New Zealand Food Safety
Haumaru Kai Aotearoa

Antimicrobial Resistance Reassessment Review: Macrolides, Later-Generation Cephalosporins, and Penicillins

AMR Risk and Antibiotic Classification

Prepared for the ACVM Team
by Awilda Baoumgren

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Contents

Page

1 Executive Summary

As part of the New Zealand Antimicrobial Resistance Action Plan, the Agricultural Compounds and Veterinary Medicines (ACVM) team has undertaken the first review of the regulatory controls applied to antibiotic-based trade name products. This review sought to determine the importance classification of macrolide, later-generation cephalosporin, and penicillin antibiotic compounds in veterinary medicines relative to their clinical use and the risk of antimicrobial resistance.

This classification of veterinary antibiotic compounds was based on the evaluation of three key areas in their risk profiles, as described in this report: chemical characteristics and mechanism of action, antimicrobial resistance (AMR) risk profile and history, and veterinary use in the New Zealand context. Each compound within these four antibiotic families was individually assessed in these areas rather than applying a classification at the family level to ensure that the differences in individual compounds and their risk profiles were reflected in the final decisions.

The outcome of these assessments was as follows:

- Currently registered macrolide compounds erythromycin, oleandomycin, spiramycin, tilmicosin, tulathromycin, and tylosin will be classed as **Critically Important antibiotics**.
- Currently registered later-generation cephalosporin compounds cefovecin, cefpodoxime, ceftiofur, and cefquinome will be classed as **Critically Important antibiotics**.
- Currently registered penicillin compounds amoxicillin, ampicillin, cloxacillin, penethamate hydriodide, penicillin G benzathine, penicillin G procaine, and penicillin procaine will be classed as **Highly Important antibiotics**.
- Although not an antibiotic in its own right, clavulanic acid will also be classed as **Highly Important** due to its use as a co-formulant with amoxicillin. This classification will also recognise its importance in directly maintaining efficacy for amoxicillin, and indirectly maintaining efficacy for other penicillins, through resistance mitigation.

Antibiotic-based trade name products containing these compounds will require changes to their product labels to reflect the new classifications and revise certain aspects of their product claims and label information. In general, these changes will include:

- a clearly evident label statement identifying the importance classification;
- revised product claims to ensure a target organism and/or clinical disease relative to the target species is included in the indications of use;
- revised dosing information to ensure appropriate treatment intervals and durations are advised; and
- inclusion of the standardised prudent use statement applicable to the product's classification ranking.

Information on how these changes apply to each affected trade name product will be provided to registrants.

Because the use and risk profiles of each antibiotic compound has a direct impact on what would be considered good agricultural practice (GAP) for that compound, a review of the applicable maximum residue levels (MRLs) was also incorporated into this review. With the exceptions of spiramycin, cefovecin, and cefpodoxime, which are only approved for use in companion animals, all antibiotic compounds in scope for this review will require new and/or

revised MRLs in food-producing animal commodities when the product-specific reassessments are complete.

2 Background and Overview

2.1 ANTIBIOTIC REVIEW AND REASSESSMENT STRATEGY

One of the key objectives of the New Zealand National Action Plan was to review the controls on antibiotic-based trade name products used in the veterinary and horticultural sectors. This is to ensure the controls applied to these products were fit for purpose to manage the risks associated with antimicrobial resistance (AMR). To achieve this, a key Year One activity was to begin work on reviewing these registrations, and to establish an ongoing reassessment programme for antimicrobials in veterinary medicines.

Because the reassessment of all registered antibiotic-based trade name products included a significant number of compounds, the decision was made to complete the reassessment work in a series of tranches. These are:

- Tranche 1: Macrolides, later-generation cephalosporins, and penicillins
- Tranche 2: Veterinary aminoglycosides, fluoroquinolones, lincosamides, and 1st/2nd generation cephalosporins
- Tranche 3: Fusidic acid, tetracyclines, sulphonamides/diaminopyrimidines, and polypeptides (zinc bacitracin and polymyxin),
- Tranche 4: Amphenicols, nitrofurans, nitroimidazoles, pleuromutilins, and virginiamycin
- Tranche 5: Horticultural aminoglycosides (streptomycin and kasugamycin).

This structure allows for a more manageable reassessment schedule while prioritising the most widely used classes (Tranche 1) for immediate evaluation. Selecting macrolides, later-generation cephalosporins, and penicillins as the first tranche also provides a baseline for assessment that incorporates multiple levels of classification risk, which was anticipated to include both the Critically Important and Highly Important categories. Since the majority of the registered antibiotics will likely fall in one of these two categories, it was important that the general considerations for both were established in the first tranche.

Due to the fact that the first tranche of reassessments will involve 19 registrants and 116 products, it was considered that a pre-reassessment review would help provide more detail and structure for the changes expected for each registration. The review would evaluate existing approved product uses and label claims, registration controls, existing New Zealand MRLs, overseas authority MRLs, and what is known about AMR risk relative to each compound and its use in New Zealand. This would then inform whether each compound is classed as Important, Highly Important, or Critically Important, and determine the changes needed for each antibiotic-based trade name product. The general process and assessment strategy established in this review will apply to the remaining tranches going forward.

2.2 MAXIMUM RESIDUE LEVEL REVIEW

Good agricultural practice (GAP) is a set of principles and agricultural methods that establishes use patterns for agricultural compounds that will achieve the intended effect while leaving the smallest amount of residue practicable without compromising efficacy. For antibiotic-based trade name products used on food-producing animals and crops, GAP

includes the prudent use of compounds to minimise the risk of developing AMR. Because this review seeks to evaluate the regulatory controls on all antibiotic-trade name products, which include controls on residues management in food-producing animal species and crops, a review of the maximum residue levels (MRLs) has been incorporated into the review work.

The goal of the MRL part of the review will be to ensure there are commodity-specific MRLs for all antibiotic agricultural compounds used in food production. Although the residue risks associated with all approved food production uses would have been assessed at registration, the historic policy for establishing MRLs was to set limits only where they exceeded the default MRL of 0.1 mg/kg. Going forward, MRLs will be set for all compounds used in all approved species and crops to ensure a greater degree of transparency for residues assessment and management in New Zealand food production. Incorporating a MRL review into this antibiotic review and reassessment work will allow for a comprehensive review of the regulatory controls on antibiotic-based trade name products while providing assurance that antibiotic residues are being effectively controlled in food-producing species and crops.

3 General Considerations

A few general considerations applicable to the regulation and proposed changes for all affected trade name products have arisen during the course of this review. The following applies to all affected products and will need to be considered and applied on a product by product basis during the reassessment appraisals.

3.1 CHANGES TO THE VETERINARIANS' CODE OF PROFESSIONAL CONDUCT

Although not yet ratified, the Veterinary Council of New Zealand (VCNZ) has finalised their changes to the Code of Professional Conduct governing veterinarians' use and authorisation of restricted veterinary medicines. As part of their statement of purpose, VCNZ has also outlined their upcoming changes to the Code regarding the prudent use of antibiotics. They include:

- reducing maximum periods of supply allowable under the Code: the new maximum periods will be four months for Critically Important antibiotics when used in any species, six months for Important and Highly Important antibiotics when used in companion animals (excluding horses), and 12 months for Important and Highly Important antibiotics when used in production animals and horses;
- an expectation that states veterinarians are not to "use antibiotics routinely for prophylactic or metaphylactic purposes in place of good clinical or animal husbandry practices";
- a "general tightening of use," requiring that veterinarians must be able to justify choice of treatment with reference to evidence (label instructions, recent peer-reviewed studies), and restrict their overall use of Critically Important antibiotics; and
- a prohibition on the advertising of antibiotics.

The recent change to the conditions of registration to prohibit the advertisement of antibiotic veterinary medicines to end users, coupled with the proposed changes outlined in this review, will complement the VCNZ changes.

3.2 CONCERNS RAISED BY THE VETERINARY PROFESSION REGARDING PATIENT UNDER-DOSING

At the New Zealand Veterinary Association (NZVA) conference in June 2018, it was raised in multiple presentations that some on-label antibiotic dose rates and intervals that were approved at the point of registration may no longer be considered best practice for that antibiotic. Although specific examples were not discussed, it raised the concern that on-label doses may be under-dosing patients and thereby increasing the potential for the development of resistance.

In light of the veterinary profession's comments, an evaluation of the available literature was undertaken as part of this review. Of the antibiotics included in this tranche, only erythromycin was identified as potentially having a lower on-label dose compared to what is currently considered best practice. It is expected that the issue of changing best practice would be more potentially relevant to older antibiotic compounds such as erythromycin and the products containing them, and/or those administered in feed or water.

Registrants will be asked to evaluate their on-label dose rates and provide a discussion of whether the existing dose rates and intervals are still considered prudent when they submit their reassessment variation application.

3.3 CLASSIFICATION OF TRADE NAME PRODUCTS CONTAINING MORE THAN ONE ANTIBIOTIC COMPOUND

Many antibiotic-based trade name products contain more than one antibiotic active ingredient. Some of these use two compounds in the same antibiotic class (e.g. ampicillin + cloxacillin – both penicillins – in an intramammary medicine), while others use antibiotic compounds from two different families (e.g. an oleandomycin + oxytetracycline + neomycin combination – a macrolide, a tetracycline, and an aminoglycoside – in an intramammary medicine). If more than one antibiotic is present in a single formulation, classification will be applied according to the highest risk compound in that combination. That means that if any of the antibiotic compounds included in the formulation are considered Critically Important, the entire product will also be considered Critically Important with respect to product claims, labelling requirements, and authorisation restrictions under the VCNZ's Code of Professional Conduct.

3.4 IDENTIFYING TRADE NAME PRODUCTS BY MPI CLASSIFICATION

Because the identification of the relative AMR importance will now be recognised at the regulatory level and will play a direct role in regulatory management from a VCNZ perspective, it is important that this classification is readily identifiable on all antibiotic products. To facilitate this, all antibiotic products will have a requirement to clearly specify that the product is considered Important, Highly Important, or Critically Important on the product label. Ideally, this classification will also be colour coded to green, amber/orange, and red to allow veterinarians to readily determine the classification of individual products.

