

Viewpoint

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Animal drug shortages limit veterinary therapeutic options and introduce artifacts in antimicrobial sales reporting

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ABSTRACT

Supply chain issues disrupt veterinary care and cause downstream consequences that alter the practice of veterinary medicine. Antimicrobials are just 1 class of pharmaceuticals that have been impacted by supply chain issues over the last couple of years. Since February 2021, 2 sponsors/manufacturers of penicillin products have reported shortages in the active pharmaceutical ingredient. With the release of the 2021 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals by the FDA, a key finding was a 19% decrease in penicillin sales and distribution from 2020 to 2021. Herein, we provide our clinician's professional perspective regarding how drug shortages, specifically that of penicillin, might contribute to misconstrued patterns in antimicrobial use and what can be done by veterinarians and the FDA to minimize the impact of an antimicrobial drug shortage on animal health and well-being.

Keywords: shortage, antimicrobial, stewardship, penicillin, availability

Disruptions in the consumer supply chain negatively impact all sectors, including veterinary medicine.¹ Increased demand, manufacturing delays, labor insufficiencies, capacity constraints, and lack of active pharmaceutical ingredients and other components associated with the COVID-19 pandemic, and its response, have coalesced to result in inadequate animal drug supplies.² To forestall this, the US FDA has encouraged that all entities, including clients, veterinarians, and manufacturers, report potential drug shortages. Once notified, the FDA Center for Veterinary Medicine (CVM) investigates the claim's

legitimacy and holds discussions with the potentially impacted drug sponsors and manufacturers. As stated by the FDA³ on their website, "The Federal Food, Drug, and Cosmetic Act defines a drug shortage as a period of time when the demand or projected demand for the drug within the US exceeds the supply of the drug." The FDA then determines if the drug is a "Medically Necessary Veterinary Product" (MNVP), a designation to classify drugs purposed to treat or prevent serious animal diseases or necessary to assure safe animal-originated food products without an adequate treatment alternative.⁴

The most important problem that results from drug shortages is the potential harm to our animal patients' health and well-being. Veterinarians swear an oath to use our knowledge and skills to protect animal health, prevent and relieve animal suffering, and promote public health. As it relates specifically

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to antimicrobial pharmaceutical agents, resorting to a different class of antimicrobial or substituting antimicrobial therapy with a nonantimicrobial alternative can result in prolonged illness or secondary infections which lead to unnecessary patient and client suffering. Antimicrobial shortages also hamper antimicrobial stewardship by narrowing antimicrobial options for veterinarians. If a preferred antimicrobial agent (“first choice”) is not available for an animal due to a shortage, veterinarians might resort to extra-label drug use, sometimes including human-label, antibiotics for common infections. Such choices may be contrary to the stewardship principles⁵ promoted by the AVMA’s Committee on Antimicrobials (CoA). Increased therapy costs and untimely euthanasia or death are extreme outcomes, which burden not only the client but also society as a result of the lost animal productivity.⁶ Direct and indirect impacts of antimicrobial drug shortages on antimicrobial resistance are currently unknown; however, short and long-term drug shortages clinically compromise animal health and well-being as well as food security, food safety, and public health.

FDA CVM does not officially recognize owner inconvenience or increased therapeutic costs as justifications to designate an approved veterinary product as MNVP. We ask whether principles of veterinary antimicrobial stewardship might support MNVP status for antimicrobial drugs.

FDA has regulatory authority to mitigate the impact of MNVP shortages by: 1) speeding up the new animal drug review and approval process; 2) recruiting and approving additional sources of finished drugs or raw materials; and 3) exercising enforcement discretion to increase veterinarians’ options in the case of drug shortages.⁷ These mechanisms are potential tools to ameliorate the consequences of drug shortages and optimize animal health and welfare. Beyond the health consequences of not having adequate veterinary drugs for patients, drug shortages have other downstream impacts, including stewardship challenges, and changing sales and distribution of veterinary drugs.

