Australian Government

Australian Pesticides and Veterinary Medicines Authority

Neomycin

Final Review Technical Report

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agricultural and Veterinary Chemicals Code (the Code), which is scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*.

The APVMA has legislated powers to reconsider the approval of an active constituent, registration of a chemical product or approval of a label at any time after it has been registered. The reconsideration process is outlined in sections 29 to 34 of Part 2, Division 4 of the Agvet Codes. The Code provides for the suspension and cancellation of approvals and registrations if it appears to the APVMA that the criteria for approval or registration are not, or are no longer, satisfied (s 41 and s 44 of Part 2, Division 5).

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product containing that chemical, or its label. The scope of each reconsideration can cover a range of areas including human health (toxicology, public health, work health and safety), the environment (environmental fate and ecotoxicology), residues and trade, chemistry, efficacy or target crop or animal safety. However, the scope of each reconsideration is determined on a case-by-case basis reflecting the specific issues raised by the new research or evidence.

The reconsideration process includes a call for data from a variety of sources, a scientific evaluation of that data and, following public consultation, a regulatory decision about the ongoing use of the chemical or product. The data required by the APVMA must be generated according to scientific principles. The APVMA conducts scientific and evidence-based risk analysis with respect to the matters of concern by analysing all the relevant information and data available.

About this document

This Technical Report is intended to provide an overview of the assessments that have been conducted by the APVMA and of the specialist advice received from external experts and advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience, thereby assisting with public understanding of the technical basis for the decision.

This document contains a summary of the assessment reports generated in the course of the chemical review of an active ingredient, including the registered product and approved labels. The document provides a summary of the APVMA's assessment, which may include details of the:

- chemistry of the active constituent
- toxicology of both the active constituent and product
- residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Further information

Further information can be obtained via the contact details provided below. More details on the chemical review process can be found on the APVMA website: www.apvma.gov.au

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1 Introduction

1.1 Executive Summary

Neomycin is an aminoglycoside antibiotic that displays bactericidal activity. It is contained in a variety of veterinary preparations for use in companion and food-producing animals. These products are used primarily to treat, prevent and/or control bacterial infections caused by various gram-negative bacteria sensitive to neomycin. The registration of neomycin was nominated for reconsideration due to concerns relating to residues violations in food-producing animals treated with oral, intramammary and injectable preparations of neomycin, and concerns relating to target animal safety. No residue or animal safety concerns were identified for topical formulations containing neomycin, or for small animal vaccines and semen extender powder preparations that contain neomycin as a preservative.

The APVMA's risk assessment related to the efficacy and target animal safety of neomycin were detailed in the Neomycin: Target animal safety risk assessment report and concluded that the risks of ototoxicity and nephrotoxicity (hearing and kidney damage) can be reduced by extending the dosage interval of parenteral (injectable) neomycin to once every 24 hours and by including appropriate precautions and contraindication statements on labels for oral and intramammary products.

The APVMA created temporary neomycin MRLs in 2004, aligned with the World Health Organisation / Food and Agriculture Organisation Food Standards Codex Alimentarius (Codex) MRLs, in recognition of the repeated MRL exceedances that were occurring at the time. Upon commencement of the reconsideration of neomycin in 2007 the APVMA published a detailed scope document highlighting the need for assessment of relevant data to establish permanent MRLs.

The APVMA's risk assessments completed during this reconsideration identified that none of the currently registered products have sufficient data to determine permanent MRLs due to the lack of product and use-pattern-specific residue depletion trials. Submissions from holders and other interested parties during the public consultation on the proposed regulatory decision argued that other evidence could be considered to support the conclusion that the use of neomycin is unlikely to have an effect that is harmful to human beings. The APVMA's final position is that unmitigated human health risks remain without sufficient data to determine appropriate MRLs and conduct relevant dietary exposure risk assessments, supported by appropriate residue decline data. However, it was determined that the human health risks relate to chronic exposure, and that acute exposure is not likely to be harmful to human beings. On this basis the recommended course of action is a conditional continuation of the registration of neomycin chemical products, that will require holders to conduct product-specific residue decline trials and to provide data to enable determination of appropriate MRLs, withholding periods and Export Slaughter Intervals within 2 years of the final decision.

It was noted that a risk to trade exists, due to the lack of permanent MRLs in Australia and the discrepancy between the current temporary MRLs and international MRLs, however current mitigations, including trade advice statements, appear to be managing the risk. It does not appear that use of neomycin products during the 2-year conditional registration period will unduly prejudice trade, although uncertainty about the level of neomycin residues remains. Data that supports creation of permanent MRLs will inform the need for additional mitigations to manage any remaining risk to trade.

1.2 Purpose of review

The scope of the neomycin review is limited to the registrations and labels of products containing neomycin which are oral, intramammary and injectable preparations and includes the following aspects of product registrations and label approvals:

- Residues and Trade:
  - Residues in treated animals arising from application in accordance with label instructions
  - Establishment of appropriate maximum residue limits (MRLs) for supported uses
  - Risks to international trade resulting from the use of neomycin in animal species producing major export commodities
- Target animal safety
  - The potential for use of the products to result in deleterious effects on target animals
  - Whether labels include adequate instructions and warning statements

The APVMA has also considered information pertaining to the chemistry (of the active and products), toxicology (health-based guidance values and poison scheduling), worker health and safety (exposure during handling and application and establishment of appropriate first aid instructions and safety directions) and whether mitigation is required to reduce risk to the environment through use of the products.

In addition to the above assessments, neomycin labels were reviewed for consistency with current APVMA policies and guidelines, including the Veterinary Labelling Code.

1.3 Product claims and use patterns

There are currently 31 products registered for use in Australia that contain neomycin. However, only 9 registered products fall within the scope of the reconsideration, including oral, intramammary or injectable antibiotic formulations containing neomycin. The remaining 22 products are not within the scope of this review.

Oral antibiotic formulations that contain neomycin include feed additive powders, water soluble powders, solid dose tablets and oral suspensions. They are used primarily to treat bacterial enteritis in food producing and companion animals, and are approved for use in cattle, calves, poultry, horses, cats and dogs. Intramammary antibiotic formulations containing neomycin are used for the treatment of mastitis in lactating cattle. Injectable neomycin products are approved for the control of neomycin sensitive organisms in horses, cattle, pigs, dogs and cats.

1.4 Mode of action

Aminoglycoside antibiotics, such as neomycin, are predominately active against aerobic gram-negative bacteria in a concentration-dependant manner, with significant post-antibiotic effect. Neomycin inhibits bacterial protein synthesis through irreversible binding to the 30 S ribosomal subunit of susceptible bacteria. Aminoglycosides have little or no action against anaerobic bacteria, as they require oxygen to cross the cell membrane (Mercer 2022, Reeves 2011). Neomycin is known to be active against strains of gram-negative bacteria (excluding *Pseudomonas*

spp.), such as E.coli, *Salmonella* and *Klebsiella* spp. and many strains of Staphylococcus aureus although treatment of staphylococci should be in conjunction with synergistic antibiotics, such as β-lactams (EMA 2002, Plumb 2002, Renshaw *et al*. 2003).

Aminoglycosides exert their antibacterial activity by interfering with protein synthesis at the membrane-associated bacterial ribosome (Riviere & Spoo 2001). This is achieved by irreversibly binding to one or more receptor proteins on the 30S subunit of the bacterial ribosome and subsequently interfering with the mRNA translation process, ultimately resulting in the production of a non-functional protein (EMA 2002, Reeves 2011). For neomycin to reach the ribosomal binding site of gram-negative bacteria, it must cross the bacterial cell wall and then the cell membrane. Initially, neomycin diffuses across the cell wall by competitive displacement of bridging divalent cations (such as Mg^{2+} or Ca^{2+}) and subsequent disruption of cross-links between adjacent lipopolysaccharides. This damages the cell wall and increases permeability, which allows the aminoglycoside to enter the periplasmic space in a passive and non-energy-dependent process. From there, it is actively transported across the cytoplasmic membrane via an oxygen- and energy-dependent interaction that is dependent on electron transport.

The bacterial cytoplasm is negatively charged with respect to the periplasm and external environment; thus, neomycin is transported across the cytoplasmic membrane by the membrane potential, where it is then able to interact with the ribosome and cause misreading of the mRNA. This further affects cell permeability, which allows more neomycin into the cell and leads to more cell disruption and eventually, cell death (Reeves 2011). The efficacy of aminoglycosides is substantially reduced in an anaerobic environment because the appropriate oxygen-dependent transport mechanisms described above are lacking (EMA 2002, Riviere & Spoo 2001).

1.4.1 Concentration-dependent killing

Aminoglycosides are bactericidal at higher concentrations, meaning they act by killing bacterial microorganisms rather than slowing or inhibiting their reproduction. They also exhibit concentration-dependent bacterial killing, where the peak concentration (C_{MAX}) is more important in determining the efficacy of bacterial killing than time above the minimum inhibitory concentration (MIC) (Freeman *et al*. 1997). Thus, it is more important to achieve optimal peak concentrations than to maintain drug concentrations slightly above the MIC for extended periods of time. While optimum ratios between the peak concentration and MIC have not yet been determined, the literature suggests that peak concentration, MIC ratios of 8:1 to 10:1 are necessary for optimal bactericidal activity while avoiding bacterial regrowth (Freeman *et al*. 1997, Huth *et al*. 2011).