3.5 STANDARDISED PRUDENT USE STATEMENTS

One of the key aspects of label information supporting the prudent use of antibiotics going forward will be a statement advising veterinarians of expectations around prudent use. The lack of a prudent use statement on product labels, and the variability in these statements when they are present, has diminished their recognition as important label information and advice. This is particularly important going forward, when each antibiotic must be clearly identified according to its established AMR risk: Critically Important, Highly Important, and Important. These categories are based on the following classification definitions, adapted from the criteria established by the World Health Organization (WHO):

Critically Important Antibiotics are antibiotic compounds that:

- have few or no suitable therapeutic alternatives in human and/or animal medicine or horticultural use in New Zealand; and
- are considered critical to the clinical treatment and resolution of disease caused by bacteria in humans, animals, and/or plants; and
- have a scientifically known and significant susceptibility to the development of AMR from either direct use or cross-resistance from another antibiotic or class of antibiotics.

Highly Important Antibiotics are antibiotic compounds that:

- are considered significantly important to the clinical treatment and resolution of disease caused by bacteria in humans, animals, and/or plants; and
- have a recognised and/or demonstrated potential for the development of AMR from either direct use or cross-resistance from another antibiotic or class of antibiotics.

Important Antibiotics are antibiotic compounds that:

- are considered important to the clinical treatment of disease in humans, animals and/or plants; and
- have characteristics that may lead to the development of AMR from either direct use or cross-resistance from another antibiotic or class of antibiotics.

To address the need for both a clear indication of the expectations around prudent use, and to ensure those expectations are proportional to each classification, it is proposed to establish a set of three standardised prudent use statements for the importance levels. These statements will be a mandatory for all antibiotic-containing product labels.

The following are the proposed statements that will be presented to the registrants for consideration.

Critically Important Antibiotics

[Active ingredient] is an antibiotic in the [antibiotic class] family and is considered Critically Important to human and animal health. Indiscriminate use of this antibiotic can contribute to the development of antibiotic resistance, and it should not be used as a first line treatment. The use of this antibiotic should be reserved for the treatment of conditions that respond poorly to other classes of antibiotic following culture and sensitivity testing, or in cases where other treatments have been clinically determined to be ineffective.

Use of this antibiotic should be limited to the minimum period needed to meet the clinical objective. Clinical response should be monitored during treatment, and choice of therapy reviewed if clinical signs of disease persist, increase, or relapse.

Highly Important Antibiotics

[Active ingredient] is an antibiotic in the [antibiotic class] family and is considered Highly Important to human and animal health. The use of this antibiotic should only be for the minimum period needed to meet the clinical objective. Clinical response to this antibiotic should be monitored during treatment, and choice of therapy reviewed if clinical signs of disease persist, increase, or relapse. In the event of treatment failure, culture and sensitivity should be considered to determine an appropriate alternative therapy. Indiscriminate use of this antibiotic can contribute to the development of antibiotic resistance.

Important Antibiotics

[Active ingredient] is an antibiotic in the [antibiotic class] family and is considered Important to human and animal health. The prophylactic and therapeutic use of this antibiotic should only be for the minimum period needed to meet the clinical objective, after alternative therapeutic and preventative measures have been considered. Indiscriminate use of this antibiotic can contribute to the development of antibiotic resistance.

These statements are based on existing prudent use statements, information from the Ministry of Health consents for existing antibiotics, and international statements on prudent use in the literature and overseas authority AMR information.

Once finalised, the wording and presentation of these statements will be mandatory like the existing animal welfare and MRL compliance regulatory statements. The expectation will be that primary labels and restricted size labels will at least have the classification clearly identified, and the full prudent use statement will be included in the secondary labelling.

The ACVM Requirements document *Labelling Veterinary Medicines* will be updated to reflect the new antibiotic-specific requirements as the reassessment progresses.

4 Macrolides and Ketolides

4.1 BACKGROUND

The macrolide class of antibiotics are primarily bacteriostatic molecules that work by binding the 50S subunit of the bacterial ribosome and inhibit protein synthesis, thereby limiting bacterial growth and replication. The compounds are generally classed by their derivation as generations of macrolides, and by their chemical ring structures: 14-, 15-, or 16- membered lactone rings carrying one or more sugars distinguishing the different antibiotics in this family. The natural macrolides are 14- or 16-membered-ring compounds, while the semisynthetic derivatives are 15-membered-ring compounds. The different structures of the naturally occurring macrolides impart different effects (for example, the 14-membered-ring macrolides can stimulate gastrointestinal mobility, while the 160member-ring macrolides do not). The 15-membered-ring semisynthetic macrolides have been derived and developed to improve the pharmacokinetics and bioavailability beyond their naturally derived counterparts.

The first generation macrolides are derived from *Streptomyces spp.* and include erythromycin, oleandomycin, spiramycin, and tylosin. Erythromycin and oleandomycin are both 14-membered-ring compounds, while spiramycin and tylosin are 16-membered-ring compounds. The second generation macrolides are semi-synthetic derivatives of first generation macrolides, and include tilmicosin (16-membered-ring, derived from tylosin), and erythromycin-derived compounds such as clarithromycin (14-membered-ring) and azithromycin (15-membered-ring); clarithromycin and azithromycin are not currently used in New Zealand registered veterinary medicines. Tulathromycin could be considered a third generation macrolide as it is a semi-synthetic 15-membered-ring molecule derived from the azalide second generation macrolides such as azithromycin.

Macrolides are classed as Highest Priority Critically Important antibiotics in human medicine by the WHO, and Critically Important antibiotics in veterinary medicine by the World Organisation for Animal Health (OIE). Antibiotics classed by the WHO as Highest Priority Critically Important are those with few therapeutic alternatives, requiring the most careful use to preserve their efficacy. Agents classed as Highest Priority Critically Important have also

been demonstrated to be susceptible to the development of AMR by either selection after direct use or cross-resistance from another agent or class.

OIE classification as Critically Important is based on a survey of the veterinary profession, and their consideration of the clinical importance of these compounds. The Critically Important classification was applied to those antibiotics that met both criteria for determining importance: antimicrobial agents that more than 50% of respondents identified as important when responding, and antimicrobial agents that were identified as essential against specific infections with a lack of sufficient therapeutic alternatives.

4.2 ANTIMICROBIAL RESISTANCE

Resistance to macrolides generally occurs as acquired resistance that is either plasmid-mediated or mutational, resulting in cross-resistance to other macrolides, lincosamides and streptogramins. The key concerns from a human health perspective is the potential for resistance in zoonotic pathogens, particularly *Campylobacter* and methicillin-resistant *Staphylococcus aureus* (MRSA). Plasmid-mediated resistance can also occur in animal-derived *Enterococcus spp.*, resulting in either enterococcal infections in humans or gene transference from enterococci to other bacteria able to colonise or infect humans. Resistance may also emerge in other staphylococci, streptococci, *Mycoplasma spp*., and *Brachyspira spp.*, by one of a number of mechanisms including plasmid-mediated, mutational alteration, and enzyme detoxification. The multiple possible resistance pathways allowing for a relative ease of resistance development, coupled with the likelihood of resistance extending to other antibiotics within the macrolide family and similar compounds like the lincosamides, results in a potentially significant impact of resistance on human and animal health extending from the use of all compounds within the macrolide family.

In New Zealand, the primary threat posed by macrolide resistance is associated with the need for macrolides, particularly azithromycin, in the human health professions. It is used as a first line treatment for pertussis in children, chlamydial and gonorrhoeal infections, and acute non-specific urethritis. It is also used as a second line treatment when other treatments are unsuitable (e.g. for the treatment of pelvic inflammatory disease when chlamydia is present and doxycycline cannot be used), or cannot be tolerated (e.g. for the treatment of pertussis in adults when erythromycin is not an option). Macrolides are also an important tool in combatting MRSA infections when cephalosporins or other therapies are not effective.

In addition to the importance of macrolides to human medicine, macrolides are considered Critically Important to veterinary medicine by the OIE, particularly in production animals. Macrolides are primarily used to treat mycoplasmal infections in pigs and poultry, digestive infections in pigs caused by *Lawsonia intracellularis*, liver abscesses in cattle caused by *Fusobacterium necrophorum*, and respiratory infections in cattle and poultry, diseases for which there are very few alternative therapies. These same indications and target species are common to New Zealand registered products.

Widespread use of macrolides has been shown to result in the rapid development of resistance in human medicine. After the introduction of clarithromycin in 1991 and azithromycin in 1992, macrolide resistance in the United States rose from approximately 10% in the early 1990s to 30% 10 years later. In 2011, azithromycin became the most commonly prescribed antibiotic owing to fewer gastrointestinal effects and once-a-day dosing; there is now a 30-35% rate of azithromycin resistance in *pneumococci* infections.[1]

A pattern of common use leading to macrolide resistance has also been found in New Zealand veterinary antibiotic use. Tilmicosin, tylosin, and tulathromycin are all approved for use in pigs, with tulathromycin being the most recent macrolide compound registered (2013). Tilmicosin and tylosin are commonly used in this sector, with both available as in-feed products. A 2008 study evaluating bacterial isolates from healthy pigs in New Zealand

[1] Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med 2013; 1:262–74.

showed that of 273 *Enterococcus spp.* samples taken from three conventional farms, 68% were found to be resistant to erythromycin despite the one and only erythromycin product approved for use in pigs being cancelled in 2004.[2] This would suggest not only a significant level of macrolide resistance, but also cross-resistance from the use of tilmicosin and tylosin in pigs.

4.3 VETERINARY MACROLIDE USE IN NEW ZEALAND

Macrolides are used in veterinary medicine mainly as alternatives to β-lactams to treat skin, respiratory, urogenital, and mycoplasmal infections. First generation macrolides have a broad spectrum activity and safety margin, and the second generation macrolides have an even broader spectrum of activity and better pharmacokinetic properties (e.g. they are more stable in acidic environments). The third generation macrolides and ketolides (also macrolide derivatives) have been developed in response to the emergence of macrolide resistant bacteria, with a narrower spectrum of activity than their predecessors. Ketolides are structurally and clinically similar to macrolides. As there are currently no registered veterinary medicine containing ketolides antibiotics, this class will not be considered further.

Currently 25 trade name products containing macrolides are registered: one erythromycin product, two oleandomycin products, a suite of three spiramycin products, three tilmicosin products, 15 tylosin products, and one tulathromycin product. The only products not approved for use in food-producing animals are the spiramycin products.

Most of the macrolides registered for use as veterinary medicines in New Zealand are veterinary-only compounds. The only antibiotic compounds directly used in human medicine are erythromycin and oleandomycin.