Section 105 of the Animal Drug User Fee Amendments of 2008 mandates that sponsors with approved or conditionally approved animal drugs containing an antimicrobial active ingredient must report sales and distribution data to FDA that complies with 21 CFR Section 514.87 Antimicrobial Animal Drug Sales and Distribution Reporting.^{8,9} In 2016, changes to the previously established reporting requirements were made to assist FDA in examining how sales and distribution of medically important antimicrobials in the major food animal species may relate to antimicrobial resistance.⁹ The report entitled “Antimicrobials sold or distributed for use in food-producing animals” is released annually, reporting on the antimicrobial sales data from the prior year and comparisons to previous years. One key finding from the 2021 report was a 19% decline in domestic penicillin sales compared with 2020.¹⁰ In comparison, sales of all other independently reported drug classes increased by 1% to 103%, except for a

negligible (–1%) decline in tetracyclines. This finding might be interpreted to suggest that the decreased sales and distribution of penicillin in 2021 was due to the shortage, but the sales data lack context to determine the reasons for the decrease.

The FDA and the US Poultry & Egg Association have jointly supported a national program to collect on-farm antimicrobial use data in US poultry production. In a recent publication¹¹ covering the turkey industry from 2013 to 2021, the antimicrobial use data showed that penicillin use declined while use of other antimicrobial classes, such as lincomycin, increased during the same period (**Figure 1**). Both of these antimicrobials are used in the drinking water of turkeys for clostridial dermatitis, one of the key diseases of turkeys that necessitates antimicrobial therapy. In addition to total milligrams of use per kg of liveweight, the authors captured the number of prescriptions by antimicrobial class and disease indication written by turkey veterinarians. From 2020 to

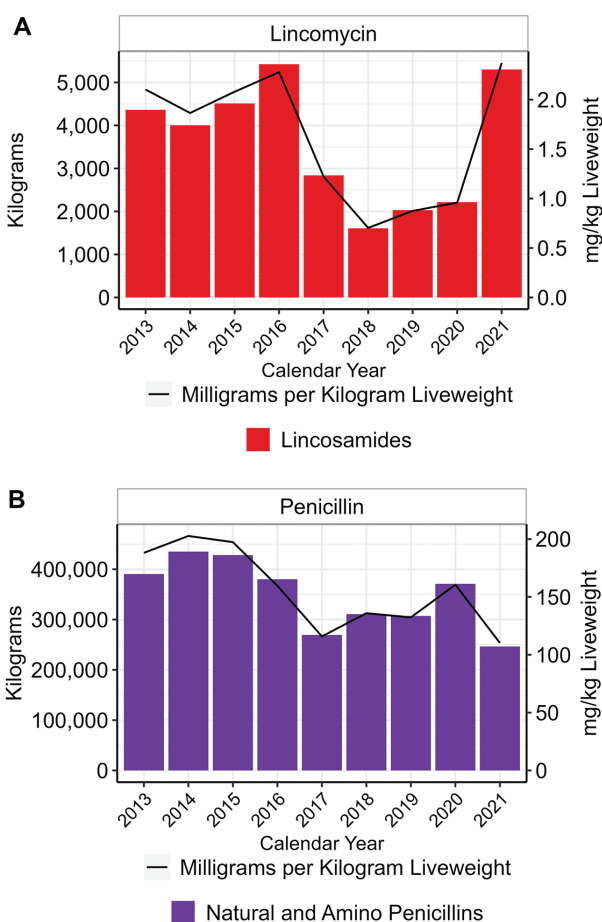


Figure 1—Medically important antimicrobials lincomycin (A) and penicillin (B) used in turkey water, 2013 to 2021. Total kilograms are shown by the bars (left y-axis) and total mg/kg liveweight are shown by the line (right y-axis). (Adapted from Singer RS, Schrag NFD, Ricke I, Apley MD. On-farm antimicrobial usage in commercial turkey production in the United States, 2013–2021. *Front Vet Sci.* 2023;10:1158943. doi:10.3389/fvets.2023.1158943. Reprinted with permission.)

