参考資料6

Australian Government
Australian Pesticides and Veterinary Medicines Authority

Antibiotic resistance risk assessments

1. Risk assessment for food-producing animals

If your application relates to the use of an antibiotic in food-producing animals, you should prepare a qualitative risk assessment addressing the possible contribution of the proposed use pattern to antibiotic resistance in food-borne microorganisms and human pathogens, and risk of consequent disease in susceptible humans.

1.1. Summary of the risk profile

In your risk assessment, you should summarise the:

- hazard characterisation
- exposure characterisation
- impact characterisation
- assessment of the uncertainty of the data used in risk assessment
- benefits of use of the antibiotic in Australian animal health
- risk characterisation.

These are discussed in more detail below.

1.1.1. Hazard characterisation

A hazard characterisation details the antibiotic-resistant microorganisms or their resistance-transferable genetic elements (that have the potential to transfer to humans) within an animal species, arising from the use of an antibiotic in an animal species.

Firstly, you should:

- state how much of the antibiotic you expect will be used in Australia, and in which geographic and/or farming areas it will be used
- list relevant microorganisms (target animal pathogens, food-borne microorganisms)
- characterise the hazard with respect to
  - the known mechanism(s) and genetics of resistance pathways in relevant microorganisms
  - details of the microbial resistance patterns in relevant microorganisms *in vitro*, such as

    - minimal inhibitory concentrations (MICs) of antibiotic against relevant microorganisms—include data from contemporary Australian isolates where available
    - the estimated development rate of expression of resistance, such as indicated from *in vitro* studies of passaged microorganisms in the presence of the antibiotic (where such information is available)
  - details of the microbial resistance patterns in relevant microorganisms that have emerged with the use of the product, the antibiotic or related substances
- identify the proposed use of the product and the target animal species
  - major food-producing species (mass medication)—for example, cattle, sheep, pigs and poultry
  - major food-producing species (individual animal treatment)—for example, cattle, sheep, pigs and poultry
  - other food-producing species (mass medication or individual animal treatment)—buffalo, deer, fish, goat, kangaroo, rabbit, bee, crustaceans, molluscs and other minor species.

Secondly, you should supply overseas data or Australian data, or both, where available. These data may include changes that have been identified in MICs of the antibiotic against isolates of relevant microorganisms collected from clinical cases, field trials, or changes identified after other uses of the antibiotic or related substances.

You should provide evidence of *in vitro* cross-resistance in relevant microorganisms with other antibiotics in

- the same antibiotic class
- other antibiotic classes.

If overseas or Australian data are not available, you should justify this with relevant scientific argument:

- assess the potential exposure of gut flora to the antimicrobial (or its metabolites) according to the following levels of exposure
  - high—in-feed or in-water medication as group treatment—the antimicrobial substance and/or its metabolites are present in the gastrointestinal tract in concentrations high enough to have an impact on microbial flora after administration
  - low— parenteral treatment or individual oral treatment—the antimicrobial substance and/or its metabolites are present in the gastrointestinal tract after administration
  - none—the antimicrobial substance and/or its metabolites are not present in the gastrointestinal tract.
- if the antibiotic (or metabolites) is likely to be present as an active substance in the large intestine of target animal species, describe
  - the known or predicted antibiotic concentrations in colonic contents, where available
  - the expected effects of the antibiotic on colonic microorganism content (including anaerobes) and resistance patterns in relevant microorganisms in target animals or animal products—if not available, provide relevant scientific argument
- describe the hazard that may be expected to arise from the proposed use pattern and the quantities and distribution of use
- categorise the probability of hazard when the product is used according to the proposed use pattern (negligible, low, medium or high).

1.1.2. Exposure characterisation

An exposure characterisation states the amount and frequency of exposure of susceptible humans to antibiotic-resistant microorganisms (or their transferable genetic elements) from animal sources.