4.4 MPI CLASSIFICATION

It is considered that all macrolides currently registered as veterinary medicines – **erythromycin, oleandomycin, spiramycin, tilmicosin, tulathromycin, and tylosin** – should be classed as **Critically Important** in New Zealand. These include erythromycin, oleandomycin, spiramycin, tilmicosin, tylosin, and tulathromycin. This is based on the following:

1. the importance of these compounds to both human and animal health in New Zealand, as evidenced by the clinical relevance of the diseases indicated for both human and veterinary treatment;
2. the need to retain macrolide efficacy to manage those diseases, particularly when suitable alternatives are unavailable;
3. the potential for macrolide resistance to develop, and the speed at which it may develop with significant use;
4. the potential for cross-resistance to develop to other compounds within the macrolide class, and other antibiotics such as lincosamides and streptogramins, regardless of ring structure/generation; and
5. international classification of macrolides as Critically Important by both the OIE and the WHO.

Although erythromycin, oleandomycin, spiramycin, tilmicosin, tylosin, and tulathromycin represent all macrolides currently registered for veterinary use in New Zealand, it is important to set the classification at the compound level rather than the entire class. This is to recognise that the science around AMR is still evolving, and the risk profiles for individual

[2] Nulsen MF, Mor MB, Lawton DEB. Antibiotic resistance among indicator bacteria isolated from healthy pigs in New Zealand. New Zealand Veterinary Journal, Volume 56, Issue 1, pp 29-35, Feb 2008

compounds may change as more is understood about resistance mechanisms and their relative risks. This also allows for individual evaluation of new macrolide compounds, or compounds new to veterinary medicine, as they emerge.

This decision aligns with the intent of the NZVA's classification of the macrolide family of compounds as 'Red' or clinically critical antimicrobials.

4.5 TRADE NAME PRODUCT IMPACTS

4.5.1 Maximum Residue Levels

Of the six antibiotic compounds registered for New Zealand veterinary use in this class, only tulathromycin has a nearly complete suite of commodity-specific MRLs for the species in which it is approved for use; a milk MRL has not been promulgated for this compound, leaving this commodity subject to the default MRL of 0.1 mg/kg. The remaining compounds are all subject to the MRL default for all commodities. Five of these compounds are approved for use in at least one food-producing animal species, and all six compounds have MRLs set by at least one overseas authority. It is therefore considered that the MRLs for all compounds approved for use in food-producing animals will need to be reviewed and new MRLs promulgated as an outcome of the reassessment.

Without prejudging the outcome of more detailed data reviews during the reassessment appraisal, the following has been determined:

Erythromycin

Use of the compound in poultry is currently subject to the application of the default MRL. It is considered that promulgated MRLs are necessary but may be considered for promulgation at 0.1 mg/kg for all tissue commodities. The egg MRL may need to be set lower than 0.1 mg/kg to ensure trade access, depending on the residue profile in eggs when used according to New Zealand GAP – China, Codex, and Japan have egg MRLs set at 0.05 mg/kg.

Because most overseas authorities including Codex have set a residue definition of 'Erythromycin A' for animal commodities, it is considered this will likely be the most appropriate option for a New Zealand promulgated definition.

Oleandomycin

Oleandomycin is currently only approved for use in cattle, with no set MRLs, despite MRLs being promulgated in Australia and China. It is considered that MRLs should be promulgated for cattle-derived commodities and milk, with the meat commodities being promulgated at 0.1 mg/kg. This would comply with both authorities that have MRLs set, while retaining the same MRL value for all meat commodities as is currently applicable. Milk residue data will need to be reviewed and a lower MRL than the currently applicable 0.1 mg/kg considered, due to the Chinese MRL being set at 0.05 mg/kg.

A residue definition of parent oleandomycin is considered appropriate for this compound.

Spiramycin

Because the only registered products containing spiramycin are approved for use in companion animals, and prohibited for use in food-producing species, it is considered that MRL promulgation is not appropriate for this compound. The application of the MRL default of 0.1 mg/kg, the maximum permissible level (MPL) default for exogenous contaminants of 0.001 mg/kg in exported products, and the action limit of

0.04 mg/kg in milk set for the National Chemical Contaminants Residues Monitoring Programme, will be sufficient to manage the residue and trade risks[3].

It is noted that the Japanese MRLs for spiramycin and a few other compounds bear the following statement for some antibiotics: "Since [antibiotic] is regarded as antibiotics or chemically synthesized antibiotic substances, [antibiotic] should not be contained in foods for which MRLs are not defined or whose name is not found in this table of MRLs." This approach could be considered for this and other companion-only compounds, as part of a statement in the MRL Notice as per section 141(b)(i) of the Food Regulations[4], to support the application of a registration conditions to prohibit the use of certain compounds in food-producing species. It is suggested that schedule is included in the Notice making an overall statement for residues that should not be found in food if used according to GAP and listing companion-animal-only compounds for which the statement applies. If strengthened to a "must" statement, this list can include prohibited substances. Alternatively, there can be separate "should" and "must" lists.

Tilmicosin

Tilmicosin is currently approved for use in cattle, sheep, and pigs, but there are only promulgated MRLs for pig-derived commodities. It is considered the MRLs will need to be promulgated for cattle- and sheep-derived commodities to ensure appropriate use of the compound according to GAP and to facilitate trade, especially considering that some authorities have MRLs set below the 0.1 mg/kg default that currently applies to these commodities. For completeness, the pig commodity MRLs should also be reviewed, though they may not require adjustment.

The current residue definition of parent tilmicosin aligns with that set by all overseas authorities. There is therefore no indication that the residue definition requires review.

Tulathromycin

Tulathromycin is approved for use in cattle, sheep, and pigs, with promulgated MRLs in place for all commodities except milk. A review of the international MRLs for cattle and pig commodities demonstrated that the current meat and offal MRLs appear to be sufficient to ensure its use according to GAP and to manage trade risk. The only international authority with tulathromycin MRLs in sheep is China, with all values set at 0.1 mg/kg; it is considered that the sheep MRLs should be reviewed during the reassessment to confirm they continue to be sufficient to manage New Zealand GAP. A milk MRL should be considered for this compound, particularly in light of the split New Zealand approval (a withholding period in place for cattle milk but a "do not use" statement for sheep milk) and the prohibition of the use of the compound in lactating animals in the EU. No other international authority has established a milk MRL for tulathromycin, even when they have established MRLs for other ruminant-derived MRLs. There are no Codex MRLs for this compound.

The current New Zealand residue definition for this compound is based on the metabolite profile of tulathromycin derivatives in tissues, which aligns with all overseas authorities except Australia and Japan. These two authorities include parent tulathromycin as part of the definition, making it the sum of parent and metabolites expressed as tulathromycin. It is considered that a review of the residue data is warranted to confirm whether the definition requires adjustment to include the parent compound.

[3] MPLs and action limits are set under the Animal Products Act, and can be found in the *Animal Products Notice: Contaminant Specifications* and the *National Programme for the Monitoring and Surveillance of Chemical Residues and Contaminants in Milk*, respectively. The *National Programme* paper is updated annually for the next year's monitoring programme.
[4] http://legislation.govt.nz/regulation/public/2015/0310/24.0/DLM6684516.html

Tylosin

Tylosin is currently subject only to the default MRLs in New Zealand, despite the fact that it is approved for use in cattle, sheep, pigs, goats, chickens, and turkeys. It is considered that a full suite of MRLs is required for this very commonly used compound to ensure the GAP use of the compound. With the exception of a milk MRL, which following a brief review may require promulgation at 0.05 mg/kg, it is considered that promulgation of MRLs at 0.1 mg/kg may be sufficient to manage the GAP use of the compound and facilitate trade. It is important however that a suite of MRLs are established, both for transparency of residues management and to establish a New Zealand residue definition.

All overseas authorities apart from the United States have established a residue definition for tylosin as 'tylosin A.' It is considered that alignment with the Codex definition, which is also 'tylosin A', will likely be the most appropriate choice for a New Zealand residue definition when one is promulgated. This will be determined based on a review of available residue data.

4.5.2 Product Registrations

The shift to classify New Zealand macrolide veterinary antibiotics will require a refinement of the current regulatory controls on these products, including the following changes:

- on-label identification of the product as one containing a Critically Important antibiotic;
- specificity in the product claims to identify a target organism and/or clinical disease, particularly those claims generalised to any organism considered susceptible to the antibiotic;
- specificity regarding treatment interval and duration for all product claims, with particular consideration for claims associated with prophylaxis. This is driven both by the risks associated with macrolide use and the requirements put in place as a condition of Ministry of Health consent: that treatment must be administered for as short a period as possible, and that tylosin, oleandomycin, and tulathromycin are only as a last resort or if no other antibiotic is suitable; and
- application of a standardised prudent use statement for all products containing a Critically Important antibiotic.

The prohibition to use spiramycin in food-producing animals is considered appropriate and should be retained.

5 Later-Generation Cephalosporins

5.1 BACKGROUND

The cephalosporins are a class of bactericidal broad spectrum β–lactam antibiotics derived from *Acremonium spp.* and are structurally similar to penicillins. They function by either binding the penicillin-binding proteins to inhibit cell wall synthesis, or by activating autolytic enzymes in the wall leading to cell lysis and bacterial death.

Unlike macrolides, which are established based on derivation of new compounds from the previous generation, the five cephalosporin generations serve to group compounds into sub-groups based on antibiotic activity. Currently only four generations of cephalosporins are used in veterinary medicine in New Zealand. The first generation cephalosporins were the first compounds discovered and have good broad-spectrum activity against Gram-positive bacteria. Second generation cephalosporins are more stable against hydrolysis by β–

lactamases and therefore have activity against Gram-negative enterobacteriaceae. Because they have a more limited spectrum of activity, the first and second generation cephalosporins are considered less important than later-generation compounds and will be considered in a separate review.

The third, fourth, and fifth generation cephalosporins are collectively grouped as the later-generation cephalosporins. These compounds have the widest spectrum of activity compared to the earlier generations and are significantly active against *Streptococci spp.* and many of the significant enterobacteriaceae. The veterinary cephalosporins currently in use in New Zealand within this group include cefovecin, cefpodoxime, ceftiofur, and cefquinome; the first three are third generation cephalosporins and the last is a fourth generation compound. Currently no fifth generation cephalosporins are registered for veterinary use; fifth generation cephalosporins will therefore not be considered further.

Their spectra of activity, particularly against more clinically important pathogens, has resulted in the WHO classifying all later-generation cephalosporins as Highest Priority Critically Important antibiotics. The OIE has classified ceftiofur and cefquinome as Critically Important, but has not classified cefovecin and cefpodoxime. It is possible that the latter compounds were not classified because the survey informing classification was structured to evaluate veterinarians' view of clinical importance, and the limited availability and use of those compounds (one product each, both used in companion species only) would likely have resulted in the surveyed vets having limited clinical experience with them.

