Proposed amendment to the Poisons Standard - 2.3 Oxytetracycline

Submission of the
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The Australian Veterinary Association

The Australian Veterinary Association (AVA) is the national organisation representing veterinarians in Australia. Our members come from all fields within the veterinary profession. Clinical practitioners work with companion animals, horses, livestock, and wildlife. Government veterinarians work with our animal health, public health, and quarantine systems while other members work in industry, research, and teaching. Veterinary students are also members of the Association.

The AVA thanks the TGA Advisory Committees for the opportunity to comment on this important issue.

Summary

An applicant has submitted an application to amend the Schedule 5 entry for *OXYTETRACYCLINE in preparations to treat superficial skin infections*.

The proposed change would mean that topical preparations of oxytetracycline for use in superficial skin infections (currently S4, and thus prescription-only) would be available over-the-counter and online to the public, to be used without veterinary oversight.

The AVA **does NOT support** the amendment for several reasons:

- All antimicrobials intended for use in animals (excluding ionophores) should be available only by prescription by a veterinarian with a valid veterinarian/client/patient relationship.[i]
- Increasing Over the Counter (OTC) access to antimicrobials contravenes contemporary standards of practice and antimicrobial stewardship principles and contributes to antimicrobial resistance (AMR) with potential harm to public health.[i]
- Animal welfare implications – Responsible use of oxytetracycline is essential as it is an important first line antimicrobial for infectious diseases across a number of species including many life-threatening infections.[ii] Topical oxytetracycline is uncommonly used in contemporary practice for the treatment of superficial digital dermatoses in animals.
- Biosecurity and Emergency Animal Disease risks are increased when veterinary oversight of veterinary medicines are removed and accurate diagnosis is not made.
- The applicant has not demonstrated a persuasive need to reschedule oxytetracycline to make the drug more accessible. There is no current impediment to supply through veterinarians.

Furthermore, the applicant has provided two reasons for therapeutic need that we address as follows:

APPLICANT REASON FOR RESCHEDULE	AVA POSITION
Oxytetracycline is a broad-spectrum bacteriostatic antibiotic that is effective against a wide range of Gram-positive and Gram-negative bacteria. Direct access to oxytetracycline benefits farmers when they do not have veterinarian access and **could serve as a first line defence against superficial infections.**	For topical infections the recommended first line of defence is provided by antiseptic and other preparations designed specifically for the cleaning and disinfection of superficial wounds. Antibacterial agents such as oxytetracycline are reserved for more serious wounds and superficial infections which are not expected to respond, or have not responded, to simple cleaning and antisepsis.
Topical veterinary applications of oxytetracycline are used in the treatment of foot rot in sheep, digital dermatitis in cattle and superficial skin infections caused by	Topical preparations of OTC are used as a prescription animal remedy following appropriate diagnosis. For example, the management of footrot in sheep requires complex and ongoing planned interventions where topical OTC is but

oxytetracycline sensitive organisms in pigs, sheep and cattle.	one of many management and therapeutic options available.

These arguments are further expanded below.

Discussion

We address the relevant matters mentioned in section 52E of the *Therapeutic Goods Act 1989,* on which the TGA is likely to base their decision:

The risks and benefits of the use of a substance

In-depth knowledge of animal health and careful consideration of how antimicrobials are used is key to reducing the development of antimicrobial resistance. Veterinarians are the professionals with the expertise to make decisions about appropriate antimicrobial use in animals and follow core principles of antimicrobial stewardship to ensure responsible use.[i,iii,iv,v] Devolving this professional decision making process creates significant risks to public health, animal health and welfare, and biosecurity.

Public health risk

Increasing over-the-counter (OTC) availability of any antimicrobial, irrespective of classification, **demonstrates poor antimicrobial stewardship**. Reducing OTC availability of antimicrobials is a priority action of the World Health Organisation global action plan on antimicrobial resistance.[vi]

A recent joint summit noted the global prevalence of over-the-counter antibiotic sales and the associated risks of AMR. It highlighted the complex transmission mechanisms of AMR among animals, humans, and through food, water, and environmental contamination as well as the potential for rapid spread of AMR across boundaries.[vii]

The summit observed the role of antimicrobial overuse as a major driver of resistance, linked to health systems, demand, supply and industry factors. The summit discussed the importance of legislation in creating an enabling environment for phasing out the over-the-counter sale of antimicrobials.[vi]

