, of achieving a therapeutic drug concentration against susceptible bacterial pathogens in target tissues. Based on these simulated results, the CLSI-approved MIC breakpoints

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for penicillin against respiratory pathogens in cattle and swine are ≤ 0.25, 0.5, and ≥ 1.0 µg/mL for the susceptible, intermediate, and resistant interpretive categories, respectively.

The new information provided by those simulations demonstrated a need to update the label dose and subsequent WDIs associated with PPG administration in both cattle and swine. Use of the current FDA-approved label doses is discouraged because those doses result in ineffective plasma drug concentrations in many situations. The AVMA's Principles of Antimicrobial Stewardship[1] state that veterinarians should avoid unnecessary administration of antimicrobials, and ineffective doses of penicillin would fall into that category.[18] Because PPG can be sold over-the-counter to nonveterinarians in some states and ELDU by laypersons without the supervision of a veterinarian is not permitted under AMDUCA, there is the potential for producers and animal owners to administer PPG at ineffective doses or in an illegal extralabel manner. Illegal ELDU of PPG may result in violative drug residues in meat or milk if the label WDTs are observed after an above-label dose is administered.[19] In the US, the FDA has established tolerances of 0.05 and 0 ppm for PPG residues in edible tissues of cattle and swine, respectively, and 0 ppm for PPG residues in milk. An increase in dose, increase in drug volume at the injection site, or change in the route of administration can prolong the duration that PPG residues remain in tissues, and thereby prolong the WDI necessary to avoid violative residues. Even the injection site (gluteal muscles vs semimembranosus or semitendinosus muscle vs neck muscles) and route (IM vs SC) can cause large differences in the pharmacokinetic profile of PPG.[20,21]

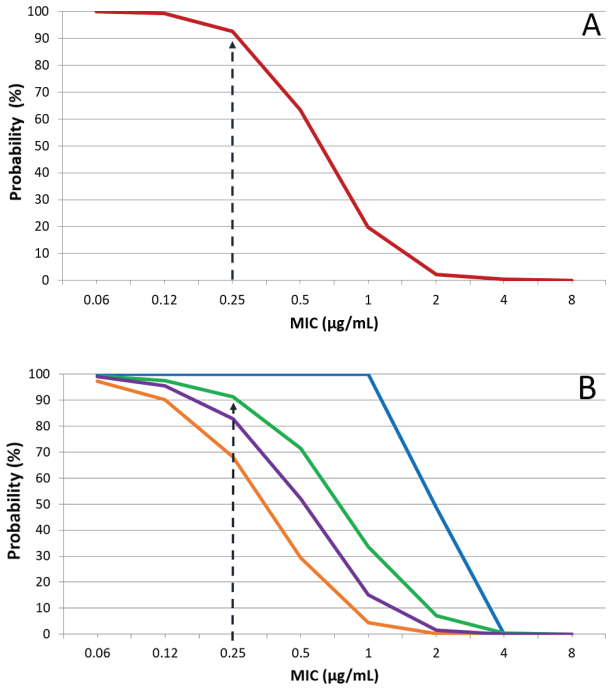

Figure 1—Plot of the probability of attaining a plasma concentration greater than the minimum inhibitory concentration breakpoint for procaine penicillin G (PPG)–susceptible respiratory pathogens (0.25 µg/mL; dashed arrow) for 50% of the dosing interval following IM administration of PPG at a dose of 22,000 U/kg to cattle (A) and doses of 15,000 (orange line), 66,000 (blue line), 33,000 (green line), and 22,000 (purple line) U/kg to swine (B) as determined by Monte Carlo simulations (MCS).

In humans, allergic reactions following consumption of foods containing penicillin residues are generally rare and dermatologic in nature[18]; however, there are reports of severe anaphylactic reactions.[22,23] To combat food safety issues and decrease the promotion of antimicrobial resistance, FARAD has developed new WDIs for penicillin in both cattle and swine.

Current WDI recommendations

Over the last 18 years, FARAD has utilized physiologically based pharmacokinetic (PBPK) models as one of many tools to estimate WDIs following ELDU in food animals.[2,24,27] Physiologically based pharmacokinetic models are mechanism-based models that aim to include physiologic- and chemical-specific parameters to simulate absorption, distribution, me-

Table 1—Estimated withdrawal intervals (WDIs) for meat and milk following extralabel administration of the procaine penicillin G (PPG) product Crysticillin (Zoetis Inc; New Animal Drug Application [NADA] No. 065-174) to cattle as determined by use of a physiologically based pharmacokinetic model[2,27] in combination with Monte Carlo simulations (1,000 iterations).