5.2 ANTIMICROBIAL RESISTANCE

Because the bactericidal activity of cephalosporins relies primarily on binding to penicillin-binding proteins (PBPs) during cell wall synthesis, the binding affinity of these proteins is integral to both activity and resistance. Resistance to cephalosporins can develop by one of three mechanisms: a loss of binding affinity between the antibiotic and the PBPs, the acquisition of β-lactam insensitive PBPs to use in cell wall synthesis, and the use of β-lactamases to inactivate the cephalosporin.

The primary concern regarding AMR and the use of later-generation cephalosporins stems from the potential for resistance to develop in the enterobacteriaceae family of bacteria. This group, which includes *Escherichia coli, Klebsiella pneumoniae,* and *Salmonella spp.,* is part of the normal flora of the mammalian gastrointestinal tract as commensal organisms and carry the potential to become opportunistic pathogens. These organisms are prone to the development of resistance due to having several potential mechanisms to obtain genes for antibiotic-deactivating enzymes, the most significant of which is the development and transmission of genes for the production of extended-spectrum β-lactamase (ESBL). The WHO has also reported that higher-generation are known to select for resistant *Salmonella* and *E. coli* in animals, and are often the only therapeutics available for managing severe *Salmonella, E. coli*, and multi-resistant enterobacteriaceae infections in humans.[5]

The rate of resistance to cephalosporins has been reported to be increasing in recent years, mainly due to the spread of extended-spectrum β-lactamase (ESBL) Gram-negative bacteria worldwide. The development of resistance by this mechanism is understood to be due to the survival and persistence of bacteria carrying the genes for ESBL and other enzymes, and the ability of these bacteria to horizontally transfer this resistance by passing on the plasmid-mediated genes to other Gram-negative organisms. It has been found that plasmids bearing ESBL genes often also carry genes for resistance to other β-lactams (e.g. penicillins), aminoglycosides, and fluoroquinolones, making them multi-resistant[6]. The increasing prevalence of ESBL-producing bacteria means a concurrent increase in resistance to other

[5] World Health Organization. Critically Important Antimicrobials for Human Medicine, 5th Revision. 2016.
[6] Rawat D and Nair D. Extended-spectrum β-lactamases in Gram Negative Bacteria. J Glob Infect Dis. 2010 Sep-Dec; 2(3): 263–274.

antibiotics, as well as the spread of a difficult to treat multi-drug-resistant infection which is capable of transferring between people and animals.

Human cases of ESBL-producing bacteria have been increasing in recent years. A 2014 report found that human cases of ESBL-producing bacteria in Korean hospitals, particularly *E. coli* isolates, increased from 3.6% in 2006 to 14.3% in 2011[7]. A similar increase contributed to ESBL-producing enterobacteriaceae isolates, particularly *E. coli*, was found in a 2006 study in London[8], and in 2014 in New Zealand. According to the New Zealand study, 2.6% of *E. coli* isolates in 2006-2008 were ESBL positive, compared to 3.8% - a 46% increase – in 2009-2011[9].

From a veterinary perspective, there is evidence of both animal to human transfer, primarily through the handling of food-producing species or food-borne transmission, and human to animal transfer in both food-producing and companion animals. The human to animal transfer pathway was evidenced by isolate typing in animal infections that demonstrated the same sequence types as isolated from human infections, and finding bacteria producing ESBL and other antibiotic-disabling enzymes in up to 8% of cultures from animals that had not been recently been treated with antibiotics[10]. This suggests that the risks associated with ESBL-producing and multi-resistant bacteria have the potential to significantly impact both human and animal health.

5.3 VETERINARY USE OF LATER-GENERATION CEPHALOSPORINS IN NEW ZEALAND

Three third generation cephalosporin antibiotic compounds are currently registered for veterinary use in New Zealand: cefovecin and cefpodoxime, and ceftiofur. Cefovecin and cefpodoxime are both used for the treatment of skin and soft tissue infections, including oral infections, in companion animals only; cefovecin is approved for use in dogs and cats, and cefpodoxime is approved for use in dogs only. Most ceftiofur products are approved for use in pigs and cattle, for the treatment of respiratory infections, reproduction-related infections, and foot rot (cattle). Four of the 11 ceftiofur products are also approved for use in horses for the treatment of respiratory infections.

Cefquinome is the only fourth generation cephalosporin currently approved for veterinary use, with one product used as an intramammary lactating cow mastitis treatment and one used as an injectable treatment in cattle and pigs. The injectable product is used in the treatment of respiratory disease in both species, *E. coli* mastitis and foot rot in cattle, and Mastitis-Metritis-Agalactia (MMA) Syndrome in pigs.

Currently 15 later-generation cephalosporin trade name products are registered: one cefovecin product, one cefpodoxime product, 11 ceftiofur products, and two cefquinome products. The cefovecin and cefpodoxime products are companion animal only, and the ceftiofur and cefquinome products are production animal only.

Of the New Zealand veterinary approved antibiotics, the only later-generation cephalosporin directly used in human medicine is cefpodoxime. The other three are recognised as veterinary-only compounds.

[7] Park, SH. Third-generation cephalosporin resistance in gram-negative bacteria in the community: a growing public health concern. Korean J Intern Med. 2014 Jan; 29(1): 27–30.
[8] Potz NA et al. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. J Antimicrob Chemother. 2006 Aug; 58(2):320-6. Epub 2006 May 30.
[9] Thomas MG et al. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand. The NZ Medical Journal 2014; 127:1394.
[10] Toombs-Ruane LJ et al. Multidrug resistant Enterobacteriaceae in New Zealand: a current Perspective. New Zealand Veterinary Journal, 65(2), 62–70, 2017

5.4 MPI CLASSIFICATION

The later-generation cephalosporins present very similar risk profiles with respect to resistance mechanisms, human and veterinary clinical importance, and relative risk for the development of resistance. Because of this, the third, fourth, and fifth generation compounds are generally considered one subgroup by international authorities when evaluating clinical use and assigning importance ranking for both human and animal health.

Like the macrolides, however, it is important to set the classification at the compound level rather than the entire class as the science around AMR risk continues to evolve. This is to ensure each compound is individually considered even if related compounds appear to have very similar or identical risk profiles at present.

Based on the information available on the third and fourth generation compounds used in veterinary medicines in New Zealand, **cefovecin, cefpodoxime, ceftiofur, and cefquinome** should be classed as **Critically Important** veterinary antibiotics in New Zealand.

It is noted that this decision aligns with the NZVA's classification of the third and fourth generation cephalosporins as 'Red' or clinically critical antimicrobials.

5.5 TRADE NAME PRODUCT IMPACTS

5.5.1 Maximum Residue Levels

Two of the four later-generation cephalosporins are used in food-producing animals. Cefquinome has a nearly complete suite of MRLs for the approved species cattle and pigs, though milk residues are subject to the default MRL instead of a commodity-specific level. Cattle and pig tissue MRLs have been set for ceftiofur, but horse-derived commodities and milk are also subject to the default MRL. It is therefore considered that the existing application of the default MRL will need to be reviewed and new MRLs promulgated for ceftiofur and cefquinome as an outcome of the reassessment.

Without prejudging the outcome of more detailed data reviews during the reassessment appraisal, the following has been determined:

Cefovecin and Cefpodoxime

These compounds are only approved for use in companion animals in New Zealand and there are no overseas limits set for any species. It is therefore proposed that no MRLs are necessary, allowing the application of the default MRLs and MPLs, and the possible application of a condition of registration prohibiting food-producing animal use, to manage the residue and trade risks.

As noted for spiramycin, a statement can be considered for the MRL Notice that states cefovecin and cefpodoxime residues should not be present.

Cefquinome

Cefquinome is currently approved for use in cattle and pigs, and MRLs are promulgated for all cattle- and pig-derived meat commodities. An initial review of the international MRLs promulgated by China and Japan confirmed that the tissue commodity MRLs currently promulgated in New Zealand are sufficient to manage trade risks and may be retained. However, milk residues are currently managed by the application of the default MRL in New Zealand, and limits have been promulgated by both China and Japan at 0.02 mg/kg. It is considered that a milk MRL should be proposed for this compound considering there are direct indications for lactating animals in the treatment of mastitis, and international MRLs below the New Zealand default. For completeness, all MRLs should be reviewed to ensure they are still sufficient to support New Zealand GAP.

The residue definition may be retained as parent cefquinome as that matches the definition applied by China and Japan. There are no other MRLs and/or residue definitions defined by any other overseas authority, including Codex.

Ceftiofur

Ceftiofur is currently approved for use in cattle, pigs, and horses, with MRLs in place for cattle- and pig-derived meat commodities. There are currently no commodity-specific MRLs promulgated for any horse-derived commodities or milk. A review of the international MRLs for cattle tissue and pig commodities demonstrated that the current MRLs appear to be sufficient to ensure its use according to GAP and to manage trade risk. It is noted that there is unlikely to be horse residue data available to inform a review. Based on a review of overseas MRLs applicable to horse-derived commodities, however, the promulgation of horse MRLs at 0.1 mg/kg will be sufficient to manage export trade risk should export trade in horse commodities resume. Similarly, the promulgation of a milk MRL at 0.1 mg/kg will also be sufficient to manage trade risk, though a lower MRL may be more appropriate. The milk MRL will be determined based on a review of residue data on file for the compound.

The current residue definition for this compound in New Zealand is desfuroylceftiofur. This aligns with existing overseas residue definitions except those set for the EU ('Sum of all residues retaining the beta lactam structure expressed as Desfuroylceftiofur') and Japan ('Sum of ceftiofur, desfuroylceftiofur, and metabolites convertible to desfuroylceftiofur by dithioerythritol, expressed as ceftiofur'). Although a review of the current definition is warranted, it is expected the definition will be retained as desfuroylceftiofur as the most commonly aligned definition and that which matches Codex.

5.5.2 Product Registrations

All of the existing products have claims and/or indication information in the product leaflet that are reasonably targeted to enterobacteriaceae-caused infections, but most labels will require at least some changes to action classification as a Critically Important antibiotic. These are:

- on-label identification of the product as one containing a Critically Important antibiotic;
- refinement of the product claims and label information to ensure that all claims identify a target organism and/or clinical disease, particularly those claims generalised to any organism considered susceptible to the antibiotic;
- specificity regarding the indication, treatment intervals, and duration of treatment. This is particularly important for claims generalised to the management of wounds rather than infections, and any claim associated with prophylaxis; and
- application of a standardised prudent use statement for all products containing a Critically Important antibiotic.