The applicant in this case states:

- *Oxytetracycline is not considered to present a significant risk in the development of antimicrobial resistance in the treatment of infections in humans.*
- *Oxytetracyclines are used in human therapeutics and are classed as antibiotics of low importance.*
- *Topical oxytetracycline absorption is negligible and the drug acts via direct contact with bacteria on the skin and in superficial lesions on external body surfaces.*

While oxytetracycline may not present a significant risk in the development of antimicrobial resistance in the treatment of infections in humans, it belongs to the tetracycline class of antibiotics. Bacteria that develop resistance mechanisms to oxytetracycline may also exhibit cross-resistance to other tetracyclines including doxycycline and minocycline, which are more commonly used in human medicine. Therefore, while oxytetracycline itself may not present a significant risk, resistance mechanisms that are selected could potentially affect the effectiveness of other tetracyclines in human medicine. Furthermore, co-selection of antimicrobial resistance determinants to other antimicrobial classes could further undermine antimicrobial effectiveness of unrelated antimicrobial classes.[viii]

Antimicrobial resistance is reported to be prevalent not only in people and animals, but in the environment, in water and soil.[ix] The uncontrolled discharge of antimicrobials into the environment

contributes to AMR. Exposure of environmental bacteria to antimicrobials may accelerate the evolution of resistance; increase the abundance and dissemination of resistance genes within the resistome that is critical to the development of clinical resistance; and increase exchange of antibiotic resistance genes between bacteria.[x] Furthermore there is evidence that human pathogens have acquired resistance from environmental bacteria.[x] Removing veterinary oversight of any antimicrobial used in animals is likely to increase overuse; inappropriate use; and increase discharge of the antimicrobial into the environment.

Animal health and welfare risk

Antimicrobial resistance in animals

Animal health and welfare is also at risk with the inappropriate use of antimicrobials. Responsible use of antimicrobials requires consideration of 21 principles.[iii-v] These include that alternatives to antimicrobials are considered, an accurate diagnosis and therapeutic plan are instigated, drug selection is appropriate, and antimicrobial resistance surveillance is undertaken. All of these require the expertise of a veterinarian. [iii-v] This requirement can be safeguarded by ensuring that all antimicrobials are assigned to Schedule 4.

Responsible use of oxytetracycline is essential as it is an important first line antimicrobial for infectious diseases across a number of species[ii,] including many life threatening infections. It is of particular importance in production animals due to:

- a low ASTAG rating and minimal use in human treatment;
- being effective against a wide range of pathogens with extended post antibiotic effect against some; and
- having well defined pharmacokinetic/ pharmacodynamic profiles underpinned by data which facilitates management of dose rate, frequency and duration of treatment or residue risks around withholding periods and export slaughter intervals.

The applicant's statement - "*Oxytetracycline is not considered to present a significant risk in the development of antimicrobial resistance in the treatment of infections in humans"* also fails to acknowledge the risk of the development of AMR against infections that occur in animals. Increased frequency of, or recurring use of, an S5 OTC preparation without veterinary advice to manage disease in animals can result in establishment and persistence of AMR genes within local microbial populations.

Increased AMR for this drug places animal health and welfare at risk. If resistance develops across a range of pathogens, extending beyond the target organism of topical treatment, veterinarians may need to manage other infectious pathogens using parenteral antimicrobials, which represent enhanced or different risk profiles. In addition to the risk to animal health and welfare, this scenario would come at additional cost to farmers. Industry may also bear the costs through the requirement of greater AMR surveillance in food-producing animals.

Potential use of ineffective treatment due to increased access

The current S5 scheduling of oxytetracyclines for ocular use provides evidence of how access without veterinary oversight can lead to poorer animal welfare outcomes. Ocular administration of oxytetracycline is not a recommended treatment for infectious bovine keratitis (pink eye in cattle)[iii] or contagious ophthalmia (pink eye in sheep)[iv]. The irritant nature of ocular oxytetracycline products, the administration frequency and the lack of efficacy data mean these treatments are not commonly recommend by veterinarians, but because they are available through rural produce stores they

remain popular with farmers.[xi] Furthermore, despite their popularity, almost half of farmers perceive them to have low or no effectiveness.[xii] The proposed amendment is likely to result in a similar situation in regards to the management of digital dermatoses and superficial skin infections of livestock species, which would be a poor animal welfare outcome.