Dose (U/kg)	Route	Dosing interval and duration	Meat WDI (d)	Milk WDI (d)
24,000	IM	Once daily for 5 days	7	6
24,000	IM	Twice daily for 5 days	8	7
33,000	IM	Once daily for 5 days	8	7
33,000	IM	Twice daily for 5 days	9	8
44,000	IM	Once daily for 5 days	8	8
44,000	IM	Twice daily for 5 days	9	9
66,000	IM	Once daily for 5 days	10	9
66,000	IM	Twice daily for 5 days	11	10

The WDIs were estimated assuming that the PPG suspension was adequately shaken and mixed prior to use and that no more than 10 mL of the mixed suspension was injected per injection site. These WDIs apply only to Crysticillin and other bioequivalent PPG products (eg, Microcillin [Anthony Products Co; NADA No. 065–0506] and Pro-Pen-G [Bimeda Animal Health Ltd; NADA No. 065–505]).

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Table 2—Estimated WDIs for meat following extralabel administration of Crysticillin to swine as determined by use of a physiologically based pharmacokinetic model[2] in combination with Monte Carlo simulations (1,000 iterations).

Dose (U/kg)	Route	Dosing interval and duration	Meat WDI (d)
24,000	IM	Once daily for 5 days	8
24,000	IM	Twice daily for 5 days	11
33,000	IM	Once daily for 5 days	9
33,000	IM	Twice daily for 5 days	14
44,000	IM	Once daily for 5 days	11
44,000	IM	Twice daily for 5 days	16
66,000	IM	Once daily for 5 days	14
66,000	IM	Twice daily for 5 days	20

The WDIs were estimated assuming that the PPG suspension was adequately shaken and mixed prior to use and that no more than 11 mL of the mixed suspension was injected per injection site.

See Table 1 for remainder of key.

tabolism, and elimination of the administered drug. Li et al[2] developed and validated a PBPK model that predicts tissue residue depletion in cattle and swine following ELDU of PPG. Monte Carlo simulation was used in combination with that PBPK model to determine when drug concentrations in tissues would fall below the FDA-established tolerances for penicillin for 99% of the cattle and swine populations. The MCS (1,000 iterations) within the PBPK model provide an output of numerical results that are based on repeating the model numerous times. It improves estimations for each pharmacokinetic parameter and accounts for intraspecies variation. This PBPK model was used to estimate WDIs after extralabel IM administration of the PPG product Crysticillin (Zoetis Inc; New Animal Drug Application [NADA] No. 065-174) to cattle **(Table 1)** and swine **(Table 2)**. The use of other formulations of PPG may result in extended WDIs for the animal byproducts. Among the FDA-approved PPG products, Microcillin (Anthony Products Co; NADA No. 065-0506) and Pro-Pen-G (Bimeda Animal Health Ltd; NADA No. 065-505) are bioequivalent to Crysticillin, and the same WDIs can be used for all 3 products. Because the penicillin tolerance is 0 ppm for edible tissues from swine, the US Food Safety Inspection Service action limit of 25 ppb for penicillin residues detected in swine tissues was used in the WDI estimates. A more conservative WDI can be calculated by use of the reported limit of detection (1.8 ppb) for a sensitive liquid chromatography–tandem mass spectrometry method based on PBPK simulation results.[2] Although there is a zero tolerance for penicillin in milk, the FDA has established a safe level of 5.0 ppb, which was used in our estimates. Graphical depictions of the estimation of meat WDIs for cattle when administered a PPG product (Crysticillin) at 5 (32,500 U/kg) and 10 (65,000 U/kg) times the label dose IM once daily for 5 days **(Figure 2)** and estimation of the milk WDI in dairy cattle when administered the same product at 10 times the label dose IM twice daily for 3 days **(Figure 3)** are provided. Those estimated WDIs pertain only to Crysticillin