The prohibition of the use of the cefovecin and cefpodoxime products in food-producing animals should also be considered, in the interest of limiting the use of these compounds to companion species for which they are intended. This will align controls on these two compounds with the existing control on spiramycin, which is also a companion-only compound and classed as Critically Important. It is also noted that, like the spiramycin products, the cefovecin and cefpodoxime products are not in forms that are practical for production animal use.

6 Penicillins

6.1 BACKGROUND

The penicillins are a class of bactericidal β–lactam antibiotics that are either naturally derived from *Penicillium spp.* or have been altered to improve their duration of activity, β–lactamase resistance, or spectrum of efficacy.

All penicillins function by inhibiting cell wall repair following bacterial replication, leaving the weakened cells susceptible to fluid ingress, cytoplasm leakage, and cell rupture. This is done by binding the β-lactam section of transpeptidases, also known as penicillin binding proteins (PBPs), disrupting the bacterial cell's ability to close 'holes' in the cell well formed during growth and replication with new peptidoglycan polymer chains. In Gram-positive bacteria, a thick peptidoglycan cell wall surrounds the entire cell, and the PBPs within that wall are the direct target of the penicillins. In Gram-negative bacteria, a thinner peptidoglycan cell wall is present, but it sits between an outer lipopolysaccharide membrane containing porins, and the inner plasma membrane of the cell. Some of the extended-spectrum semi-synthetics (amoxicillin and ampicillin) are able to traverse the outer membrane of some Gram-negative bacteria through the porins and attach the PBPs in the cell wall.

Penicillin G, or benzylpenicillin, is the oldest known antibiotic, naturally derived from the *Penicillium notatum* fungus in 1928 and first used as a commercial therapeutic in 1942. The procaine (penicillin G procaine and procaine penicillin) and benzathine (penicillin G benzathine) variants were the earliest altered versions of benzylpenicillin, which were produced to make them longer acting than their natural counterpart. The delayed release and absorption profile is a mechanism of a depot effect at the injection site, with both penicillin G procaine and penicillin G benzathine are hydrolysed to release benzylpenicillin on absorption.

By contrast, the semi-synthetics amoxicillin, ampicillin, and cloxacillin are compounds where the chemical structure of benzylpenicillin has been altered to extend the bacterial spectrum and/or ease of administration; the final antibiotic released from the drug formulation and absorbed by the patient is the altered compound itself and not benzylpenicillin. Cloxacillin has been structurally altered to make it resistant to β–lactamases, enzymes produced by bacteria to inactivate the activity of the penicillin by hydrolysing the β–lactam ring that binds PBPs. This is achieved by making the molecule larger, which prevents inactivation by β–lactamases but at the same time narrows its spectrum of bactericidal activity.

Amoxicillin and ampicillin have both been synthesised to extend their spectrum of activity against many Gram-negative bacilli and make them more stable *in vivo* to allow more than parenteral administration. The trade-off for these benefits, however, is that they are generally less effective than benzylpenicillin against Gram-positive cocci, and both have retained their sensitivity to β–lactamases. To counteract this sensitivity, penicillins can be co-formulated with either compounds that inactivate β–lactamases, or with other antibiotic compounds resistant to β–lactamases, to preserve the antibiotic product's efficacy.

In New Zealand veterinary products, amoxicillin is often co-formulated with the β–lactamase inactivating compound clavulanic acid, present in the formulations as potassium clavulanate. Clavulanic acid is a semi-synthetic β-lactam compound that was originally isolated from *Streptomyces clavuligerus,* which has negligible antibacterial activity in its own right. Its primary function in the amoxicillin/clavulanic acid combinations is to act as a rapid and potent inhibitor of the enzymatic degradation of amoxicillin by binding the β-lactamases at the site of their activity with their own β–lactam ring. This irreversibly binds the clavulanic acid molecule to the enzyme, permanently inactivating both.

The β–lactamase sensitivity of ampicillin always mitigated in New Zealand veterinary products by co-formulating it with cloxacillin, which is structurally resistant to the enzymes. The pairing of ampicillin and cloxacillin results in a formulation that has a broader spectrum

of activity contributed by the ampicillin, and continued efficacy in the presence of β–lactamases contributed by cloxacillin.

The WHO has split the classification of penicillins into two groups: a Critically Important listing for 'natural' penicillins or benzylpenicillins, aminopenicillins, and antipseudomonal penicillins, and a Highly Important listing for amidinopenicillins and anti-staphylococcal penicillins. With respect to the antibiotic compounds used in New Zealand veterinary medicines, this would place amoxicillin, ampicillin, penicillin G benzathine, penicillin G procaine, and penethamate hydriodide in the WHO's Critically Important category (with acknowledgment that penethamate hydriodide is only used in veterinary medicine), and cloxacillin (anti-staphylococcal) in the WHO's Highly Important category. The antipseudomonal penicillins and amidinopenicillins are not currently approved for use in veterinary medicinal trade name products in New Zealand and will not be considered further in this review.

The rationale for the WHO groupings is as follows:

Critically Important listing for benzylpenicillins and aminopenicillins

- Limited therapy available to treat serious bacterial infections in people caused by syphilis (natural penicillins), *Listeria*, *Enterococcus* spp. (aminopenicillins), and multi-drug resistant *Pseudomonas spp*. (antipseudomonal) in certain geographical settings; and
- Penicillins are used to treat infections in people caused by either bacteria that may be transmitted from non-human source, or bacteria that may acquire resistance genes from non-human sources, including *Enterococcus* spp., *Enterobacteriaceae* including *Salmonella* and *E. coli*, and *Pseudomonas aeruginosa*.

Highly Important listing for anti-staphylococcal penicillins

- In certain geographical settings, the anti-staphylococcal penicillins may be the sole, or one of limited available therapies, for staphylococcal infections including *S. aureus*; and
- Anti-staphylococcal penicillins may be needed to treat infections caused by the transmission of *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), from non-human sources.

All penicillins are considered to be Very Critically Important to veterinary medicine with respect to clinical imporance in the OIE rankings.

6.2 ANTIMICROBIAL RESISTANCE

Penicillin resistance has existed since shortly after its discovery, with the first documented reference to the discovery of penicillinase-producing *E. coli in vitro* in 1940. Penicillin resistant *S. aureus* was already being found in hospitalised patients in 1942, the same year penicillin G was commercially available. The diagnosis of penicillin resistance led to the development of first semisynthetic penicillins, with methicillin being introduced in 1959 and ampicillin two years later. Due to continued widespread use and overuse, more than 80% of medically cultured *S. aureus* was penicillin resistant by the late 1960s[11].

Resistance to penicillins can develop when either the bacterial population is able to produce penicillinases such as β-lactamases, or when the bacteria are able to alter their PBP production and/or cell wall structure to be more resistant to the action of the antibiotics. As discussed in section 6.1, The effect of β-lactamases are generally managed through the use of cloxacillin, structurally altered to be resistant to β-lactamases, or through co-formulation of β-lactamase sensitive compounds. The most common approaches are to co-formulate

[11] Lowy, FD. Review Antimicrobial resistance: the example of Staphylococcus aureus. J Clin Invest. 2003 May; 111(9):1265-73.

ampicillin with cloxacillin, and amoxicillin with clavulanic acid, to provide a β-lactamase inactivation function.

Combined therapies are still susceptible to resistance, however, particularly for the amoxicillin-clavulanic acid combination. This is usually occurs when bacteria adapt by overproducing β–lactamases, overwhelming the ability of cloxacillin to mitigate ampicillin's sensitivity, or the ability of clavulanic acid to inactivate the enzymes. Like other types of resistance mechanisms, this adaptation to hypersynthesise β–lactamases is generally attributed to overuse: the development of amoxicillin-clavulanic acid resistance in *E. coli* infections in humans has been directly attributed to over-prescribing[12]. The amoxicillin clavulanic acid resistance profiles in veterinary medicine varies: a 2011 European review paper found very little evidence of resistance in animal species[13], while a 2013 US study found *E. coli* resistance in dogs and cats in as high as 40% of the isolates cultured[14]. This indicates that although the risk is mitigated by the use of clavulanic acid as a co-formulant, and the incidence of veterinary resistance to the amoxicillin-clavulanic acid combination may not be as high as in human patients, the risk of resistance is still present and must be mitigated by prudent use.

Resistance associated with the production of penicillin-binding proteins appears in one of two ways: either by the bacteria developing the capability to overproduce bacterial PBPs and overwhelm the ability of the penicillin to inhibit cell wall repair, or by altering the structure of the PBPs they produce to make them resistant to penicillin binding. The key resistance mechanism for MRSA is the presence of PBP2A, an altered PBP that is resistant to penicillin binding and can continue to repair and maintain cell walls in the presence of antibiotics. The genes responsible for the production of penicillinases and altered PBPs can occur spontaneously through mutation or can be passed from one bacterial cell to another cells through plasmid transference or conjugation. A third mechanism is by overexpression of efflux pumps to actively expel antibiotics out of the cell, though this is a less common mechanism most often associated with the development of biofilms.[15]

Despite the ease at which penicillin resistance can develop, the rates of AMR in New Zealand remain relatively low. For example, the incidence of clinical disease caused by MRSA has nearly doubled in an eight-year period, increasing from 10.2 per 100,000 in 2009 to 19.9 per 100,000 in 2017. It is noted, however, that the rate in 2009 may be underestimated due to a change in monitoring and sampling techniques, and the most recent data appears to show the rate has remained around 20 per 100,000 in the last three surveys (2014, 2015, and 2017)[16]. The epidemiology of MRSA-caused disease is also changing in New Zealand, with the first community-associated cases reported in the mid-2000s[17] and 10.8% of infections characterised as community patients in 2017.[18] Overall, however, the incidence of disease caused by MRSA remains low in New Zealand compared to other developed nations like the UK and US[19].