1.4.2 Post-antibiotic effect

Aminoglycosides also exhibit a post-antibiotic effect (PAE), where bactericidal action persists after serum concentrations of neomycin drop below the MIC (Reeves 2011, Riviere & Spoo 2001). The exact mechanism of PAE has not yet been determined. The PAE of aminoglycosides is dependent on the:

- bacterial strain and its MIC
- duration of exposure of bacteria to the aminoglycoside
- inherent potency of the aminoglycoside
- concentration of the aminoglycosides (the higher the concentration, the longer the duration of the PAE).

Longer intervals between dosing (e.g. once-daily dosing) that provide a drug-free period in which bacteria are not exposed to the drug appear to preserve bactericidal activity of aminoglycosides and reduce the risk of antimicrobial resistance (AMR), as well as toxicity (Freeman *et al*. 1997). Studies in animal models have shown that the degree of cochlear damage induced by aminoglycosides is more dependent on the total daily dose than the frequency with which it is administered. It has been hypothesized that extended-interval dosing may result in less saturation of cochlear cells and accumulation of aminoglycosides than more frequent administration (Freeman *et al*. 1997).

1.4.3 Pharmacokinetics and metabolism

1.4.3.1 Absorption

Neomycin is a positively charged molecule with a high degree of polarity. This translates to very poor gastrointestinal absorption, typically less than 10%. However, substantial disruption of the intestinal mucosa, as may occur during cases of enteritis may increase gastrointestinal permeability and drug absorption. This is of particular concern in animals with impaired renal function where excretion of the absorbed drug is also compromised, potentially resulting in neomycin accumulation and subsequent nephrotoxicity (Mercer 2022).

Intramuscular administration of neomycin results in fast and near complete systemic absorption. Intramammary administration of aminoglycosides such as neomycin results in effective local concentration without significant systemic absorption. However, there is some concern relating to local tissue residues and residues in milk following intramammary administration which will be addressed in this review.

1.4.3.2 Distribution, metabolism and excretion

Neomycin binds weakly to plasma proteins, is poorly lipid-soluble and is highly polar at physiological pH. These characteristics generally reduce its systemic distribution and ability to cross cell membranes. However, accumulation of aminoglycosides and its metabolites is known to occur in the endolymph of the inner ear and the renal tubules.

Orally administered aminoglycosides are eliminated unchanged in the faeces in healthy animals. Following parenteral administration, neomycin is excreted unchanged primarily by renal glomerular filtration, with 80 to 90% of administered neomycin excreted in the urine (within 24 hours following intramuscular administration) (Reeves 2011, Riviere & Spoo 2001, Huth *et al*. 2011).

Glomerular filtration rates vary between species and are usually less in neonates, which are generally more sensitive to aminoglycosides (Mercer 2022). Furthermore, excretion varies as a result of changes to glomerular filtration rates in association with both cardiovascular and renal function, age, etc., and the half-life varies in response to the volume of extracellular fluid.

Aminoglycosides have relatively short plasma half-lives of approximately one hour in carnivores and 2 to 3 hours in herbivores and the elimination kinetics generally follow a 3-compartment model.

- First ‘deep’ phase: binding of drug in renal tubular cell
- β-phase: approximately 90% of the drug is excreted unchanged from the kidneys

Second ‘deep’ (or γ phase): remaining drug excreted over protracted period (gradual release from renal intracellular binding sites; terminal elimination half-life 20 to 200 hours)

2 Chemistry

Neomycin is a mixture of compounds, principally the largest component, neomycin B, neomycin C which is an isomer of neomycin B and comprises 3 to 15% of the mixture, and minor compounds, such as neomycin A, which present at lower levels (less than 2%). Neomycin is most commonly available as the sulfate salt.

There are monographs for neomycin sulfate in the British Pharmacopeia (BP) and the US Pharmacopeia (USP). The BP monograph stipulates a minimum content (potency) of 680 IU/mg (dried substance), while the USP stipulates a potency equivalent to not less than 600 µg of neomycin per mg, calculated on the dried basis. The active contents for both monographs are determined using microbial assay methods.

The BP monograph for neomycin sulfate also specifies appearance, solubility, identification, pH, specific optical rotation, related substances (impurities), sulfate (27.0 to 31.0%), loss on drying (maximum 8.0%) and sulfated ash (maximum 1.0%). The USP monograph of neomycin sulfate also includes tests for identification, impurities, contents of neomycin A and C relative to B, pH and loss on drying with the same limits as those in the BP monograph. Limits for sterility and bacterial endotoxins can additionally be specified if required.

2.1 Active constituent

Tables 1 and 2 below show the nomenclature, structural formula and key physicochemical properties of the active constituent neomycin.

Table 1: Nomenclature and structural formula of the active constituent neomycin

Parameter	Nomenclature and structure
Common name (AAN, BP, BAN)	Neomycin (sulfate)
IUPAC name	(2*R*,3*S*,4*R*,5*R*,6*R*)-5-amino-2-(aminomethyl)-6-[(1*R*,2*R*,3*S*,4*R*,6*S*)-4,6-diamino-2-[(2*S*,3*R*,4*S*,5*R*)-4-[(2*R*,3*R*,4*R*,5*S*,6*S*)-3-amino-6-(aminomethyl)-4,5-dihydroxyoxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol;sulfuric acid
CAS registry numbers	1404-04-2 (neomycin), 1405-10-3 (neomycin sulfate – unspecified sulfate content), 119-04-0 (neomycin B), 25389-98-4 (neomycin B sulfate (1:1)), 4146-30-9 (neomycin B sulfate (1:3))
Molecular formula (unspecified sulfate content)	$C_{23}H_{46}N_6O_{13}$,xH_2SO_4
Molecular weight	614.644 g/mol (neomycin base)

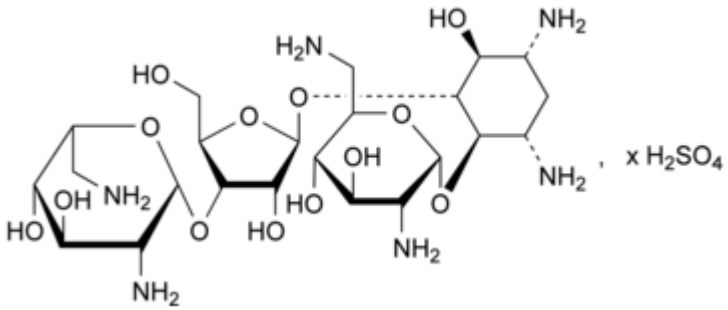
Parameter	Nomenclature and structure
Structural formula (neomycin B sulfate)	
Chemical family	Aminoglycoside

Table 2: Key physicochemical properties of the active constituent neomycin

Parameter	Physicochemical property
Colour	White or yellowish-white, hygroscopic
Physical state	Powder
Specific rotation	+53.5 to +59.0 (dried substance)
pH	5.0 to 7.5 in a water solution containing 33 mg of neomycin per mL
Solubility in water	Very soluble in water, very slightly soluble in alcohol, practically insoluble in acetone

The APVMA has confirmed that the sources of neomycin (as the sulfate) as an active constituent for use in veterinary products within the scope of the reconsideration comply with standards set by the European Pharmacopoeia, British Pharmacopoeia or United States Pharmacopoeia.

2.2 Products

At the time of the proposed regulatory decision, published in February 2024, there were 25 registered products containing neomycin (sulfate) as an active constituent, with a further 6 vaccine products containing neomycin as a preservative. However, only 9 registered products fell within the scope of the reconsideration (oral, injectable or intramammary products) of neomycin. In the interim, 2 products have ceased to be registered, leaving the 7 products listed in Table 3 in scope of the reconsideration.

Table 3: Currently registered products containing neomycin within scope of the reconsideration

Registration number	Product name	Holder	Formulation type
36026	Scourban Oral Anti-Diarrhoeal Suspension	Elanco Australasia Pty Ltd	Oral solution/suspension
49788	Scour-X Oral Anti-Diarrhoeal Suspension	Ausrichter Pty Ltd	Oral solution/suspension
52782	CCD Neomycin (Neomycin Sulphate Water Soluble Powder)	Ccd Animal Health Pty Ltd	Oral powder
67805	Abbeyneo Antibiotic Feed Additive	Abbey Laboratories Pty Ltd	Oral powder
46414	Neo-Sulcin Scour Tablets	Jurox Pty Ltd	Oral tablet
36237	Jurox Neomycin Sulfate Injection	Jurox Pty Ltd	Parenteral liquid/solution/suspension
49851	Mastalone Intramammary Suspension or Lactating Cows	Zoetis Australia Pty Ltd	Intramammary suspension

The formulation of the products, stability, shelf life, storage conditions and associated label directions have been considered and the APVMA is satisfied that these remain appropriate, except for the:

- stability and shelf life of products where an interim shelf life applies
- storage statements on the labels of products, which should be updated to reflect current labelling practice. In particular, statements prohibiting storage under freezing conditions for liquid products in Table 3 and statements requiring protection from light for all products in Table 3 should be included to prevent degradation of the active constituent during storage.

The active constituent is expressed on product labels as either neomycin (as neomycin sulfate) or neomycin sulfate. The current standard for the expression of the active is to specify the concentration of neomycin (as neomycin sulfate). This expression provides information on the concentration of the active moiety (the neomycin itself) and allows for easier comparison with other forms of neomycin, such as neomycin hydrochloride, in the event that such products were registered. It is further noted that this convention is widely used for other antibiotics, such as gentamicin sulfate and by other regulatory agencies such as the UK Veterinary Medicines Directorate.

2.3 Recommendations

The APVMA remains satisfied with respect to the chemistry and manufacturing aspects of the safety and efficacy criteria for neomycin products and notes that the expression of the active constituent on product labels should be amended to neomycin (as neomycin sulfate).