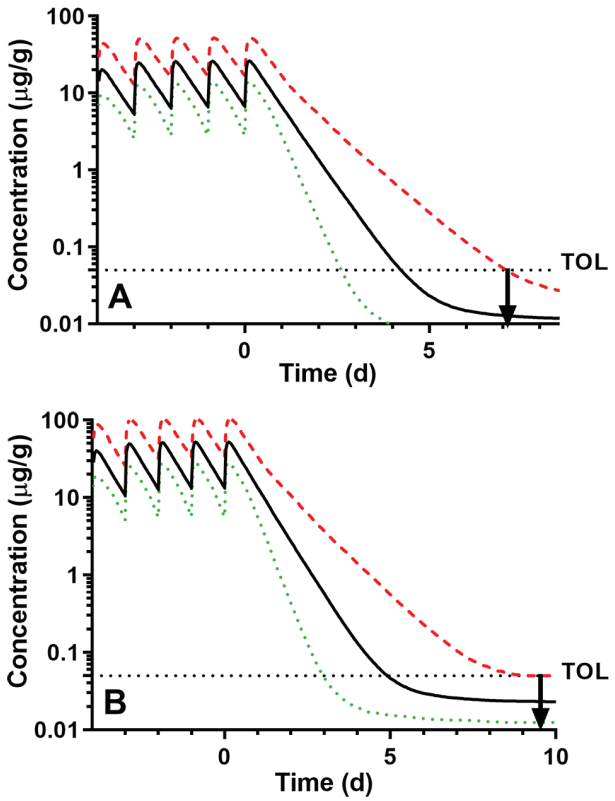

Figure 2—Graphical depiction of estimation of the meat withdrawal interval (WDI) for the PPG product Crysticillin (Zoetis Inc; New Animal Drug Application No. 065-174) in cattle following IM administration of the drug at 5 (32,500 U/kg; A) and 10 (65,000 U/kg; B) times the label dose once daily for 5 days as determined by use of a previously validated physiologically based pharmacokinetic (PBPK) model[2] in combination with MCS. The simulation involved 1,000 iterations to estimate the PPG concentration in the target tissue (liver). The 99th percentile (dashed red line), median (50th percentile; solid black line), and first percentile (green dotted line) were plotted and compared with the FDA-established tolerance (0.05 µg/g; black dotted line) for PPG in edible tissues. The WDI was defined as the duration between discontinuation of drug administration and the point at which the estimated liver PPG concentration was below the tolerance for 99% of the population. The estimated WDI was 8 days for the 32,000 U/kg dose (5 times the label dose) and 10 days for the 65,000 U/kg dose (10 times the label dose). When Crysticillin is administered in accordance with the label, the meat withdrawal time is 4 days for cattle. TOL = Tolerance.

and its bioequivalents (Microcillin and Pro-Pen-G). Other PPG formulations will have different WDIs because we have insufficient data to estimate the WDI using this model. The WDI estimates for other PPG formulations are estimated as described.[28]

Differences in parenteral administration

The route of administration can directly affect and possibly extend the WDI. Subcutaneous injection may be less harmful to meat quality. However, SC injection has been associated with hematoma formation, local inflammatory reactions, and scar tissue formation.

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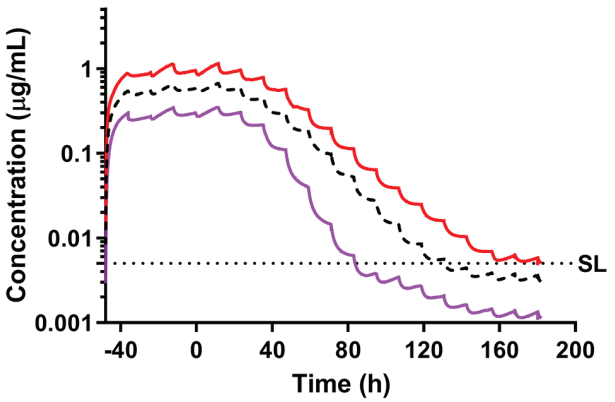