The other major concern for New Zealand with respect to penicillin resistance in the context of veterinary use is the emergence of ESBLs, particularly ESBL-producing *Enterobacteriaceae* (ESBL-E). The overall risks associated with ESBLs, and the potential for

[12] Oteo, J et al. Increased Amoxicillin–Clavulanic Acid Resistance in Escherichia coli Blood Isolates, Spain. Emerg Infect Dis. 2008 Aug; 14(8): 1259–1262
[13] Belmar-Liberato R et al. Amoxicillin and amoxicillin-clavulanic acid resistance in veterinary medicine –the situation in Europe: a review. Veterinarni Medicina, 56, 2011 (1): 473-485.
[14] Thungrat K et al. Antimicrobial susceptibility patterns of clinical Escherichia coli isolates from dogs and cats in the United States: January 2008 trhough January 2013. Vet Microbiol 2015 Sep 30; 179(3-4): 287-95.
[15] Soto, S. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm. Virulence. 2013 Apr 1; 4(3): 223–229.
[16] Hefernan H, Bakker S. 2017 survey of methicillin methicillin-resistant Staphylococcus aureus (MRSA). Porirua, New Zealand: Nosocomial Infections Laboratory, Institute of Environmental Science and Research Ltd; 2018.
[17] Institute of Environmental Science and Research Limited. Annual survey of methicillin-resistant staphylococcus aureus (MRSA), 2006. Porirua, New Zealand: Institute of Environmental Science and Research Limited.
[18] Hefernan H, Bakker S. 2017 survey of methicillin methicillin-resistant Staphylococcus aureus (MRSA). Porirua, New Zealand: Nosocomial Infections Laboratory, Institute of Environmental Science and Research Ltd; 2018.
[19] Center for Disease Dynamics, Economics & Policy. State of the world's antibiotics, 2015. Washington, D.C., USA: CDDEP; 2015.

resistance to impact cephalosporin efficacy as well as penicillin efficacy, is discussed elsewhere in this report. ESBL-E was first identified in New Zealand in the 1990s and is now endemic in the New Zealand community. Like MRSA, infections due to ESBL-E remain lower in New Zealand than in other developed nations but overall rates have been found to be increasing in the South Pacific[20]. Although there is currently little evidence to suggest ESBL-E is found in production animals, it has been isolated in pets in New Zealand and therefore poses a zoonotic threat[21].

Overall, the critical risk associated with penicillin resistance is the fact that all β-lactam antibiotics function through the same mechanism: the inhibition of cell wall synthesis through the binding of PBPs. As such, cross-resistance can develop to all penicillins, though the anti-staphylococcal penicillins like cloxacillin pose a less significant risk due to way the molecule is altered to make it physically larger and its narrower spectrum of activity.

6.3 VETERINARY PENICILLIN USE IN NEW ZEALAND

Currently 74 penicillin-based veterinary medicine trade name products are registered in New Zealand. Of these, 27 are amoxicillin-based formulations intended for use in either companion-only, production only, or mixed species products. Another 21 contain benzylpenicillins alone or in combination with a second benzylpenicillin (e.g. penicillin G benzathine and penicillin G procaine in a single formulation) in mixed species. The remaining products are 12 cloxacillin-based products intended for dry or lactating cow mastitis management, 12 cloxacillin/ampicillin products intended for dry and lactating cow mastitis management, one cloxacillin based ophthalmic product, and one cloxacillin/penicillin G procaine product for mastitis management in lactating cows.

6.4 MPI CLASSIFICATION

Given the widespread use of penicillins in veterinary medicine, and the broad potential for the development of resistance coupled with the WHO classification, the MPI classification for antibiotics in this class needs to be carefully considered. As previously discussed, cloxacillin has been classified by the WHO as a Highly Important anti-staphylococcal penicillin, while amoxicillin, ampicillin, penicillin G benzathine, penicillin G procaine, and penethamate hydriodide have all been classed as Critically Important. The WHO's Critically Important classification for most penicillins is primarily due to the international prevalence of certain infections that have limited therapeutic options, and the zoonotic potential of *Enterococcus* spp., *Enterobacteriaceae* spp., and *P. aeruginosa*.

The Ministry of Health identifies listeriosis as occurring infrequently and sporadically in New Zealand, though outbreaks do occur. Listeriosis is a notifiable disease here, requiring blood culture for a definitive patient diagnosis and testing of all suspect infection sources. In 2017, the reporting rate for listeriosis was 0.4 per 100,000 and was on the decline (it was 0.8 per 100,000 in 2016)[22]. Treatment of choice is amoxicillin or co-trimoxazole, though antibiotics are only indicated for symptomatic and asymptomatic people who are considered a high risk for complications (e.g. infants, and pregnant, elderly, or immunocompromised adults).

Human medicine treatment guidelines for the other noted pathogens indicate there are available alternatives to the penicillins in New Zealand, such as linezolid for the management of refractory and resistant bacteria. A Ministry of Health guideline on the management of multidrug resistant bacteria such as ESBLs also recommends the use of carbapenems as the first line treatment, reserving a β-lactam/ β-lactam inhibitor combination like

[20] Sheng WH, et al. Distribution of extended-spectrum β-lactamases, AmpC β-lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). Antimicrobial Agents and Chemotherapy 2013; 57(7):2981–2988.
[21] Toombs-Ruane LJ, et al. Multidrug resistant Enterobacteriaceae in New Zealand: a current perspective. New Zealand Veterinary Journal 2017; 65(2):62–70.
[22] The Institute of Environmental Science and Research Ltd. Notifiable Diseases in New Zealand: Annual Report 2017. Porirua, New Zealand. 2019.

amoxicillin/clavulanic acid for less serious infections such as urinary tract infections[23]. Although carbapenems are broadly considered β-lactams, their unique molecular structure makes them both highly effective against Gram-negative and Gram-positive bacteria including resistant organisms, and resistant to the action of β-lactamases that may be influenced by use of the other penicillins. It is important to note carbapenems are not used in veterinary medicine in New Zealand.

Further, the two main resistance determinants for carbapenems are the production of carbapenemases, a specific type of β-lactamase, and efflux pumps capable of expelling antibiotics from the bacterial cell. The production of carbapenemases appear to be associated with the use and/or overuse of carbapenems, since the majority of β-lactamases that affect other β-lactam antibiotics (the penicillins) do not have a similar effect on the unique structure on the individual carbapenems[24,25]. The efflux pump mechanism is less specific and can lead to carbapenems resistance associated with multidrug resistance since quinolones, penicillins, cephalosporins, and aminoglycosides are all potential targets for efflux pump expulsion[26]. This mechanism seems to be mostly focused on the carbapenem meropenem, so may not affect all carbapenems equally.

Although β-lactam resistance is a real threat given the ease at which resistance can develop across the class, the availability of therapeutic alternatives in the event of the development of β-lactam resistance in New Zealand, the complete lack of carbapenems use in New Zealand veterinary medicine, and the lack of β-lactam resistance found in the 2009-10 baseline survey conducted by MPI despite its common use in animals suggest that the risk of β-lactam resistance is not as critical in New Zealand as in other regions.

Because the WHO classification is based on limited available alternative therapies in the face of multidrug resistance and β-lactam resistance, it is considered that the New Zealand classification of the currently registered veterinary penicillins – **amoxicillin, ampicillin, cloxacillin, penethamate hydriodide, penicillin G benzathine, penicillin G procaine, and penicillin procaine –** can be set at **Highly Important** provided the product claims and use patterns are refined to ensure prudent use and limited prophylactic use. This classification is supported by the existing penicillin-specific Ministry of Health consents for amoxicillin, ampicillin, cloxacillin, penethamate hydriodide, and the benzylpenicillins, which state that the compounds were at the time of consent "not essential to human health" and there was "no objection to registration for veterinary use". The 'blanket approval' given by the Ministry of Health excluded "anti-pseudomonal penicillins such as carboxypenicillins, ureidopenicillins, and mecillinam family penicillins". Currently no veterinary medicines containing any of those compounds or subfamilies of penicillins are registered in New Zealand.

Although it does not have any antibiotic properties in its own right, the importance of clavulanic acid to the efficacy of amoxicillin indicates the need for it to have its own importance classification. Based on its exclusive use as an amoxicillin co-formulant in New Zealand products, and the potential for resistance to develop against the combination, clavulanic acid (and the amoxicillin-clavulanic acid combination) will also be classed as **Highly Important**.

Because the MPI classifications and NZVA's 'traffic light' system are both designed around a three-tier structure, MPI's classification of all currently registered veterinary penicillins as Highly Important may appear to conflict with the NZVA's ranking of these compounds. In the NZVA system, procaine penicillin G, penicillin V, procaine benzyl penicillin, penethamate hydriodide, and benzathine penicillin are classed as 'green' antimicrobials, whereas the semi-synthetic penicillins ampicillin, amoxicillin (and clavulanic acid), cloxacillin, and nafcillin are classed as 'yellow' antimicrobials. The MPI classification however has determined all

[23] Ministry of Health. 2007. Guidelines for the Control of Multidrug-resistant Organisms in New Zealand.
[24] Meletis G. Carbapenem resistance: overview of the problem and future perspectives. Ther Adv Infect Dis. 2016 Feb; 3(1): 15–21.
[25] Codjoe F. Carbapenem Resistance: A Review. Med Sci (Basel). 2018 Mar; 6(1): 1.
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currently registered penicillins to be Highly Important, which could be interpreted as similar to classification in NZVA's intermediate 'yellow' category.

It is important to note that while the NZVA system and the MPI classifications correspond to one another, they are not identical. The MPI classifications have been designed as way to designate the relative AMR risk and clinical importance of the compound as it is approved for use in New Zealand, and to signal that information to the veterinarian and end user. The NZVA system on the other hand is structured around providing advice on prudent clinical use of antibiotics for veterinary patients. The NZVA 'traffic light' system is organised as follows: compounds in the 'green' category are to be used for first-line clinical therapy, compounds in the 'yellow' category are to be used for second-line therapy or for certain clinical conditions caused by organisms susceptible to those compounds, and compounds in the 'red' category are to be used for the treatment of refractory cases or where there is enough diagnostic evidence to indicate a clinical need for their use.

Despite these categories, there is an expectation that veterinarians will following the NZVA's therapeutic guidelines for all antibiotic use regardless of their ranking in the system, and that placement in the 'green' category no more signals a lower need for prudent use than placement in the 'red' category signals that compounds are not to be used at all. Because of this, it is considered that the MPI classification of all currently approved veterinary penicillins as Highly Important from an AMR risk perspective does not conflict with the NZVA's split categorisation of penicillins based on the clinical and diagnostic expectations for antibiotic use.

The AMR profile of β-lactams will need to be reviewed periodically as part of the ongoing reassessment programme for antibiotics dictated by the New Zealand National Action Plan. This will ensure the classification of these compounds as Highly Important will remain appropriate.