2021, the prescriptions written for clostridial dermatitis with penicillin declined with a concomitant increase in lincosamide prescriptions (**Figure 2**). Taken

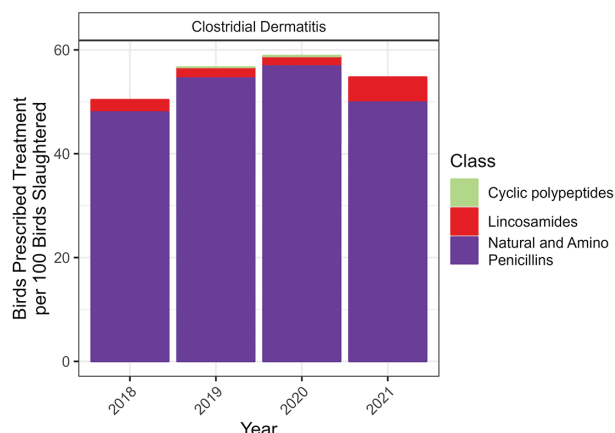


Figure 2—Number of water-soluble prescriptions for each antimicrobial class used for clostridial dermatitis, 2018 to 2021. The figure depicts the number of prescriptions per 100 birds slaughtered. (Adapted from Singer RS, Schrag NFD, Ricke I, Apley MD. On-farm antimicrobial usage in commercial turkey production in the United States, 2013–2021. *Front Vet Sci.* 2023;10:1158943. doi:10.3389/fvets.2023.1158943. Reprinted with permission.)

collectively this data may be interpreted as a clear example of a drug shortage influencing veterinary prescribing behavior, which is not in alignment with the principles of good antimicrobial stewardship. The AVMA’s CoA acknowledges that different metrics for antimicrobial use are often correlated and urges care be taken when drawing comparisons and conclusions.¹² Upon investigation, the AVMA’s CoA highlights 1 potential explanation for this decline in penicillin sales and use described herein: veterinary drug shortages.

In February 2021, Bimeda, Inc. notified FDA of a shortage in water-soluble penicillin G potassium and injectable penicillin G procaine due to unavailability of the active pharmaceutical ingredient.² In March 2021, Huvepharma Inc. also reported a shortage of penicillin G potassium.² For at least 9 months of 2021, 3 penicillin products were in short supply.² While the market share of these products is unclear, the decrease in sales has a close temporal association with the penicillin shortage. The penicillin shortage impacted veterinary practice. Penicillin (in both formulations) is important for streptococcal infections in horses as well as food animals. Without penicillin, veterinarians were forced to consider alternative antimicrobial agents.

Several other comparative decreases in penicillin sales might suggest that the drug shortage was a contributing factor. The 2021 FDA’s Animal Drug User Fee Act report indicated that 2021 penicillin sales were lower than the previous 10 years.⁷ Considering the relatively consistent reporting of penicillin sales in 2018, 2019, and 2020, the decline of approximately 100,000 kg in sales in 1 year might be an artifact caused by shortage in supply as opposed to a conscientious

reduction in purchasing of the drug. Further, water-soluble penicillin sales declined by 18% between 2020 and 2021. Notably, 2 of the 3 penicillin products on the shortage list are water soluble.

Many factors, including drug shortages, are likely associated with the rise and fall of antimicrobial sales, distribution, and use. While antimicrobial stewardship and overall antimicrobial reduction practices likely impact these trends, we posit that they are unlikely to be the only drivers for the observed shifts. The change in penicillin sales between 2020 and 2021 highlights this assertion, demonstrating that drug availability issues might be most strongly associated with this reduction.