Products subject to an interim shelf life should be required to provide stability data for assessment to allow the validity of the interim shelf to be confirmed and approved.

Storage statements on all product labels should be revised to meet current practice regarding protection from freezing temperatures for liquid products and protection from light for all products. This includes the addition of ‘do not freeze’ statements on liquid products and ‘protect from light’ statements on all products where low temperature stability data and photostability data have not been previously provided and assessed to demonstrate that these statements are not required.

3 Human health

Although human health including toxicology and worker health and safety was not in the scope of the reconsideration, the APVMA has conducted a review of the available information.

3.1 Evaluation of toxicology

The toxicity of neomycin is well characterised. Neomycin is used as a human therapeutic agent in certain circumstances however, it is associated with a risk of ototoxicity and kidney damage. On a conservative basis, the point of departure for assessment of occupational health and safety is 6 mg/kg bw/day, the no observed adverse effect level (NOAEL) upon which the acceptable daily intake (ADI) is set. This NOAEL was set on the basis of ototoxicity observed at the next higher dose in a 3-month dietary study in guinea pigs. A margin of exposure of at least 100 is considered suitable, including 10x for interspecies differences and 10x for intraspecies difference. This is considered a very conservative basis for risk assessment, particularly given that doses of up to 12 g per day (equating to approximately 150 mg/kg bw/day) are approved for oral administration to adults (in the US).

The oral absorption of neomycin is very low, with most of the orally administered neomycin being excreted unchanged in the faeces. It is estimated that around 0.6% of orally administered neomycin is available systemically. Dermal absorption of neomycin is extremely limited (James *et al* 1970).

3.2 Poisons scheduling

As shown in Table 4 below, neomycin is currently listed as a schedule 4 poison in the Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard).

Table 4: Scheduling of neomycin in the Poisons Standard

Schedule	Title	Description
Schedule 4	Prescription only medicines and prescription animal remedies	Substances, the use or supply of which should be by or on the order of persons permitted by state or territory legislation to prescribe and should be available from a pharmacist on prescription.

3.3 Worker health and safety

The exposure to workers dispensing neomycin products is dependent on the formulation and use pattern associated with each of the individual product types. The product formulations which fall within the scope of this reconsideration have been considered below.

3.3.1 Feed additive powder formulations

Neomycin is present in powder formulations at 600 mg/kg product for use as feed additives for pigs, poultry and cattle. The powders are mixed with a small quantity of feed before blending into larger quantities.
The recommended dose rate is 8 to 22 mg neomycin/kg bw/day. Medicated feed is to be used for 3 to 5 days for the treatment of bacterial scours in poultry, pigs and cattle.

Powdered feed additives are mixed with feed prior to blending into larger quantities. There is potential for inhalational exposure to the neomycin powder, as well as limited dermal exposure during mixing of the feed. Given the medicated feed is to be provided for 3 to 5 days, it is considered possible that the entire batch of feed may be mixed on a single occasion.

Maximum exposure is considered likely to be associated with the treatment of a large number of cattle, based on quantity of neomycin required for their average bodyweight. At the maximum dose of 22 mg neomycin/kg bw/day, adult cattle may receive up to 15.4 g of neomycin. It is considered possible that an individual may mix feed for 5 days of treatment on a single occasion. The maximum number of cattle considered likely to be treated with this treated food is 200, leading to a possible maximum exposure of 15.4 kg on a single day (15.4 g × 5 day × 200 animals).

The majority of exposure resulting from mixing treated feed is considered likely to result from inhalation of released dust particles, with dermal exposure considered to be minimal. Neomycin powder formulations are likely to have at least 75% of the formulation in the inhalable fraction with particles <10 µm. Based on estimates of unit exposure derived from the properties of the dry flowable powder of 19.7 µg/kg active constituent, handing 15.4 kg would lead to a total exposure of 304 µg per day. Assuming an inhalation absorption factor of one, and a bodyweight of 80 kg, this would lead to a total daily exposure of 3.8 µg/kg bw/day.

The systemic dose achieved from the oral NOAEL is estimated to be 0.036 mg/kg bw/day (0.6% of 6 mg/kg bw/day). This estimated exposure of 3.6 µg/kg bw/day, or 0.0036 mg/kg bw/day, is only 10-fold lower than the point of departure. However, it is noted that neomycin is used therapeutically in humans, with systemic doses achieved during therapeutic use of several orders of magnitude higher than the worst-case dose anticipated during occupational use. On this basis, personal protective equipment to reduced systemic exposure is not required. However, based on good operational practice, the use of a dust mask when handling powder formulations is recommended. It is also considered that there is a potential for powdered formulations to irritate the eyes based on their physical properties. The statement *'May irritate the eyes. Avoid contact with eyes'* is recommended, and it is also recommended that the safety directions *'When using the product, wear a disposable dust mask covering the nose and mouth'* and *'Wash hands after use'* be included on the product labels for feed additive powder formulations.

3.3.2 Oral suspension and tablets

Neomycin sulfate is present in oral suspension formulations in combination with a number of other substances to assist in rehydration for the treatment of diarrhoea and gastroenteritis and scour/pneumonia complex in a range of species. Products are administered orally at 2 mL/3 kg in small animals, and 30 mL (54 mg neomycin sulfate) per 25 kg in calves and horses, given twice daily. Treatment is given for a 3- to 5- day period.

A tablet formulation is also available containing 250 mg neomycin sulfate/tablet, to be dosed at one tablet per 35 kg bw, administered twice daily.

As these products are administered directly, there is limited potential for inhalation exposure, and dermal exposure is also anticipated to be negligible.

It is recommended that the safety direction *'Wash hands after use'* be included on the product labels for both the oral suspension and tablet formulations for direct treatment of animals.

3.3.3 Solution for injection

Neomycin sulfate is available as solution for injections, either as the sole active constituent or in combination with procaine penicillin. In horses, cattle, sheep and pigs, neomycin sulfate is administered at up to 5 mg/kg bw, either 2 or 3 times per day. In dogs and cats, it is administered at 10 mg/kg bw daily, in divided doses.

There is not anticipated to be dermal exposure related to the administration of an injectable solution to animals. The highest risk associated with these products is that associated with needle stick injury. Additional precautions to minimise the risk of needle stick injury, such as the use of protective gloves, are not considered necessary, given the use of neomycin as a human therapeutic.

It is recommended that the safety direction: *'Wash hands after use'* be included on the product labels for injectable formulations for direct treatment of animals.

3.3.4 Intramammary preparation

A number of products containing neomycin sulfate in combination with other antibiotics are available for the treatment of mastitis in cattle. Exposure from the use of these products will be primarily dermal, and systemic exposure to those administering the preparations is anticipated to be below levels of concern.

It is recommended that the safety direction: *'Wash hands after use'* be included on the product labels for intramammary preparations.

3.4 Recommendations

Although human health including worker health and safety were not formally included in the scope of this reconsideration, the following first aid instructions and safety directions are recommended for neomycin formulations. These recommendations will be included in the First Aid and Safety Direction Handbook.

3.4.1 First aid instructions

Table 5 shows the entry for neomycin in the Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals (the FAISD Handbook).

Table 5: FAISD Handbook – existing entry

Substance	Notes	First aid instructions	Warning statements and general safety precautions
Neomycin		a	

The code 'a' in Table 5 above refers to the following first aid instruction:

> If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26, New Zealand 0800 764 766.

The first aid instructions entry is considered appropriate and should remain unchanged.

3.4.2 Safety directions – Oral (liquid), oral (tablet), injectable and intramammary formulations

Table 6 below shows new entries to the FAISD Handbook for neomycin.

Table 6: FAISD Handbook – new entry

Substance	Formulation	Statement codes
Neomycin	AL, OI, PA, TB	351

The statement codes translate into the following safety directions:

Table 7: FAISD Handbook – new entry, translation of statement codes to safety directions

Safety directions	Code
Wash hands after use	351

The following safety directions should be added to supported oral (liquid), oral (tablet), injectable and intramammary formulations containing neomycin:

> Wash hands after use.

3.4.3 Safety directions – Powder formulations

Table 8 below shows new entries to the FAISD Handbook statement codes for powder formulations of neomycin.

Table 8: FAISD Handbook – new entry

Substance	Formulation	Statement codes
Neomycin	PD	160 162 210 162 279 283 290 306 351

The statement codes translate into the following safety directions:

Table 9: FAISD Handbook – new entry, translation of statement codes to safety directions

Safety directions	Code
May irritate the eyes.	160 162
Avoid contact with eyes.	210 162
When using the product, wear a disposable dust mask covering the nose and mouth.	279 283 290 306
Wash hands after use.	351

The following safety directions should be added to supported powder formulations containing neomycin:

> May irritate the eyes. Avoid contact with eyes. When using the product, wear a disposable dust mask covering the nose and mouth. Wash hands after use.

4 Residues and trade

4.1 Current residues definition and maximum residue limits

The current residue definition for neomycin in the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023 (MRL Standard) is expressed as 'inhibitory substance, identified as neomycin'.

Current entries in Table 1 of the MRL Standard for neomycin are summarised in Table 10 below:

Table 10: Entries for neomycin in Table 1 of the MRL Standard

Compound	Food			MRL (mg/kg)
Neomycin				
	PE	0112	Eggs	T0.5
	MO	0098	Kidney of cattle, goats, pigs and sheep	T10
	MO	0099	Liver of cattle, goats, pigs and sheep	T0.5
	MF	0100	Mammalian fats {except Milk fats}	T0.5
	MM	0095	Meat (mammalian)	T0.5
	ML	0106	Milks	T1.5
			Poultry kidney	T10
			Poultry, liver	T0.5
	PM	0110	Poultry meat	T0.5

There are no entries for neomycin in either Table 4 or Table 5 of the MRL Standard.