You should describe:

- routes of exposure
- levels of carriage of food-borne microorganisms in populations of the target animal species

- the potential for contamination of food commodities on farms (such as eggs or milk), at abattoirs (such as meat) or at other relevant locations of harvest
- the potential for contamination and amplification along the food chain, including processing, storage, distribution and preparation
- contamination prevention programs along the food chain, providing details of
  - the effectiveness and reliability of codes of practice and Hazard Analysis and Critical Control Points (HACCP) programs relating to contamination
  - the effectiveness and reliability of process controls to destroy or inhibit microorganisms
  - microorganism survival and potential for growth, reduction or dilution in food along the food chain (processing, storage, distribution and preparation) with respect to temperature, time, pH, water activity and microbial interaction
- the intended use of foods and consumption patterns
- the probability and extent of human exposure in the general human population (negligible, low, medium or high).

You should also give details of:

- the demonstrated establishment of antibiotic-resistant microorganisms (of animal origin) in the general human population and in susceptible humans
- factors that are believed to influence food-borne microorganism distribution and secondary spread from a point source to a range of susceptible humans (including characterisation, variability and distribution)
- populations of susceptible humans with respect to relevant microorganisms
- the probability of spread to susceptible humans (negligible, low, medium or high)
- the probability and extent of exposure of susceptible humans to resistant microorganisms from animal sources (negligible, low, medium or high).

1.1.3. Impact characterisation

An impact characterisation is the evaluation of infections (caused by antibiotic-resistant pathogens of animal origin) in susceptible humans.

You should rank the antibiotic with regard to the perceived or known clinical importance of the class of antibiotics to humans. Table 1 is based on the Expert Advisory Group on Antimicrobial Resistance (EAGAR) document titled *EAGAR importance ratings and summary of antibiotic uses in humans in Australia* (2006 – no longer readily available), and may be used as a guide.

Table 1: Descriptions and examples of EAGAR importance ratings

EAGAR importance rating	Description	Examples

High	Essential antibiotics for treatment of human infections for which there are few or no alternatives for many infections—these have also been called 'critical', 'last-resort' or 'last-line' antibiotics	**Antibacterials:** antipseudomonal penicillins, piperacillin-tazobactam, third and fourth generation cephalosporins, carbapenems, monobactams, certain aminoglycosides, oxazolidinones, glycopeptides, fluoroquinolones, streptogramins, antimycobacterials, antileprotics, ansamycins, fusidanes, colistin **Antifungals:** polyenes such as nystatin; allylamines such as terbinafine
Medium	Antibiotics for which there are other alternatives available, but fewer than for those classified as low	**Antibacterials:** amoxycillin-clavulanate, antistaphylococcal penicillins, first and second generation cephalosporins, certain aminoglycosides, lincosamides, nitroimidazoles, non-fluorinated quinolones **Antifungals:** polyenes such as amphotericin; imidazoles such as bifonazole, clotrimazole, econazole, isoconazole, ketoconazole, miconazole; triazoles such as fluconazole; morpholines such as amorolfine; Griseofulvins
Low	Antibiotics for which there are a reasonable number of alternative agents in different classes available to treat most infections, even if antibiotic resistance develops	**Antibacterials:** benzylpenicillin, certain aminoglycosides, macrolides, tetracyclines, sulphonamide-trimethoprim combinations, bacitracin, polymyxin B, amphenicols, nitrofurans **Antifungals:** thiocarbamates such as tolnaftate
Nil	Classes of antibiotics with no equivalents in human medicine	Polyether ionophores, bambermycins

In your impact characterisation, you should also:

- present a dose–response analysis—a description of the relationship between the frequency and magnitude of exposure of humans (dose) to antibiotic-resistant, food-borne microorganisms and the severity and/or frequency of the impact (response), including an estimate of the critical threshold of exposure required to cause infection in susceptible humans
- describe the severity, morbidity and mortality of antibiotic-resistant diseases
- state the expected numbers of infections and deaths
- outline the impact on human health and quality of life, including the range of susceptible humans expected to be affected
- categorise the probability of antibiotic-resistant infection development in susceptible humans (negligible, low, medium or high).

1.1.4. Assessment of the uncertainty of the data used in the risk assessment

You should assess how much of the uncertainty of the data used in the risk assessment is due to inherent variability and measurement error, and how much is due to lack of information or understanding.