Figure 3—Graphical depiction of estimation of the milk WDI for the PPG product Crysticillin in cattle following IM administration of the drug at 10 times (65,000 U/kg) the label dose twice daily for 3 days as determined by use of a previously validated PBPK model[27] in combination with MCS. The simulation involved 1,000 iterations to estimate the PPG concentration in milk. The 99th percentile (red line), median (50th percentile; dashed black line), and first percentile (purple line) were plotted and compared with the FDA-accepted safe level (0.005 µg/g) of PPG in milk. The WDI was defined as the duration between discontinuation of drug administration and the point at which the estimated milk PPG concentration was below the safe level for 99% of the population. The estimated WDI for milk was 182 hours for the described dosage. When Crysticillin is administered in accordance with the label, the milk withdrawal time is 48 hours for dairy cows. SL = Safe level. (Reprinted with permission from Li M, Gehring R, Riviere JE, Lin Z. Probabilistic physiologically based pharmacokinetic model for penicillin G in milk from dairy cows following intramammary or intramuscular administrations. *Toxicol Sci.* 2018;164[1]:85–100.)

These reactions can alter the absorption rate of PPG, thereby delaying the apparent elimination half-life of the drug and prolonging the WDI for animal byproducts.[21] Multiple studies have demonstrated that the route of administration and injection site play a role in the absorption and elimination of PPG. For example, the elimination half-life of PPG is prolonged following SC administration in the neck, compared with IM administration in the neck or gluteal muscles.[1,26,29–30]

In addition to the route and site of administration, the volume injected can play a role in the absorption, distribution, and elimination of PPG. In the US, Beef Quality Assurance guidelines[29] recommend that no more than 10 mL of any drug be injected at any 1 site. Injection of a larger volume at a single site may delay drug absorption and create a depot effect resulting in slow drug absorption over an extended period of time, prolonging the risk for violative drug residues. Injection of > 10 mL of PPG at a single site can increase the risk for drug entrapment that results in erratic, higher, and more prolonged tissue residues. Interspecies pharmacokinetic differences can also extend WDIs.

As stated previously, PPG is a suspension and requires vigorous shaking to ensure even dispersion of the active ingredient throughout the bottle. If the bottle is not adequately shaken, the drug concentration in the volume withdrawn will be lower than stated on the label and the drug concentration will be increased in the remaining contents of the bottle. Thus, the drug concentration in any subsequent doses withdrawn from that bottle will be higher than expected, which could lead to violative residues if the WDI is not appropriately extended. Unfortunately, that effect is difficult to estimate given the potential variability in the concentration administered. Therefore, proper mixing of PPG prior to administration is critical to avoid this issue.

Conclusions

Because the general consensus among veterinarians and pharmacologists is that the label doses of PPG are clinically ineffective in cattle and swine, practitioners often increase the dose or frequency of administration of that drug. An increase in dose or dosing frequency represents ELDU and requires the observation of extended WDIs. Assuming products containing only PPG are used, injection site volume recommendations are followed, and the route of administration and proper use of the drug are ensured, the WDIs provided by FARAD in this digest can be used for a variety of commonly used PPG dosing regimens in cattle and swine. If PPG is used in any other extralabel manner, veterinarians are strongly encouraged to contact FARAD for a WDI recommendation. Veterinarians and producers are strongly encouraged to adhere to all FDA regulations regarding legal ELDU.

Acknowledgments

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References

1. Antimicrobial stewardship definition and core principles. AVMA. Accessed May 15, 2021. https://www.avma.org/resources-tools/avma-policies/antimicrobial-stewardship-definition-and-core-principles
2. Li M, Gehring R, Riviere JE, Lin Z. Development and application of a population physiologically based pharmacokinetic model for penicillin G in swine and cattle for food safety assessment. *Food Chem Toxicol.* 2017;107(pt A):74–87.
3. CLSI. *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals.* 5th ed. Clinical and Laboratory Standards Institute; 2020.
4. Riviere J, Papich MG. *Veterinary Pharmacology and Therapeutics.* 10th ed. Wiley-Blackwell; 2018:867–877.
5. Martinez MN, Papich MG, Drusano GL. Dosing regimen matters: the importance of early intervention and rapid attainment of pharmacokinetic/pharmacodynamic target. *Antimicrob Agents Chemother.* 2012;56(6):2795–2805.
6. Yáñez JA, Remsberg CM, Sayre CL, Forrest ML, Davies NM. Flip-flop pharmacokinetics – delivering a reversal of disposition: challenges and opportunities during drug development. *Ther Deliv.* 2011;2(5):643–672.
7. Riviere JE. *Comparative Pharmacokinetics: Principles, Techniques and Applications.* 2nd ed. Wiley; 2011.
8. DeDonder KD, Gehring R, Baynes RE, et al. Effects of new sampling protocols on procaine penicillin G withdrawal intervals for cattle. *J Am Vet Med Assoc.* 2013;243(10):1408–1412.