4.2 Reconsideration of the residue definition for neomycin

The current Australian residues definition for neomycin is expressed as 'Inhibitory substance, identified as neomycin'. For the detection of neomycin, instrumental methods are now available in addition to microbiological assay methods which were available when the current residue definition was established. It is understood that contemporary chromatography methods for analysis of neomycin have several advantages in contemporary practice over microbiological method in terms of precision, accuracy, and shorter testing time.

As neomycin is subject to negligible metabolism in animals, it is considered appropriate to align the Australian residue definition (marker compound) of neomycin to that established by Codex as 'neomycin'. The microbiological and instrumental methods are considered comparable for the quantification of neomycin, therefore residues data which utilised the microbiological method are considered relevant to the proposed residue definition of 'neomycin'.

4.3 Residues risk assessment

The available residues data that is relevant to currently approved use patterns for neomycin in food producing species (cattle, sheep, pigs and poultry) are considered in this section. Horses are not generally considered a food producing species in Australia, however appropriate label instructions to manage potential residue concerns in horses will be considered.

The residues risk assessment is aimed at addressing consumer safety, and for setting appropriate withholding periods (WHP), re-treatment intervals and export slaughter intervals (ESI) on product labels. It is critical that the APVMA have access to residues data that was generated utilising the specific formulation of the product registration in question. This is consistent with the APVMA residue guidance and VICH guidelines that clearly states the test product employed in the study should be representative of the commercial formulation.

The use of neomycin in cattle, horses, pigs, poultry and sheep are considered below, separated based on the routes of administration and products.

4.3.1 Solution for injection

There is 1 neomycin product registered for injection into cattle, sheep, pigs and horses; product number 36237, which contains 200 mg/mL neomycin sulfate. An additional product, number 37241, which was considered during the reconsideration has since been cancelled at the request of the holder.

4.3.1.1 Product 36237

Residues data is not available for cattle, sheep, pig and horse tissues for this product. The available cattle, sheep and pig tissue studies involved a dose rate of 5 mg neomycin/kg bw (24 hrs apart for 3 days) (De Kleyne 1989a, 1989b, 1989c). This differs from label dose rate of 2 to 4 mg neomycin/kg bw (every 8 to 12 hours) for product 36237. It is also noted that the current meat withholding period of 10 days was not addressed in this study (sampling from 28 days). A cattle milk residue study is available for a similar formulation (Barbiers *et. al*. 1965), but it involved a dose rate of 10 mg/kg bw, which is higher than the label dose rate of 2 to 4 mg/kg for this product and is therefore not considered relevant to this label use.

In the absence of cattle tissue, cattle milk, sheep tissue and pig tissue residue data addressing this product formulation and use patterns, there is insufficient data to enable a robust assessment of the residue depletion profile for this formulation when administered to cattle, sheep and pigs via injection; and a WHP, re-treatment interval and ESI cannot be determined. The ongoing use of product 36237 in cattle, horses, pigs, and sheep is therefore not supported.

4.3.2 Feed additive powder formulation

There is one neomycin product registered for oral administration in feed to cattle, pigs and poultry. This is registered product number 67805, which contains 600 g/kg neomycin (as sulfate).

4.3.2.1 Product 67805

Resides data is not available for cattle tissues, cattle milk, pig tissues and poultry for this feed additive product.

The available oral in feed trial for cattle tissue involved a combination of active ingredients, neomycin and terramycin, and a dose rate of 10 mg neomycin/kg bw (Hawbaker & Hart 1967a). This is similar to the lowest label dose rate of 8 mg/kg bw, but lower than the highest label dose rate of 22 mg/kg bw. The dosage duration (once daily for 10 days) in the trial was longer than the label duration of 3 to 5 days. It is also noted that the available study only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.18 and 0.38 mg/kg depending on tissue and sampling time were higher than the limits of quantification of contemporary methods for neomycin.

There is no available oral in feed trial for cattle milk for the active ingredient neomycin.

The available neomycin oral in feed trial for pig tissue involved a dose rate of 10 mg neomycin/kg bw, which is similar to the lowest label dose rate of 8 mg/kg bw but lower than the highest label dose rate of 22 mg/kg bw (Liu *et. Al.* 1981). The dosage duration (once daily for 10 days) in the trial was longer than the label duration of 3 to 5 days while tissues samples were only collected at 3 and 5 days after treatment and not at the meat WHP of 20 days. It is also noted this study only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.16 and 0.31 mg/kg depending on tissue were higher than the limits of quantification of contemporary methods for neomycin. There were 3 additional oral in feed trials available for pig tissues involving neomycin co-formulated with terramycin or lincomycin (Davis & Hart 1966, Davis & Hart 1967, Liu *et. Al.* 1981), which were not considered relevant to product 67805.

Three chicken studies and one turkey study addressed oral in feed administration that were generated using neomycin in combination with terramycin. These trials involved administration of a ration containing 140 g neomycin/tonne (140 ppm) and 200 g terramycin/tonne (200 ppm) for 21 consecutive days (Bentley & Williams 1966, Newkirk & Hart 1966a, Newkirk & Hart 1966b, Newkirk & Hart 1966c). This dosage regime is significantly different to the dosage regime which is registered for poultry (8 to 22 mg neomycin/kg bw for 3 to 5 days). It is also noted that these studies predominantly involved only 3 birds per sampling time point, half the number of 6 birds per sampling time which is the contemporary standard for poultry trials specified in APVMA and VICH guidance.

A fourth study relevant to oral in feed administration to chickens involved administration of a ration containing 154 or 770 ppm of neomycin for the first 3 days of their life (Liu 1984), which again is significantly different to the registered dosage regime of product 67805. This study involved the sampling of 45 chicks (treated as day olds) per timepoint, but the tissue samples were pooled for analysis and is not considered to be relevant to current label uses.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and the feed additive product, there is insufficient residues data to enable a robust assessment of the residue depletion profile for this neomycin products when administered to cattle, pigs and poultry via treated feed; and a WHP, re-treatment interval and ESI (for cattle and pig uses) cannot be determined. The use of product 67805 in cattle, pigs and poultry is therefore not supported.

4.3.3 Oral suspension formulations

There are 2 neomycin products registered for oral solution administration to cattle (including calves) and horses. These are registered product numbers 36026 and 49788, which contain 54 mg/30 mL neomycin sulfate and other active ingredients.

4.3.3.1 Products 36026 and 49788

Resides data is not available for cattle tissues, cattle milk and horse tissues for these oral suspension products.

The 3 available residue depletion studies relevant to oral solution (drench) administration of neomycin to cattle involved single dose at 10 mg/kg bw for 5 to 10 consecutive days (Newkirk & Hart 1966d, Hawbaker & Hart 1967b, Hawbaker & Hart 1967c). The formulations used in these studies and the dosage regime is different to that registered for products 36026 and 49788 (2.16 mg/kg twice daily for a minimum of 5 days). It is also noted that these 3 studies only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.17 and 0.5 mg/kg, which is higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and these oral suspension products, there is insufficient residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to cattle via oral solution; and a WHP, re-treatment interval and ESI cannot be determined. The use of products 36026 and 49788 in cattle is therefore not supported.

The use of neomycin on horses is supported from a residues perspective, provided the restraint 'DO NOT USE in horses that may be used for human consumption' is added to the label, and the current meat WHPs for horses is removed.

4.3.4 Oral solution as water additive

There is one neomycin product registered for oral in water administration for poultry. This is registered product number 52782, which contains 600 g/kg neomycin as sulfate.

4.3.4.1 Product 52782

Resides data is not available for poultry for this oral in water administration product.

The available residue studies relevant to oral in water administration to broiler chickens and ducks address a dose rate of 30 mg neomycin/kg bw administered for 7 or 21 consecutive days for chickens and ducks respectively (Newkirk & Urban 1966, Ibayashi *et al*. 1994). This dosage regime is significantly different to the maximum dosage regime which is registered for poultry (100 mg neomycin/kg bw for 3 to 5 days). It is also noted that the chicken and duck studies involved only 3 birds per sampling time point, half the number of 6 birds per sampling time which is the contemporary standard for poultry specified in APVMA and VICH guidance.

The available studies relevant to oral in water administration to turkeys address a dose rate of 22 mg neomycin/kg bw administered for 5 consecutive days, but do not address the maximum registered dose rate of 100 mg neomycin/kg bw (Marren 1995). It is also noted that the limit of determination of 0.5 mg/kg in this study was higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the treatment regimens between the residue trials discussed above and this product, and because the available poultry studies do not meet contemporary standards with regards to sample number and limits of quantification, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to all poultry via water; and a WHP and re-treatment interval cannot be determined. The use of product 52782 in poultry is therefore not supported.

4.3.5 Oral tablet formulation

There is one neomycin product registered for tablet administration to cattle, including calves, and horses. This is registered product number 46414, which contains the antibiotics neomycin (250 mg/tablet), sulfadimidine (750 mg/tablet) and sulfadiazine (750 mg/tablet), hyoscine and vitamins.

4.3.5.1 Product 46414

Resides data is not available for cattle tissues, cattle milk and horse tissues for this oral tablet product.