6.5 TRADE NAME PRODUCT IMPACTS

6.5.1 Maximum Residue Levels

Currently no commodity-specific MRLs for any of the seven penicillin compounds are approved for veterinary use, despite the use of all seven compounds in at least one production animal species. It is therefore considered that commodity-specific MRLs will need to be established for all veterinary penicillins going forward.

With the exception of cloxacillin MRLs for sheep and benzylpenicillin MRLs for horses, promulgated MRLs are likely to be lower than the 0.1 mg/kg default MRL currently applied to all commodities. This may or may not impact the withholding periods currently approved for the affected products. Because there was a historical policy of applying the default MRL when residues were found to be <0.1 mg/kg, the actual residue levels present at the end of the withholding period may still comply with a lower MRL without adjustment to the withholding periods. The withholding periods will be considered alongside the proposed MRLs during the reassessment.

Without prejudging the outcome of more detailed data reviews during the reassessment appraisal, the following has been determined:

Amoxicillin and Amoxicillin-clavulanic acid combinations

Amoxicillin is used in cattle, pigs, and sheep, with a full suite of overseas limits set by Australia, China, Codex, the EU and Japan, pig commodity limits set in Canada, and cattle commodity limits set in the US. A residue definition and amoxicillin MRLs will need to be established for all commodities and milk to manage the GAP use of this compound and the associated trade risks.

The amoxicillin-clavulanic acid combination is approved for use in cattle and companion animal species. Clavulanic acid has attracted a full set of bovine MRLs in the EU, Japan, and Australia, and as an active ingredient used in a food-producing species it is subject to the requirement for compliance with a MRL in New Zealand. A residue definition and MRLs will also need to be promulgated for all commodities and milk to manage GAP for clavulanic acid.

Ampicillin

Ampicillin is only used in cattle in New Zealand, exclusively as a dairy cow intramammary (dry cows and lactating cows). It is therefore important that a residue definition and MRLs are established for milk and cattle tissues going forward. Overseas limits have been established for cattle in Canada, China, the EU, Japan, and the US, with an Australian limit set for milk only. There are no Codex MRLs for ampicillin.

Cloxacillin

Cloxacillin is used in cattle, sheep, and horses in New Zealand. The EU and Japan both have applicable MRLs for all three species, while China has established MRLs for cattle, and Canada and the US have focused entirely on cattle. Australia has only a milk MRL established, and an exemption for ophthalmic use of cloxacillin in cattle and sheep. There are no Codex MRLs for this compound. It is considered that a full suite of MRLs are required to manage the GAP use of cloxacillin and the associated trade risks; horse MRLs are likely to be promulgated at 0.1 mg/kg to manage GAP and export trade risk should export trade in horse commodities resume.

Penethamate hydriodide, Penicillin G Benzathine, Penicillin G Procaine, and Penicillin Procaine

These four antibiotic compounds are all variations on the use of benzylpenicillin. Penethamate hydriodide is a prodrug of benzylpenicillin, while the other three are variant compounds that release benzylpenicillin after administration. Of the overseas authorities that have established MRLs for these compounds, Australia makes a distinction between penethamate hydriodide and penicillin G benzathine (residue definition: benzylpenicillin) and the two procaine formulations (residue definition: procaine penicillin), and Codex has established a set of MRLs referred to as "benzylpenicillin/procaine benzylpenicillin" indicating that MRLs for all four compounds can be collapsed into a single set of values. The specificity of the MRLs promulgated for New Zealand, i.e. whether penethamate hydriodide, procaine penicillin, or all four compounds should stand alone as unique compounds with individual suites of MRLs is to be determined. With the exception of Australia, which has established a higher overall MRL for tissue commodities for procaine penicillin than benzylpenicillin, overseas authorities largely apply the same MRLs to tissue commodities (0.05 mg/kg) and milk (0.004 mg/kg) for all four compounds.

6.5.2 Product Registrations

The classification of the currently registered penicillin compounds as Highly Important will be contingent on ensuring the labels are sufficiently specific and supportive of prudent use.

Most of the 75 existing penicillin-based products have generalised "susceptible to penicillins" type of claims, and very few provide specific target pathogens and/or diseases. Even most of the intramammary lactating and dry cow products either generalise their claims to "mastitis" or do not mention the indication at all. In addition, very few products have any form of AMR warning statement, and those that do are generalised to warning against using penicillins infections caused by organisms with penicillin resistance even when specific target

organisms or disease states are not identified. All currently registered products will therefore need some level of label revision, and some will need significant revision on reassessment.

In general, the changes that will need to be actioned for amoxicillin, ampicillin, cloxacillin, penethamate hydriodide, and benzylpenicillin-based products include the following:

- on-label identification of the product as one containing a Highly Important antibiotic;
- revision of all product labels to at least specify a target disease and the Gram-positive or Gram-negative identifier for target pathogens as part of a product claim. Where possible, specific infections and/or pathogens should be specified;
- reconsideration of the wording of claims related to prophylactic use and extended therapy to ensure they adequately support prudent use;
- more specificity regarding the indication, treatment intervals, and duration of treatment. Although strictly mandatory for all Critically Important antibiotics and their use patterns, the need for specific treatment intervals and indications will support the prudent use of Highly Important antibiotics. Duration of treatment and advice when to cease therapy in favour of additional diagnostic testing and/or a different antibiotic should be advised to veterinarians as part of the use pattern; and
- application of a standardised prudent use statement for all products containing a Highly Important antibiotic.

7 Reassessment of registered veterinary medicines

7.1 REASSESSMENT APPLICATIONS

With the completion of the review of registered macrolide, third and fourth generation cephalosporin, and penicillin antibiotic active ingredients, the next step will be progressing the changes outlined in this review at the product level. The registrants of the affected products as listed in the Appendix will be asked to submit applications to vary each product's registration. Each application will need to address the following risk areas relative to the individual product's risk profile and AMR classification.

7.1.1 Efficacy, Safety and Antimicrobial Resistance

Registrants will be asked to provide a technical discussion of each product's currently approved use patterns and target species. This includes treatment and retreatment intervals, dosing levels, and target classes/species, with supporting information as needed. The aim of this discussion will be to confirm that the currently approved use patterns are still fit for purpose and sufficiently detailed to manage the risks of under-dosing and antimicrobial resistance. If a change to the actual recommended dose or interval is required to achieve this, the registrant will be asked to provide evidence to support the revised dosing information relative to the new dose and/or interval's efficacy and safety in the target class and species.

7.1.2 Residues

Many of the antibiotic compounds captured by this review will require the promulgation of new or revised MRLs to effectively manage the residues in treated food-producing animals. For compounds that already have a suite of complete or incomplete MRLs, registrants will be asked to provide comment on the existing MRLs and any amendments they consider necessary to effectively manage the residue and trade risks. For compounds that do not have promulgated New Zealand MRLs, registrants will be asked to provide a discussion of

the most appropriate MRLs and residue definitions to promulgate for each unique compound for which they own an affected product. If a registrant holds residue data that supports their position regarding MRLs, they will be asked to provide this to help inform the MRL-related decisions.

It is again noted that the MRL considerations associated with this review and subsequent reassessments are not specific to antimicrobial resistance. The MRLs are being considered as a separate piece of work incorporated into the reassessments to limit the regulatory burden of two separate reviews and reassessment processes.

7.1.3 Product labels

Registrants are expected to conduct a full review of each product label to ensure the label content will provide sufficient information to the authorising veterinarian to allow for informed decisions on prudent use and AMR risk. At a minimum, each product label will require the following changes:

1. identification of the product as one containing either a Highly Important antibiotic or a Critically Important antibiotic, as per the outcomes of this review;
2. addition of the standardised prudent use statement associated with the Highly Important or Critically Important classification assigned to that product's active ingredient(s); and
3. review and revision of the claims and indications as discussed in sections 4.5.2 (macrolides), 5.5.2 (third and fourth generation cephalosporins, and 6.5.2 (penicillins) of this report.

Registrants are encouraged to review all product labels in their entirety to ensure that all information is fit for purpose relative to the product's risk profile and intended prudent use.

7.2 REASSESSMENT PROCESS

Once applications for all affected products have been received, they will be formally received for assessment. They will then be publicly notified as reassessment applications according to the requirements of section 14 of the ACVM Act, with a close date for receipt of submissions on that notification set at 30 working days after the date of publication. After the public notification period has ended, the technical assessment of the applications will progress as per any other application evaluated by MPI, with a regulatory time frame of 40 working days. Registrants will be contacted during assessment if there are any questions or concerns regarding individual applications.

At the end of assessment, all applications will be submitted for review and Delegate approval of the outcomes of the assessment and its associated changes. Once approval has been granted, registrants will be informed of the outcomes of the assessment and presented with their amended approval. The time frame allowed for product and label changes will be considered and determined on a case by case basis. MRL promulgation will be progressed in the next round following completion of the assessment.

8 Appendix: Affected trade name products

MACROLIDES				
Sub-Category	**Active Ingredient**	**ACVM Reg No.**	**Trade Name**	**Registrant**
First Generation, 14-member-ring	Erythromycin	A005893	Erythrosol	Bayer NZ
First Generation, 14-member-ring	Oleandomycin	A000829	Mastalone	Zoetis NZ
First Generation, 14-member-ring	Oleandomycin	A009341	Mastiguard Milking Cow.	Virbac NZ
First Generation, 16-member-ring	Spiramycin	A005098	Stomorgyl 10	Boehringer Ingelheim AH
First Generation, 16-member-ring	Spiramycin	A006397	Stomorgyl 2	Boehringer Ingelheim AH
First Generation, 16-member-ring	Spiramycin	A006817	Stomorgyl 20	Boehringer Ingelheim AH
Second generation, 16-member-ring	Tilmicosin	A006133	Micotil 300	Elanco Australasia
Second generation, 16-member-ring	Tilmicosin	A007515	Pulmotil 200	Elanco Australasia
Second generation, 16-member-ring	Tilmicosin	A011195	TilmoVet 300 Injection	Agrihealth NZ
First Generation, 16-member-ring	Tylosin	A000086	Tylan Soluble	Elanco Australasia
First Generation, 16-member-ring	Tylosin	A000907	Elanco Australasia	Elanco Australasia
First Generation, 16-member-ring	Tylosin	A005804	Tylan 250	Elanco Australasia
First Generation, 16-member-ring	Tylosin	A006340	Tylo 200 Injection	Kela N.V.
First Generation, 16-member-ring	Tylosin	A009713	Tyloguard.	Virbac NZ
First Generation, 16-member-ring	Tylosin	A010006	Tyloject	Bayer NZ
First Generation, 16-member-ring	Tylosin	A010039	Pharmasin 100% Soluble	Agrihealth NZ
First Generation, 16-member-ring	Tylosin	A010313	Tylosin Base Injection	Bayer NZ
First Generation, 16-member-ring	Tylosin	A010451	Pharmasin 25% Granular Premix	Agrihealth NZ
First Generation, 16-member-ring	Tylosin	A010637	Tylomix 250	VetPak
First Generation, 16-member-ring	Tylosin	A010685	Pharmasin 10% Granular Premix	Agrihealth NZ
First Generation, 16-member-ring	Tylosin	A010714	Tylosin 300 Injection	Bayer NZ
First Generation, 16-member-ring	Tylosin	A010772	Tylofen	Bayer NZ
First Generation, 16-member-ring	Tylosin	A010807	TyloVet Injection	Agrihealth NZ
First Generation, 16-member-ring	Tylosin	A010984	Neove 200 Tylosin Injection	Neove Pharma Australia
Third generation, 15-member-ring	Tulathromycin	A010814	Draxxin Injectable Antibiotic Solution	Zoetis NZ