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9. VetGRAM. FARAD. Accessed June 3, 2021. www.farad.org/vetgram/search.asp
10. Ambrose PG. Monte Carlo simulation in the evaluation of susceptibility breakpoints: predicting the future: insights from the society of infectious diseases pharmacists. *Pharmacotherapy*. 2006;26(1):129–134.
11. Trang M, Dudley MN, Bhavnani SM. Use of Monte Carlo simulation and considerations for PK-PD targets to support antibacterial dose selection. *Curr Opin Pharmacol*. 2017;36:107–113.
12. Bateman KG, Martin SW, Shewen PE, Menzies PI. An evaluation of antimicrobial therapy for undifferentiated bovine respiratory disease. *Can Vet J*. 1990;31(10):689–696.
13. Mechor GD, Jim GK, Janzen ED. Comparison of penicillin, oxytetracycline, and trimethoprim-sulfadoxine in the treatment of acute undifferentiated bovine respiratory disease. *Can Vet J*. 1988;29(5):438–443.
14. English PB. The therapeutic use of penicillin: the relationship between dose rate and plasma concentration after parenteral administration of benzylpenicillin (penicillin G). *Vet Rec*. 1965;77:810–814.
15. Turnidge JD. The pharmacodynamics of β-lactams. *Clin Infect Dis*. 1998;27(1):10–22.
16. Teske RH, Rollins LD, Carter GG. Penicillin and dihydrostreptomycin serum concentrations after administration in single and repeated doses to feeder steers. *J Am Vet Med Assoc*. 1972;160(6):873–878.
17. Hjerpe CA, Routen TA. Practical and theoretical considerations concerning treatment of bacterial pneumonia in feedlot cattle, with special reference to antimicrobic therapy. In: *Proceedings of the 9th Annual Convention of AABP*. American Association of Bovine Practitioners; 1976:97–140.
18. 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(3):317–327.
19. 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(4):223–230.
20. Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). FDA. Accessed May 15, 2021. https://www.fda.gov/animal-veterinary/guidance-regulations/animal-medicinal-drug-use-clarification-act-1994-amduca
21. Sundlof SF. Drug and chemical residues in livestock. *Vet Clin North Am Food Anim Pract*. 1989;5(2):411–449.
22. Lindemayr H, Knobler R, Kraft D, Baumgartner W. Challenge of penicillin-allergic volunteers with penicillin-contaminated meat. *Allergy*. 1981;36(7):471–478.
23. Wicher K, Reisman RE, Arbesman CE. Allergic reaction to penicillin in milk. *JAMA*. 1969;208(1):143–145.
24. Craigmill AL. A physiologically based pharmacokinetic model for oxytetracycline residues in sheep. *J Vet Pharmacol Ther*. 2003;26(1):55–63.
25. Luthman J, Jacobsson SO. Distribution of penicillin G in serum and tissue cage fluid in cattle. *Acta Vet Scand*. 1986;27(3):313–325.
26. Riviere JE, Webb AI, Craigmill AL. Primer on estimating withdrawal times after extralabel drug use. *J Am Vet Med Assoc*. 1998;213(7):966–968.
27. Li M, Gehring R, Riviere JE, Lin Z. Probabilistic physiologically based pharmacokinetic model for penicillin G in milk from dairy cows following intramammary or intramuscular administrations. *Toxicol Sci*. 2018;164(1):85–100.
28. Bengtsson B, Franklin A, Lutman J, Jacobsson SO. Concentrations of sulphadimidine, oxytetracycline and penicillin G in serum, synovial fluid and tissue cage fluid after parenteral administration to calves. *J Vet Pharmacol Ther*. 1989;12(1):37–45.
29. Beef Quality Assurance. Accessed April 21, 2021. https://www.bqa.org/
30. Gehring R, Baynes RE, Craigmill AL, Riviere JE. Feasibility of using half-life multipliers to estimate extended withdrawal intervals following the extralabel use of drugs in food-producing animals. *J Food Prot*. 2004;67(3):555–560.

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