The 2 available cattle bolus trials use a different formulation and involved a dose rate of 10 mg neomycin/kg bw (Hawbaker & Hart 1966, Hawbaker & Hart 1967d), which is higher than the label dose rate of 7.14 mg neomycin/kg bw for product 46414. It is also noted that the 2 available studies only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.25 and 0.37 mg/kg depending on tissue were higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and this oral tablet product, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin for this formulation when administered to cattle via a tablet; and a WHP, re-treatment interval and ESI cannot be determined. The use of product 67805 in cattle is therefore not supported.

The use of neomycin on horses is supported from a residues perspective, provided the restraint ‘DO NOT USE in horses that may be used for human consumption’ is added to the label, and the current meat WHP for horses is removed.

4.3.6 Intramammary preparations

There is 1 neomycin product registered for intramammary administration to lactating cows: product number 49851, which contains neomycin, oleandomycin and oxytetracycline.

4.3.6.1 Product 49851

Adequate residues data is not available for cattle tissues and cattle milk for this product.

Although one study provided in confidence in response to the proposed regulatory decision stated that ‘Mastalone residues in milk were detectable for a maximum of 60 hours after last treatment’ no information to support this assertion was available in the study.

While other residues data generated using a combination of neomycin and lincomycin is available, residues data for neomycin co-formulated with oleandomycin and oxytetracycline were not available. Milk (Deluyker *et al*. 1996) and tissue (Nouws *et al*. 1997) studies using a different neomycin product administered at the registered dose rate of 100 mg neomycin in each of the 4 quarters for 3 days. However, differences between the test formulation and the registered product prevent a robust assessment of the residue depletion profile for neomycin when product 49851 is administered to cattle via an intramammary route. Further, the milk study however involved sampling up to 120 hours (5 days) after the last infusion and therefore did not address the current milk withholding period of 7

days. Similarly for tissues, the study addressed sampling times of one, 7, 14 and 21 days after the last infusion and did not address the current meat withholding period of 30 days.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and this product, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to cattle via an intramammary route; and WHPs, re-treatment interval and ESI cannot be determined. The ongoing use of product 49851 in lactating cows is therefore not supported.

4.4 Trade considerations

Commodities of animal origin, such as meat, offal and dairy products are considered to be major export commodities. Residues in these commodities resulting from the veterinary uses of neomycin may have the potential to unduly prejudice international trade. Cattle, pig, sheep, goat and poultry tissues, cattle dairy product, and eggs are indicated as major Australian export food commodities. The significant export markets for Australian beef, sheep, pig and offal are listed in the Agricultural Data Guidelines – Pesticides: Overseas trade (Part 5B).

The MRLs in Table 14 have been established in major trading markets for meat, milk, eggs and offal products.

Table 11: Neomycin MRLs in some of Australia's major trading markets for animal commodities

Commodity	Neomycin MRLs (mg/kg)					
	Australia (current)	CODEX[1]	USA[2]	EU[3]	Japan[4]	Korea[5]
	Inhibitory substance, identified as neomycin	Neomycin	Neomycin	Neomycin B	Neomycin B	
Cattle tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Kidney 9 Liver 5.5 Muscle 0.5 Fat 0.5	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Milk	Milk T1.5	Milk 1.5	Milk 0.15	Milk 1.5	Milk 2	Milk 0.5
Sheep tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Fat 0.5 Kidney 9 Liver 5.5 Muscle 0.5 Milk 1.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5

Commodity	Australia (current)	CODEX[1]	USA[2]	EU[3]	Japan[4]	Korea[5]
	Inhibitory substance, identified as neomycin	Neomycin	Neomycin	Neomycin B	Neomycin B	
Pig tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Fat/skin 0.5 Kidney 9 Liver 5.5 Muscle 0.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Poultry	Kidney T10 Liver T0.5 Meat T0.5	Chicken/duck/ turkey: Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Turkeys: Kidney 7.2 Liver 3.6 Muscle 1.2	Fat/skin 0.5 Kidney 9 Liver 5.5 Muscle 0.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Chicken/duck/ turkey: Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Eggs	T0.5	Eggs 0.5		Eggs 0.5	Eggs 0.5	Poultry egg 0.5

Export of treated produce containing finite (measurable) residues of neomycin may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country. An Export Slaughter Interval (ESI) can help manage the potential risk to trade in meat and offal arising from the use of products containing neomycin.

ESIs have not previously been established for currently registered neomycin products. However, consideration of appropriate ESIs are required for cattle, sheep and pig uses of neomycin to bring the trade advice statements on product labels up to contemporary standards and to prevent an undue risk to international trade.

[1] Food and Agriculture Organisation of the United Nations (FAO), 2024. *Codex online databases – CODEXALIMENTARIUS FAO-WHO*, FAO website.

[2] Electronic Code of Federal Regulations (eCFR), 2024. *Title 21, Chapter I, Subchapter E, Part 556, Subpart B – Specific Tolerances for Residues of Approved and Conditionally Approved New Animal Drugs*, eCFR website.

[3] EUR-Lex, 2023. *Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin*, EUR-Lex website.

[4] Japan Food Chemical Research Foundation (JPCRF), 2024. *List of limit amounts of pesticides, veterinary drugs, and feed additives remaining in food*, JPCRF website.

[5] Korean Ministry of Food and Drug Safety, 2024. *Veterinary Drugs MRLs*, Ministry of Food and Drug Safety website.

4.5 Dietary exposure assessment

The following health standards currently established in the APVMA lists for acceptable daily intakes for agricultural and veterinary chemicals are considered to be appropriate.

Table 12: Neomycin health based guidance values

Compound	Dietary Standard, mg/kg bw		No Observable Adverse Effect Level (NOaEL), mg/kg bw	Uncertainty factor	Reference (APVMA/OCS/JMPR, date)
Neomycin	ADI	0.06	6 (JECFA 96)	100	28/2/1986, OCS
	ARfD	Not established by APVMA or JECFA			

4.5.1 JECFA theoretical maximum daily intake

The APVMA utilises the JECFA approach to MRL-setting where chronic exposure to total residues is estimated by multiplying the components of the conservative JECFA food basket (consisting of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat) by the 'Temporary Maximum Residue Limits (TMRLs)' in each food (muscle, liver, kidney, skin/fat) at a specified sampling time, and summing the total residues to determine the 'Theoretical Maximum Daily Intake' (TMDI)[6]. These values are shows in Table 16 below.

Table 13: Theoretical Maximum Daily Intake for neomycin residues

Edible tissue	MRL (mg/kg)#	Ratio of marker residue to total residues *	Daily consumption (kg/person)	Daily intake residues (mg/person)
Fat	T 0.5	1	0.05	0.025
Liver	T 0.5	1	0.1	0.05
Kidney	T 10	1	0.05	0.500
Muscle	T 0.5	1	0.3	0.15
Total				0.725
Percentage of ADI (using the JECFA diet)				20.17%

The highest neomycin temporary MRL for mammalian tissues, has been used in the calculation as a worst case.

Table 16 above demonstrates that the 'JECFA dietary intake' associated with the temporary MRLs for neomycin is below the ADI.

[6] Food and Agriculture Organization of the United Nations and World Health Organization (FAO), 2011. *Environmental Health Criteria 240 – Principles and Methods for the Risk Assessment of Chemicals in Food*.

4.5.2 Chronic Dietary Exposure Assessment

The chronic dietary exposure to neomycin is estimated by the National Estimated Daily Intake (NEDI) calculation, encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the FSANZ 2017 Food Consumption Datapack. The 2017 Datapack contains food consumption data from the latest national nutrition survey (2011–12 National Nutrition and Physical Activity Survey). The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for neomycin reflecting the current temporary MRLs is equivalent to <1% of the ADI of 0.06 mg/kg bw/day.

4.5.3 Acute dietary exposure

An ARfD has not been established because it is not considered necessary by the APVMA or JECFA for neomycin and a NESTI calculation has therefore not been performed.

4.6 Residues and Trade recommendations

Noting that the absence of relevant residue decline studies prevents assessment of chronic dietary exposure risks, or determination of relevant MRLs or ESIs, no uses of products containing neomycin on food producing animals are supported on an ongoing basis. As the human health risk assessment found that acute exposure risk is low, and previous dietary exposure assessments found that dietary consumption at the current, temporary, MRLs would be below the ADI, it is recommended that a condition be imposed on the continued registration of all neomycin chemical products that requires the holders to conduct relevant product and use pattern specific residue decline trials and submit the data to the APVMA for assessment within 2 years of the final decision on the reconsideration.

4.6.1 Uses supported from a residues and trade perspective

Use of neomycin products on cats and dogs (non-food producing species) are supported from a residues and trade perspective.

4.6.2 Uses conditionally supported from a residues and trade perspective

The following uses of neomycin are not supported based on insufficient relevant residues data. Use of:

- feed additive powder product (67805) in poultry, pigs, cattle and horses
- oral solution in water product (52782) in poultry
- intramammary suspension products (49851) in lactating cows
- certain injectable products (36237) in cattle, horses, sheep and pigs
- oral suspension product (36026,49788) in calves and horses
- oral tablets products (46414) in calves and horses.

Continued registration subject to a condition as recommended above is acceptable from a residues and trade perspective, noting that assessment of data provided in compliance with the condition may require variations to the current instructions or relevant particulars of the products or labels in order for the APVMA to remain satisfied of the safety and trade criteria.

4.6.3 Proposed Amendments to the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

No residue decline data relevant to registered neomycin products is available to the APVMA. The Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023 will not be amended with respect to neomycin MRLs, with temporary MRLs remaining in place pending submission of data sufficient to calculate permanent MRLs, as a condition of continued registration. The amended residue definition of 'neomycin' will replace the previous definition of 'Inhibitory substance, identified as neomycin' in recognition of the availability of instrumental methods of detection of neomycin and to harmonise with the Codex definition.