As shown above, voluntary flock-level on-farm antimicrobial reports from US turkey producers also exhibited a similar decline in penicillin use during the same time period.¹⁰ The authors found turkey veterinarians were switching to other antimicrobial therapies because of the penicillin shortage. This example illustrates that a drug shortage, in this case penicillin, can alter drug use patterns at both the national and farm levels. AVMA’s CoA is not aware of another instance in which a drug shortage, rather than a policy change (eg, GFI numbers 209 and 213), substantially lowered antimicrobial sales of any veterinary drug.

Veterinary drug shortages must be taken seriously. Shortages like that of penicillin during the COVID-19 pandemic have multiple effects on veterinary practice. The need to cease therapy, temporarily or permanently, is possibly the most important outcome of a drug shortage for veterinarians, clients, and patients.

Future Directions to Combat Veterinary Drug Shortages

Drug availability and shortages when experienced at the veterinarian-client-patient level should engage veterinarians in the reporting process. To maximize a relationship with veterinarians, the authors recommend that FDA take the following steps to improve stakeholder communication and encourage the FDA to:

Provide an option for anonymized reporting of drug availability issues to prevent under-reporting because the party fears a data breach or publicity. We recommend the development of a web submission portal in addition to email submissions. All submissions should provide the submitter with a unique reference number that can be used to track the report on an online portal. Further, if the submitter would like a follow-up, we propose that FDA make that option available during submission.

Establish a communication pathway with veterinary professionals and industry organizations, including the AVMA and its Allied partners, to deliver timely and comprehensive data shortage and availability reports.

Communicate to affected veterinarians (if requested at the time of reporting) and professional organizations how each report is classified.

Provide clarity on which drugs do and do not meet the definition of a MNVP. Periodically review criteria and solicit input from veterinary professionals.

Recommendations for Veterinarians to Combat Veterinary Drug Shortages

Veterinarians should report when lack of availability of an animal drug results in a shortage. These reports can be made directly to the FDA CVM (AnimalDrugShortages@fda.hhs.gov). Include the drug name and nature of the issue in the email. In addition, it is recommended to inform your representative veterinary organization, who can also discuss the drug shortage with FDA.

A list of current² and resolved¹³ veterinary drug shortages are available on the FDA's website. Only FDA-designated drug shortages appear on these sites. Therefore, if veterinarians have experienced a shortage and the drug isn't listed on the website, report it to the FDA CVM.

FDA uses these reports to determine if there is actual or potential shortage. For veterinarians or their clients and patients, there is not a functional difference between an actual or potential shortage, since both produce interruptions in drug supply and the necessity to alter prescribing or, at worst, forego therapy. Once identified, FDA determines if the drug is a MNVP and, if so, creates an action plan with drug sponsors/manufacturers and professional organizations to address the shortage. There is currently no FDA-recognized list defining antimicrobials by their importance to veterinary medicine; thus, the assignment of MNVP status to a drug may be influenced by the Agency's discretion.

Recommendation to FDA CVM to Combat Veterinary Drug Shortages

Establish a US list of antimicrobial agents of veterinary importance for food animals which informs regulatory officials who may be unfamiliar with prescribing preferences to prioritize and mitigate availability issues. Such a list would allow FDA to more clearly communicate if an antimicrobial is a MNVP and increase regulatory options to mitigate a drug shortage. Further, FDA should engage with partners like AVMA, Animal Health Institute, Generic Animal Drug Alliance, and other appropriate stakeholders to understand the unique factors that could result in limited or no availability of an antimicrobial and establish a means to address issues in real-time to protect veterinary practitioners, producers, animal health, and food security.

We encourage FDA CVM to continue to evaluate ways they might exercise regulatory discretion to resolve drug shortages, including those of a non-MNVP. We believe active communication between FDA CVM, veterinarians, animal health industry, and veterinary organizations can ensure that drug shortages, particularly those involving antimicrobials, are recognized, investigated, and evaluated in the proper context for their potential effect on animal health, food supply and safety, and antimicrobial stewardship.

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