CEPHALOSPORINS				
Sub-Category	**Active Ingredient**	**ACVM Reg No.**	**Trade Name**	**Registrant**
3rd Generation Cephalosporin	Cefovecin	A010032	Convenia	Zoetis NZ
3rd Generation Cephalosporin	Cefpodoxime	A010299	Simplicef	Zoetis NZ
4th Generation Cephalosporin	Cefquinome	A008116	Cobactan LC	Schering-Plough AH
4th Generation Cephalosporin	Cefquinome	A008163	Cobactan 2.5% Injection	Schering-Plough AH
3rd Generation Cephalosporin	Ceftiofur	A006812	Excenel	Zoetis NZ
3rd Generation Cephalosporin	Ceftiofur	A009971	Calefur	Dechra Veterinary Products NZ
3rd Generation Cephalosporin	Ceftiofur	A009978	Cefaguard	Virbac NZ
3rd Generation Cephalosporin	Ceftiofur	A010150	Excede LA Sterile Suspension.	Zoetis NZ
3rd Generation Cephalosporin	Ceftiofur	A010184	Ceftiject	Bayer NZ
3rd Generation Cephalosporin	Ceftiofur	A010418	Ceftiject RTU	Bayer NZ
3rd Generation Cephalosporin	Ceftiofur	A010691	Eficur	Hipra NZ
3rd Generation Cephalosporin	Ceftiofur	A010697	Cefaject	Bayer NZ
3rd Generation Cephalosporin	Ceftiofur	A010848	Kelacef	Kela N.V.
3rd Generation Cephalosporin	Ceftiofur	A011026	Norocef RTU	Norbrook NZ
3rd Generation Cephalosporin	Ceftiofur	A011314	Excenel Flow	Zoetis NZ

PENICILLINS				
Sub-Category	**Active Ingredient**	**ACVM Reg No.**	**Trade Name**	**Registrant**
Aminopenicillin	Amoxicillin	A007057	Bimoxyl LA	Bimeda NZ
Aminopenicillin	Amoxicillin	A007471	Longamox	Ethical Agents Vet Marketing
Aminopenicillin	Amoxicillin	A007782	Moxylan 50mg Tablets Broad Spectrum Antibiotic Tablets	Jurox NZ
Aminopenicillin	Amoxicillin	A007784	Moxylan 200mg Tablets Broad Spectrum Antibiotic	Jurox NZ
Aminopenicillin	Amoxicillin	A007785	Moxylan Aqueous Drops Broad Spectrum Antibiotic	Jurox NZ
Aminopenicillin	Amoxicillin	A007786	Moxylan Ready-To-Use Injection Broad Spectrum Antibiotic	Jurox NZ
Aminopenicillin	Amoxicillin	A007812	Vetrimoxin LA	Ceva Animal Health NZ
Aminopenicillin	Amoxicillin	A007950	Betamox LA	Norbrook NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A004925	Clavulox Palatable Drops	Zoetis NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A005722	Clavulox Ready To Use Injection	Zoetis NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A005945	Clavulox LC	Zoetis NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A008113	Vetamox Tablets 625mg	Ethical Agents Vet Marketing
Aminopenicillin	Amoxicillin + Potassium clavulanate	A008139	Clavulox Palatable Tablets Broad Spectrum Antibiotic 250mg	Zoetis NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A008140	Clavulox Palatable Tablets Broad Spectrum Antibiotic 50mg	Zoetis NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A008141	Clavulox Palatable Tablets Broad Spectrum Antibiotic 500mg	Zoetis NZ

Aminopenicillin	Amoxicillin + Potassium clavulanate	A008295	Noroclav Injection	Norbrook NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009010	Noroclav Tablets	Norbrook NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009506	Clavet LC	Norbrook NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009570	Clavubactin	Le Vet Beheer B.V.
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009737	Noroclav Tablets 500mg	Norbrook NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009853	Juroclav 50 Broad Spectrum Antibiotic Tablets	Jurox NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009854	Juroclav 250 Broad Spectrum Antibiotic Tablets	Jurox NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009855	Juroclav 500 Broad Spectrum Antibiotic Tablets	Jurox NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A009912	Lactaclav	Bayer NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A010050	Clavobay LC	Bayer NZ
Aminopenicillin	Amoxicillin + Potassium clavulanate	A010121	Clavaseptin Palatable Tablets	Ethical Agents Vet Marketing
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A004495	Bovaclox Dry Cow	Schering-Plough AH
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A005092	DryClox DC AF	Bayer NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A006811	DryClox Xtra AF	Bayer NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A008038	Cloxamp DC 500	Norbrook NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A008039	Cloxamp DC 600	Norbrook NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A008146	Lactaclox LC	Norbrook NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A009020	Bovaclox DC Xtra	Norbrook NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A011025	DC Duo	Bayer NZ

Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A011125	DryClox Xtra	Bayer NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A011126	DryClox DC	Bayer NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A011433	Duramast DC 500	Norbrook NZ
Aminopenicillin/ Antistaphylococcal	Ampicillin + Cloxacillin	A011434	Duramast DC 600	Norbrook NZ
Antistaphylococcal Penicillins	Cloxacillin	A000888	Orbenin Dry Cow	Zoetis NZ
Antistaphylococcal Penicillins	Cloxacillin	A003664	Orbenin LA	Zoetis NZ
Antistaphylococcal Penicillins	Cloxacillin	A004751	Orbenin Eye Ointment	Zoetis NZ
Antistaphylococcal Penicillins	Cloxacillin	A005108	Cloxagel 1000 DC	Virbac NZ
Antistaphylococcal Penicillins	Cloxacillin	A006036	Orbenin Enduro	Zoetis NZ
Antistaphylococcal Penicillins	Cloxacillin	A007297	Zeromast	Bimeda NZ
Antistaphylococcal Penicillins	Cloxacillin	A007725	Juraclox L.A. 600 Dry Cow Long Acting Intramammary Suspension	Jurox NZ
Antistaphylococcal Penicillins	Cloxacillin	A007862	Durodry	Norbrook NZ
Antistaphylococcal Penicillins	Cloxacillin	A009281	Noroclox DC 600	Norbrook NZ
Antistaphylococcal Penicillins	Cloxacillin	A010279	Nitroclox LA	Virbac NZ
Antistaphylococcal Penicillins	Cloxacillin	A010792	Ultraclox 24	Bayer NZ
Antistaphylococcal Penicillins	Cloxacillin	A011173	CloxaSeal 600	Norbrook NZ
Antistaphylococcal Penicillins	Cloxacillin	A011435	Soloclox DC 600	Norbrook NZ
Antistaphylococcal/ Benzylpenicillin	Cloxacillin + Pen Procaine	A010884	PenClox 1200	Virbac NZ
Benzylpenicillin	Penethamate hydriodide	A000593	Mamyzin	Boehringer Ingelheim
Benzylpenicillin	Penethamate hydriodide	A009423	Penethaject	Bayer NZ
Benzylpenicillin	Penethamate hydriodide	A010920	Penethaject RTU	Bayer NZ
Benzylpenicillin	Pen G Benzathine + Pen Procaine	A004183	Duplocillin LA	Schering-Plough AH

Benzylpenicillin	Pen G Benzathine + Pen Procaine	A006308	Intracillin LA	Virbac NZ
Benzylpenicillin	Pen G Benzathine + Pen Procaine	A006592	Tripen LA	Ethical Agents Vet Marketing
Benzylpenicillin	Pen G Benzathine + Pen Procaine	A007187	Ovipen	Virbac NZ
Benzylpenicillin	Pen G Benzathine + Pen Procaine	A010614	Procaine Penicillin 30	Bayer NZ
Benzylpenicillin	Pen G Procaine	A004256	Depocillin	Schering-Plough AH
Benzylpenicillin	Pen G Procaine	A005301	Intracillin 300 Injection	Virbac NZ
Benzylpenicillin	Pen G Procaine	A007186	Bovipen	Virbac NZ
Benzylpenicillin	Pen G Procaine	A007518	Intracillin High Potency 500	Virbac NZ
Benzylpenicillin	Pen G Procaine	A007787	Intracillin 1000 Milking Cow	Virbac NZ
Benzylpenicillin	Pen G Procaine	A007798	Phoenix Pharmacillin 300	Kela N.V.
Benzylpenicillin	Pen G Procaine	A007922	Ultrapen LA	Norbrook NZ
Benzylpenicillin	Pen G Procaine	A007973	Norocillin	Norbrook NZ
Benzylpenicillin	Pen G Procaine	A008037	Masticillin	Virbac NZ
Benzylpenicillin	Pen G Procaine	A009768	Lactapen	Bayer NZ
Benzylpenicillin	Pen G Procaine	A009860	Lactapen G	Bayer NZ
Benzylpenicillin	Pen G Procaine	A010101	Propercillin	Troy Laboratories
Benzylpenicillin	Pen G Procaine	A010348	VETGUARD PenG-300 Injection	Troy Laboratories
Benzylpenicillin	Pen G Procaine	A011715	Lactacillin	Virbac NZ
Benzylpenicillin	Pen G Procaine	A011716	Mastipen	Virbac NZ
Benzylpenicillin	Pen G Procaine	A011574	Ethicillin	Ethical Agents Vet Marketing