Table 14: Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

Code		Commodity	MRL (mg/kg)
PE	0112	Eggs	T0.5
MO	0098	Kidney of cattle, goats, pigs and sheep	T10
MO	0099	Liver of cattle, goats, pigs and sheep	T0.5
MF	0100	Mammalian fats {except Milk fat}	T0.5
MM	0095	Meat (mammalian)	T0.5
ML	0106	Milks	T1.5
		Poultry, kidney	T10
		Poultry, liver	T0.5
PM	0110	Poultry meat	T0.5

Table 15: Amendments to Table 3 of the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

Compound	Residue	
	Delete	Add
Neomycin	Inhibitory substance, identified as neomycin	Neomycin

5 Environmental safety

While no specific environmental concerns have been identified resulting from the use of neomycin, consideration of the existing environmental protection and disposal statements on the relevant labels is appropriate.

5.1 Recommendations

5.1.1 Environmental protection statement

For large containers (i.e., >1 kg or >1 L), the following statement is required:

> Do not contaminate wetlands or water courses with this product or used containers.

5.1.2 Disposal statements

Disposal statements for small containers and packaging (i.e. up to 1 kg or 1 L), the following statement is required:

> Dispose of container by wrapping with paper and putting in garbage.

5.1.2.1 Disposal statements for injectable products

In addition to the disposal statements for small containers, the following statement is required where a disposal sharp is distributed with a product or is expected to be used with a product, and sales of the product are not restricted to veterinarians.

> Discarded needles/sharps should immediately be placed in a designated and appropriately labelled ‘sharps’ container.

5.1.2.2 Disposal statements for feed additives in large containers

The following statements are required for feed additive products, depending on the packaging material (i.e., >1 kg).

> **Paper or cardboard containers and paper material bags**: Shake container into medicated feed. Do not dispose of undiluted chemicals on-site. Break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.
>
> **Plastic bags:** Single-rinse or shake container into the medicated feed. Do not dispose of undiluted chemicals on-site. Puncture bag and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.
>
> **Metal drums and plastic containers**: Triple-rinse the container into the medicated feed. Do not dispose of undiluted chemicals on-site. If recycling, replace cap and return clean container to recycler

or designated collection point. If not recycling, break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

5.1.2.3 Disposal statements for oral solutions in large containers

The following statements are required for oral solution products which are supplied in large containers (i.e. >1 L).

Triple-rinse container and dispose of rinsate in compliance with relevant local, state or territory government regulations. Do not dispose of undiluted chemicals on-site. If recycling, replace cap and return clean container to recycler or designated collection point. If not recycling, break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

6 Target animal safety

The APVMA published its consideration of target animal safety for product containing neomycin in January 2017 – *Neomycin: Target animal safety risk assessment report*. The assessment concluded that the use of neomycin products registered at that time were generally safe to use in individual animals without renal impairment at recommended doses and routes of administration. No new products containing neomycin which would fall within the scope of this reconsideration have been registered since the publication of this report.

The assessment considered information available to the APVMA including a literature review of information available in the public domain, as well as adverse experience reports (AERs) provided to the APVMA and animal safety studies provided by registrants.

The most frequently reported adverse experience report (AER) was for injection site reactions in horses. The frequency of both Australian and global AERs was low and many appeared to be related to reactions to the procaine benzylpenicillin in one of the neomycin-containing parenteral products, which is no longer registered for use in Australia.

The information considered indicates that, when administered in high concentrations, for prolonged durations, and/or more than once daily, neomycin may cause nephrotoxicity and/or ototoxicity. This is particularly the case for parenteral formulations. However, the risk of developing nephrotoxicity or ototoxicity from either parenteral or oral formulations increases if the animal has compromised renal function, gastrointestinal inflammation or is receiving another potentially nephrotoxic drug concomitantly.

A close examination of the information considered for food-producing animals suggests that parenteral neomycin-containing products are generally safe to use in healthy target species at recommended dose rates and routes of administration, and noted that the risk of toxicity can be reduced by extending the treatment interval to once per 24 hours, while oral products are safe to use provided the duration of treatment is restricted, and intramammary products are safe to use in the target species at the recommended dose rate and duration.

As a prescription animal remedy, products containing neomycin can only be prescribed by a veterinarian and used under veterinary supervision. However, additional label warnings in relation to the application of neomycin products are recommended. This includes warnings about the possibility of nephrotoxicity and ototoxicity in food-producing animals and contraindications for the use of neomycin-containing products in animals with compromised renal function, gastrointestinal inflammation or those receiving other potentially nephrotoxic drugs. For parenteral products, the maximum duration of treatment should be clearly indicated, and recommended dosage regimens should be based on extended-interval administration that allows for concentration-dependent killing and avoids extended periods of trough concentrations that lead to accumulation of neomycin. For oral products, the potential for adverse effects following prolonged treatment and clear instructions to re-establish diagnosis if no clinical improvement is seen following the recommended duration of treatment should be included on product labels.

Evidence of local irritation resulting from use of intramammary products was noted.

6.1 Conclusions and recommendations

Consideration of the published and unpublished information concerning neomycin use in food-producing animals indicates that neomycin-containing products are generally safe to use in animals without renal impairment at the

recommended doses and routes of administration. Information considered under this reconsideration and global and Australian AERs show a low incidence of problems encountered in food-producing animals, when used according to the label directions.

While it is appreciated that the global and Australian incidence of adverse experiences related to the use of neomycin-containing products is low, it is apparent that administration of neomycin at high doses and/or for prolonged duration can be associated with nephrotoxicity and ototoxicity. These should be noted as possible adverse reactions on product labels and the recommended maximum duration of treatment should be clearly indicated.

The risk of nephrotoxicity following parenteral administration of neomycin-containing products decreases when extended-interval (once daily) administration is employed. This information is critical from a toxicity perspective and should be clearly outlined on product labels. The package inserts for parenteral products should elaborate on the importance of once-daily dosing that achieves concentration-dependent killing and sub-toxic trough concentrations, as well as the post-antibiotic effects association with treatment with neomycin.

The risk of developing nephrotoxicity and/or ototoxicity is increased in animals with compromised renal function, gastrointestinal inflammation and those being treated with other potentially nephrotoxic drugs. These situations should be listed as contraindications on product labels.

6.1.1 Label recommendations

The directions for use should indicate a dosage regimen of 24-hour dose interval for parenteral products.

The following contraindication is recommended for all products:

> Not to be used in animals with compromised renal function, gastrointestinal inflammation and those being treated with other potentially nephrotoxic drugs.

The following precaution statement is recommended for all parenteral products:

> Neomycin exhibits concentration-dependent killing and a post-antibiotic effect. Repeated daily administration or overdosage with neomycin can cause renal damage and deafness. The risk of toxicity can be reduced by extending the dosage interval to 24 hours. Care should be taken in animals with known or suspected impaired renal function. Care should be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs. Where practical, it is recommended to weigh young animals to ensure accurate dosage calculation based on bodyweight.

The risk of nephrotoxicity following oral administration of neomycin-containing products increases when the duration of treatment is prolonged. This information is critical from a toxicity perspective and should be clearly outlined on product labels. The package inserts for parenteral products should elaborate on the importance of re-establishing the diagnosis if no improvement is observed following the recommended duration of treatment.

The following precaution statement is recommended for all oral products:

> Neomycin exhibits concentration dependent killing and a post-antibiotic effect. Overdosage with neomycin can cause renal damage and deafness. Care should be taken in animals with known or

suspected impaired renal function. While this is unlikely at therapeutic doses, care should be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs. Where practical, it is recommended to weigh young animals to ensure accurate dosage calculation based on bodyweight.

For all products that recommend a minimum duration of treatment of 5 days for salmonellosis the following direction should be included:

If no improvement is seen after 5 days, the diagnosis should be reestablished.

For all intra-mammary products the following precaution statement is recommended:

Neomycin exhibits concentration-dependent killing and a post-antibiotic effect. Overdosage with neomycin can cause renal damage and deafness. While this is unlikely at therapeutic doses, care should be taken in animals with known or suspected impaired renal function. Care should also be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs.

Based on evidence for local irritation following intra-mammary infusion of neomycin for the treatment of mastitis in dairy cattle, the following precaution statement would also be recommended for all intra-mammary products: product labelling.

If abnormal milk, redness, irritation or swelling persists or increases, discontinue use and redetermine diagnosis.

7 Efficacy

Each product has previously been assessed as meeting the efficacy criteria if used according to the approved label directions. Based on the review of the information available for neomycin oral, intramammary and injectable products, the APVMA supports the continued use of oral and intramammary products from an efficacy perspective.

8 Antimicrobial resistance

Antimicrobial resistance (AMR) occurs when an organism develops resistance to an antimicrobial that is being used to treat it. AMR can develop wherever antibiotics are used, and the level of use increases the likelihood of resistance developing. This is a global public health, animal health and welfare concern. The development and spread of AMR are influenced by both human and animal antimicrobial use.

8.1 Global perspective

Globally several studies have reported variable degrees of AMR in neomycin (Yang *et al*. 2021, Wongtawan *et al*. 2022, Ripon *et al*. 2023, El-Adawy *et al*. 2023). Neomycin is listed as critically important for human use in the World Health Organisation's (WHO) list of Critically Important Antimicrobials for Human Medicine (WHO 2019). The WHO recommends the use of this list to help formulate and prioritise risk assessment and risk management strategies for AMR. Neomycin is also on the list of Veterinary Critically Important Antimicrobial Agents (VCIA) as per the World Organisation for Animal Health's (WOAH, founded as OIE) list of antimicrobial agents of veterinary importance (OIE 2021). The inclusion of neomycin in these lists demonstrates that neomycin is an antimicrobial of global importance for both human and veterinary use and should be included in antimicrobial susceptibility programmes. However, the WHO also recognises nation specific considerations should be taken into account, and that this list may vary from country to country (WHO 2019).