Biosecurity and Emergency Animal Disease risks

One of the emergency animal diseases of most concern to Australia is Foot and Mouth Disease (FMD). Dermatological diseases localised to the feet of these species are a differential diagnosis for FMD.[xiii] In sheep and goats the lameness is often the initial clinical sign of FMD followed by lesion development.[xiv] Reducing veterinary oversight of these diseases could result in a delay in diagnosis of a FMD incursion into Australia, which would have a huge animal welfare, economic and social impact. Should Australia experience a large outbreak of a disease such as FMD in several states, the cost to the nation has been estimated at more than $80 billion over 10 years.

The purposes for which a substance is to be used and the extent of use of a substance

The applicant states that "*topical veterinary applications of oxytetracycline are used in the treatment of foot rot in sheep, digital dermatitis in cattle and superficial skin infections caused by oxytetracycline sensitive organisms in pigs, sheep and cattle".* Contemporary treatment (which includes consideration of antimicrobial stewardship accounts and efficacy of treatment) of superficial skin infections generally does not include topical oxytetracycline.

Footrot or other digital dermatoses in sheep

Contemporary treatment of footrot or other digital dermatoses in sheep is commonly addressed by environmental and herd management and foot bathing with zinc sulfate.[xv] Antimicrobials are only indicated in severe cases, and these should be administered parenterally.[iv]

Digital dermatitis in Cattle

Treatment of footrot in cattle is commonly addressed by debridement of affected tissue and systemic antimicrobial therapy is considered essential for effective treatment.[xvi] Although papillomatous digital dermatitis can be effectively treated with topical application of oxytetracycline, a diagnosis must be established before treatment is initiated, underscoring the importance of veterinary involvement in supply of the veterinary medicine.[iii,xvii]

Superficial skin infections caused by oxytetracycline sensitive organisms in pigs, sheep and cattle

In order for topical oxytetracycline to be effective in the management of superficial skin infections, oxytetracycline sensitive organisms need to be identified. This requires veterinary knowledge and expertise to assess the skin lesions, determine the likelihood of infectious organisms and if further identification is required undertake appropriate microbiological diagnostic tests. The use of any antimicrobial - irrespective of route - without diagnosis (which requires veterinary knowledge) is irresponsible, does not conform with the core principles of appropriate use of antimicrobials [i,iii-v] and can result in poor animal welfare outcomes.

The applicant states "Direct access to oxytetracycline benefits farmers when they do not have veterinarian access and could serve as a first line defence against superficial infections."

Compared to some other countries, Australia has a high level of access to veterinary expertise, and there is no impediment to supply through veterinarians. Whenever use is indicated, veterinarians can supply S4 medications by telemedicine or other remote means, once an initial relationship with the client and knowledge of their flock or herd has been established. With effective transport services the rapid provision of product is possible even for the most remote properties.

The potential for abuse of a substance

The current S5 scheduling of oxytetracycline preparations for ocular use in animals provides evidence of how removing veterinary oversight can lead to potential abuse of a substance. Veterinarians commonly report that schedule 5 ocular preparations of oxytetracycline are used off label by lay people in a range of circumstances that places animal health and welfare at risk. An example of this is the anecdotal evidence of the propensity for the APVMA registered Schedule 5 ocular oxytetracycline spray to be used in dogs involved in hunting feral pigs that are wounded. Of course, over-the-counter availability of additional oxytetracycline products can readily, without any barriers, be used in any animal species - including humans.

Any other matters necessary to protect public health

Reducing OTC availability of antimicrobials is a priority action of the World Health Organisation global action plan on antimicrobial resistance. Amending the Schedule 5 entry for *OXYTETRACYCLINE in preparations to treat superficial skin infections* causes increased risk to public health and can only be done in opposition to the recommendations of the World Health Organisation.

Corrections

With respect to the Australian and International Regulations provided by TGA in their summary of oxytetracycline, we offer the following corrections:

According to the APVMA PubCRIS database there are 42 products registered and 32 active constituents approved. The product types that are in SCHEDULE 4 are principally injections and feed additives, but also include one foaming pessary for intrauterine use and 2 dermatological products. Two ophthalmic products are in SCHEDULE 5.

The FDA animal drugs database includes 53 currently approved products that include oxytetracycline as a constituent.

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[iii] Antimicrobial prescribing guidelines for dairy cattle 2022

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[v] Antimicrobial prescribing guidelines for pigs

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