8.2 Australian situation

The Australian Strategic and Technical Advisory Group on Antimicrobial Resistance (ASTAG) maintains a list of Antibacterial Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia. This list provides information to regulators and users of antibacterials on their importance in the treatment of infections in animals and humans, and the seriousness of the consequences should resistance emerge or be amplified. In this list, neomycin is categorised as an antibiotic with a low importance rating for human and animal health in Australia (ASTAG 2018). A low importance rating signifies that there are a reasonable number of alternative antibacterials in different classes available to treat or prevent most human infections even if antibiotic resistance develops.

In classifying neomycin with a low importance rating for Australia, ASTAG has considered the WHO list of Critically Important Antimicrobials for Human Medicine and the WOAH List of Antimicrobial Agents of Veterinary Importance, along with the local context, Australian surveillance data and available alternative antibiotics. It is specified that the list of Antibacterial Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia has precedence over all other lists, including the WHO's list, to ensure the Australian context is taken into account while determining the requirement for AMR assessment (ASTAG 2018).

Further, to ensure the availability of evidence-based, best practice and nationally consistent approaches to Antimicrobial Stewardship (AMS) across human health and animal health sectors, the Australian Veterinary Association (AVA), under Australia's Antimicrobial Resistance Strategy – 2020 and Beyond, also provides advice on the veterinary use of antibiotics critical to human health. Neomycin is categorised for first line use in animals by the AVA (AVA 2017), where veterinarians are advised to consider using first line antimicrobials along with alternative treatment approaches following a diagnosis. Antimicrobials categorised for second line use should be

limited to where first line antibiotics have been shown to be ineffective, and third line antimicrobials are reserved for last resort use where no other options are available.

For veterinary medicinal use, neomycin is only approved in Australia for the treatment of bacterial infections and as an antimicrobial for use in semen extenders and vaccines. The use of antibiotics as growth promotant (at sub-therapeutic levels) has raised the most concern about selection pressure for AMR. To combat this issue, as per the recommendations from Joint Expert Technical Advisory Committee on Antimicrobial Resistance (JETACAR), no APVMA registered neomycin products include claims for growth promotion, weight gain or feed efficiency. Further, in Australia, all neomycin products are listed as Schedule 4 'prescription only medicine' substances in the Poisons Standard, which limits availability of these products to cases which have been evaluated by a qualified veterinarian. Moreover, neomycin is not registered in Australia for parenteral use in human medicine.

While it is noted that a few recent Australian studies have reported AMR in neomycin (Sahibzada *et al*. 2020, Demiaud and Tee 2022), veterinary antimicrobial products containing neomycin are considered to have a 'low importance' rating for human and animal health in Australia with regards to the development of AMR. The APVMA acknowledges that AMR is a serious concern for all antibiotic products. Considering that there is no reported increase in transfer of neomycin resistant strains among bacteria of major importance in both animals and humans in Australia and no increased reports of cross-resistance with other antimicrobials, the APVMA made a decision not to broaden the scope of the review. APVMA acknowledges that AMR exists for neomycin and to delay its progression, APVMA recommends inclusion of AMR specific label statements.

8.3 Recommendations

It is recommended that the following directions/statements should be included in the label instructions for neomycin products used orally, intravenously or intramammary to help reduce the likelihood of AMR developing, as outlined in the APVMA Veterinary Labelling Code.

Under Statement of Claims

> Indiscriminate use of [name of the product] may contribute to the development of antibiotic resistance.

Under General Directions

> Prudent Use: Veterinarian must assess the clinical need for antimicrobials prior to prescription and must communicate the risk of antimicrobial resistance in humans and the need for prudent use in animals. Culture and sensitivity tests may be performed when appropriate to determine susceptibility of the causative organism(s). Empirical therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

It is recommended that the following directions/statements should be included in the label instructions for neomycin products used as a feed additive or additive for animal drinking water to help reduce the likelihood of AMR developing, as outlined in the APVMA Veterinary Labelling Code.

Under Dosage and Administration for feed additive products

Make sure that the animal/s being treated consume all the medicated feed.

Under Dosage and Administration for products used as an additive to animal drinking water

Make sure that the animal/s being treated consume all the medicated water.

Limits have been placed on the ‘off-label’ prescribing of veterinary medicines by Australian Veterinary Association (AVA prescribing guidelines, 2023), Department of Agriculture, Fisheries and Forestry (COAG Reforms, 201022) and APVMA (Veterinary Labelling Code, 2022), by providing guidance to comply with all regulatory label restraint statements. Furthermore, Department of Agriculture, Fisheries and Forestry (Buller *et al*., 2014) and Australian Veterinary Association (AVA prescribing guidelines, 2023) have posed restrictions on the off-label use of Neomycin in food producing animals in Australia. Therefore, the following RESTRAINTS are recommended for neomycin products to prevent their overuse or off-label use.

DO NOT prescribe [Name of Product], prior to investigating the use of non-antibiotic options. If [Name of Product] is indicated and selected for use, prudent prescribing practices (appropriate dose, duration and frequency) should be followed to minimise treatment failure while limiting the possible emergence of antimicrobial resistance.

Appendix

Appendix A – Summary of changes

Product number					
36237	2A – parenteral liquid/solution/ suspension	Dogs, cats	Cattle, horses, sheep, pigs	Insufficient residues data for cattle, horses, sheep and pigs.	Add condition related to completion of residue studies on cattle, horses, sheep and pigs and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions and storage instructions.
36026	3A – oral solution/ suspension	Dogs, cats	Cattle (calves) horses	Insufficient residues data for calves and horses.	Add condition related to completion of residue studies on cattle and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions, environmental protection statement and storage instructions.
49788	3A – oral solution/ suspension	Dogs, cats	Cattle (calves) horses	Insufficient residues data for calves and horses.	Add condition related to completion of residue studies on cattle and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions,

[7] Conditional registration will require product-specific residues studies for each target animal species to be provided to the APVMA within 2 years of the date of the decision on the reconsideration of neomycin.

Product number	Formulation type	Uses supported	Uses supported with conditional registration[7]	Reason for conditional registration	Variations to registrations and approvals as an outcome of reconsideration
					environmental protection statement and storage instructions.
46414	3D – oral tablet	none	Cattle (calves), horses	Insufficient residues data for calves and horses.	Add condition related to completion of residue studies on cattle and horses and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements. Contraindications, dosage and administration directions, general directions, safety directions and storage instructions.
67805	3H – oral powder, pre-mix	none	Poultry, pigs, cattle	Insufficient residues data for poultry, pigs and cattle.	Add condition related to completion of residue studies on poultry, cattle, and pigs and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements. Contraindications, dosage and administration directions, general directions, safety directions and storage instructions.
52782	3H – oral powder, pre-mix	none	Poultry	Insufficient residues data for poultry.	Add condition related to completion of residue studies on poultry and associated MRLs and withholding periods and supply of the results to the APVMA. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements. Contraindications, dosage and administration directions, general directions, safety directions and storage instructions.
49851	4E – misc. intra mammary	none	Lactating cows	Insufficient residues data for lactating cows.	Add condition related to completion of residue studies on lactating cows and associated MRLs and withholding periods and supply of the results to the APVMA.

Product number	Formulation type	Uses supported	Uses supported with conditional registration[7]	Reason for conditional registration	Variations to registrations and approvals as an outcome of reconsideration
					Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements. Contraindications, dosage and administration directions, general directions, safety directions and storage instructions.

Appendix B – Summary of submissions to consultation on proposed decisions

The APVMA received 23 written submissions in response to the publication of the proposed regulatory decisions for the reconsideration of neomycin chemical product registrations and label approvals for oral, intramammary and injectable preparations being conducted under Part 2, Division 4 of the Agvet Code. The APVMA received permission to publish 12 of these submissions, which are available on the APVMA website. A summary of the submissions is listed in Table 16 and the APVMA's considerations of these submissions are summarised below. Confidential submissions commented on several issues, including the implications for animal welfare and antimicrobial stewardship programs, as well as providing scientific argument in favour of retaining neomycin product registrations. The confidential submissions have been considered by the APVMA but are not discussed further.

Table 16: Published submissions in response to the proposed regulatory decision on the reconsideration of neomycin

Submitter	Comments
Aurora Dairies	Argued to retain registration of Mastalone (product 49851). Raised concerns regarding the implications of the proposed decisions for antimicrobial stewardship and animal welfare. Claimed that neomycin MRL exceedances have not been reported in cattle tissue over the last 11 years.
Ausrichter Pty Ltd	Argued to retain registration of Scour-X Oral Anti-Diarrhoeal Suspension (product 49788), claiming that treated animals would not enter the food chain. Discussed the metabolism of neomycin and the international regulatory status of neomycin. Identified that the Neomycin Review Technical Report erroneously considered the product 49788 to be used twice daily rather than once daily.
Australia Chicken Meat Federation	Supported decision to cancel the registration of neomycin products that are used within the poultry industry and noted the availability of viable alternatives.
Australian Dairy Farmers	Argued to retain registration of neomycin products. Raised concerns regarding the implications of the proposed decision to cancel the registration of intramammary neomycin products primarily based on lack of data, noting animal welfare concerns and that they unaware of any risks to health or trade posed by use of the product.
Australian Pork Limited	Argued to retain registration of neomycin products. Raised antimicrobial stewardship concerns, animal welfare concerns and noted limited MRL exceedances in pig products over the last 11 years.
Australian Veterinary Association	Argued to retain registration of neomycin products. Raised animal welfare concerns, antimicrobial stewardship concerns, and noted that they are unaware of any residues issues that would warrant cancellation of the product.
Dairy Australia	Argued to retain registration of Mastalone (product 47851). Raised concerns regarding the potential impact of cancellation of neomycin products for intramammary treatment of mastitis on the dairy industry, noting antimicrobial stewardship concerns and animal welfare concerns. Also noted limited residues exceedances in cattle meat products over the last 10 years or in milk products over the last 25 years. Argued that data indicates there is limited systemic absorption of neomycin when administered via the intramammary route. Asserts there is a minimal likelihood that the use of neomycin intramammary products would pose a risk to international trade.

Submitter	Comments
Dorrigo Plateau Vet Clinic	Argued to retain registration of Mastalone (product 47851). Raised concerns regarding the implications of the proposed decision to cancel the registration of an intramammary neomycin product based the effectiveness of the product.
Geovet	Argued to retain registration of Mastalone (product 47851). Raised concerns regarding the implications of the proposed decision to cancel the registration of an intramammary neomycin product based on the impact on industry and animal welfare concerns.
Production Animal Veterinary Services	Argued to retain registration of Mastalone (product 47851). Raised concerns regarding the implications of the proposed decision to cancel the registration of an intramammary neomycin product based on the impact on industry and animal welfare concerns.
Rivalea Australia	Argued to retain registration of neomycin products. Raised antimicrobial stewardship concerns, animal welfare concerns and noted limited residues exceedances in pig products over the last 11 years.
SunPork	Argued to retain registration of neomycin products. Raised antimicrobial stewardship concerns, animal welfare concerns and noted limited residues exceedances in pig products over the last 11 years.

Consideration of submissions

Matters beyond scope of reconsideration

Commercial impact of the regulatory decision as proposed and failure to consider benefits.

A number of submissions argued against the proposed decision to cancel certain neomycin products based on antimicrobial stewardship concerns, animal welfare concerns and the impact on dairy, cattle and pig industries.

> **APVMA Response:** These matters are beyond the scope of the statutory safety, efficacy, trade and labelling criteria and the APVMA is not able to consider them during the reconsideration.

Requests for extended reconsideration timeframe

Several submissions requested an extension of existing timeframes for the reconsideration and the proposed phase out period.

> **APVMA Response:** Having considered the submissions, the APVMA's final regulatory decision has resulted in variations to the instructions for use to enhance the protections for worker safety and the environment, but did not result in immediate cancellations of any products. Holders are required to provide the APVMA with product and use-specific residue studies within 2 years as a condition of continued registration.

Support for the regulatory decision as proposed

Viable alternatives

The Australia Chicken Meat Federation supported the APVMA's proposed decision to cancel neomycin products that are used within the poultry industry and noted the availability of viable alternatives.

APVMA Response: These submissions are noted.

Label amendments

Several submissions supported the APVMA's proposed decision to vary label instructions with respect to the outcomes of the human health, chemistry, target animal safety, environment and antimicrobial resistance scientific risk assessments.

APVMA Response: These submissions are noted.

Errors in the Draft Neomycin Review Technical Report

Ausrichter Pty Ltd identified that the residues section of the Draft Neomycin Review Technical Report erroneously states their product 49788 - Scour-X Oral Anti-Diarrhoeal Suspension is used twice daily rather than daily.

APVMA response:

This has been noted.

One submission questioned the terminology used in Table 16 in the Draft Neomycin Review Technical Report, suggesting that the value calculated is the 'Theoretical Maximum Daily Intake (TMDI)' rather than the 'Estimated daily intake'.

APVMA Response:

We acknowledge that in the JECFA dietary intake estimation, neomycin MRLs were used (as worst case scenario) as opposed to median residues as is the case for EDI. The chronic dietary exposure, based on temporary MRLs, was considered acceptable at <21% of ADI using JECFA diet.

Residues and trade risk assessment

Arguments that the risk to human health is low

Most submissions disagreed with the APVMA's residues and trade risk assessment on several grounds. These included that:

- International regulators, governing bodies and non-government organisations, including the European Medicines Agency (EMA), European Food Safety Authority (EFSA) and the Food and Agriculture Organisation (FAO) have assessed studies related to residues of neomycin and identified levels of neomycin residues in food that are acceptable for human safety.

- Australian temporary MRLs, set in 2004, are consistent with the findings of those organisations and aligned with the recommendations of the Codex Alimentarius Committee.
- Residue monitoring conducted by the National Residue Survey and private organisations has resulted in very few or no detections of neomycin in animal commodities, including beef, pork, poultry, milk and eggs since the temporary MRLs were established.

APVMA Response:

The APVMA is not able to rely on summaries of residues depletion studies presented in international reports to be satisfied that products registered in Australia continue to meet the safety and trade criteria. Without access to the full datasets within these reports, the APVMA is not able to assess the relevance and reliability of these studies with respect to products registered in Australia.

Temporary MRLs are occasionally set by the APVMA, to enable further experimental work to be carried out to generate data that is sufficient to allow long term satisfaction that products meet the statutory criteria. In the case of neomycin, uncertainties remain regarding the residues that will be present after the current withholding periods have elapsed for reasons that are discussed below. These uncertainties mean that although the risk to human health through dietary exposure is expected to be low, especially through acute and short term exposure, the APVMA does not have adequate information to be satisfied that long term dietary exposure will not exceed the ADI, leading to an unacceptable lifetime exposure risk.

Residue monitoring data indicating low or no detections of neomycin in commodities support the view that dietary exposure to neomycin is not common. However, monitoring data cannot be used for the APVMA's risk assessments as there no information about whether the tested commodities are derived from animals that were treated with neomycin and, if so, which type of treatment was applied, the dose, duration, time after last treatment, re-treatment interval and whether any other treatments were also applied.

Non-mandatory matters relevant to the statutory criteria

One submission noted that when considering whether a product meets the safety criteria, it is not mandatory for the APVMA to have regard to the matter at subsection 5A(3)(b)(iii) of the Agvet Code *'whether any trials or laboratory experiments have been carried out to determine the residues of the product and if so, the results of those trials or experiments and whether those results show that the residues of the product will not be greater than limits that the APVMA has approved or approves'*

APVMA Response:

It is the APVMA's view that the Agvet Code allows discretion in this regard because agricultural or veterinary chemical products may be registered for use in situations that are not related to food production. However, where a product is intended to be used in or on a crop or animal intended for human consumption, it would be negligent of the APVMA not to consider the level of residues that may result from its use and whether that residue is an undue hazard to people or likely to have an effect that is harmful to human beings.

Scientific argument with reference to published and proprietary studies

Several submissions provided publicly available scientific reports, or proprietary studies, with data on the pharmacokinetics, distribution, metabolism, excretion and target animal safety of neomycin products generally. These studies did not include trials conducted with currently registered products or equivalent formulations and were generally conducted using treatment regimens that differed from the instructions for administration of registered products. One study was submitted in confidence, purportedly related to residues of a commercial product, however the data in the study did not support this assertion.

APVMA Response:

It is not possible to confidently predict the effect of any interactions between active constituents and other excipients or with secondary active constituents in a product on the absorption, distribution, metabolism and excretion of a product based on data generated using a product with a different formulation or using a significantly different treatment regimen (dose, duration, withholding period and retreatment interval).

This means that although the evidence available does not refute the hypothesis that neomycin residues will be lower than the relevant MRL once the current withholding period has elapsed, it is also not sufficient to demonstrate that residues will not exceed the MRL or to allow prediction of a withholding period that will prevent MRL exceedances.

Arguments that the risk to trade is low

A number of submissions questioned the requirement for additional food-safety (marker-residues depletion) trials that meet contemporary design recommendations for the APVMA to be satisfied that neomycin products meet the trade criteria. It was asserted that any risks to trade are successfully being managed with parameters currently in place, as no significant trade incidents involving neomycin have been reported during the decades-long registration of neomycin chemical products.

APVMA Response:

As noted above, uncertainty about the expected level of neomycin residues in commodities from treated animals remains due to the lack of studies relevant to the commercial neomycin products registered in Australia. Although the evidence does suggest that the risk to trade is low. The APVMA establishes export slaughter intervals (ESI) to minimise risk to overseas trade. The ESI is data driven and is applied where importing countries have set a lower MRL than is used in Australia, or expect no residue. The data required as a condition of the continued registration of neomycin products will be suitable to determine appropriate ESIs.

Acronyms and abbreviations

Shortened term	Full term
ADI	Acceptable daily intake (for humans)
AER	Adverse experience report
AMR	Antimicrobial resistance
ARfD	Acute reference dose
ASTAG	Australian Strategic and Technical Advisory Group
BP	British Pharmacopeia
Bw	Bodyweight
EDI	Estimated daily intake
ESI	Export slaughter interval
FAO	Food and Agriculture Organization of the United Nations
G	Gram
Kg	Kilogram
L	Litre
Mg	Milligram
MIC	Minimum inhibitory concentration
mL	Millilitre
MRL	Maximum residue limit
NEDI	National estimated Daily Intake
NESTI	National Estimated Short-Term Intake
NOAEL	No Observed Adverse Effect Level
PAE	Post-antibiotic effect
USP	US Pharmacopeia
WHP	Withholding period

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