1.1.5. Benefits of use of the antibiotic in Australian animal health

You should describe:

- the benefits of use of the antibiotic in Australian animal health
- the groups that benefit from taking the risk of using the antibiotic
- the groups that bear the risk and would benefit from risk management
- the risk–benefit distribution in Australian society, including the relative importance of the class of antibiotics in animals and humans.

1.1.6. Risk characterisation

A risk characterisation states the probability of disease due to infection in susceptible humans after exposure to antibiotic-resistant microorganisms (or their transferable genetic elements) of animal origin and the severity of the impact of exposure on susceptible humans.

You should justify your risk characterisation.

1.2. Summary of the risk assessment

You should summarise the risk profile, including a 3 x 4 matrix such as the example given in Table 2.

Place a tick in each column that characterises the hazard, the exposure and the impact. For example, if the hazard is high, the exposure is low and the impact is negligible, a tick is placed in the ‘high’ column for hazard, in the ‘low’ column for exposure and in the ‘negligible’ column for impact.

Table 2: Example risk profile matrix

	Negligible risk	Low risk	Medium risk	High risk
Hazard				**x**
Exposure		**x**		
Impact	**x**			

Separate risk summaries may be necessary for different bacterial species.

1.3. Recommendation

You should present a recommendation in support of the proposed use pattern of the antibiotic, providing suggestions for risk management, including mitigation and minimisation.

2. Risk assessment for non-food-producing animals

For antibiotics to be used in non-food-producing animals, a risk assessment should address risks associated with the potential transfer of antimicrobial-resistant bacteria or their genetic material from non-food-producing animals, such as companion animals, to humans.

A risk assessment for non-food-producing animals should be qualitative and based on scientific argument and data. Overseas data, Australian data or both should be supplied where available.

You should cover the following points in the risk assessment:

- the identification of relevant microorganisms of zoonotic potential

- the identification of relevant microorganisms that may be found in the animals' faeces (for example, *Campylobacter* species, *Escherichia coli*, *Enterococcus* species, *Salmonella* species), urine (for example, *E. coli*), skin or nares (for example, *Staphylococcus intermedius*, *S. aureus*) or saliva
- consideration of possible routes of exposure, including
  - direct contact with animal faeces
  - indirect contact with animal faeces (through grooming or stroking animals or being licked by animals)
  - direct or indirect contact with resistant bacterial pathogens on the animal's skin or nares, or in the animal's mouth or urine
- consideration of different exposure risks for different human population groups. Separate risk summaries may be necessary for
  - members of the general public
  - specific population groups that are in frequent and sometimes prolonged contact with companion animals (such as families with pets, veterinary staff, kennel staff, elderly persons in retirement homes or hospitalised patients in contact with 'pets-as-therapy' animals)
  - young children with higher risks associated with poor hygiene
- consideration of horses as potential food-producing animals (if horses are a target species).

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The Australian Pesticides and Veterinary Medicines Authority acknowledges the traditional owners and custodians of country throughout Australia and acknowledges their continuing connection to land, sea and community. We pay our respects to the people, the cultures and the elders past, present and emerging.

Australian Government
Australian Pesticides and Veterinary Medicines Authority

Antibiotic resistance

1. Introduction

Antimicrobial resistance is a global public health and animal health concern. Its development and spread is influenced by both human and non-human antimicrobial usage.

Antimicrobial resistance is a property of bacteria that enables them to grow in the presence of antibiotic concentrations that would normally kill or suppress the growth of susceptible bacteria. It occurs naturally in some genera of bacteria and in others it is acquired. The antibiotic resistance of greatest concern is that which is acquired by bacteria through genetic mutations or through movement of antibiotic-resistance genes from one bacterium to another. Continued use of an antibiotic in the presence of resistance allows those resistant bacteria to survive and become dominant within the bacterial flora. This selection of resistant bacteria is more likely to occur when the exposure of bacteria to antibiotics is greatest, for example when:

- there is overuse and inappropriate use of antibiotics (for example, by medical practitioners or veterinarians, or on farms)
- antibiotics are used at low doses for long periods of time
- there is a high bacterial load
- there is a high level of resistant bacteria present in the environment or clinical situation.

In approving active constituents and registering veterinary chemical products, the APVMA must be satisfied of certain statutory criteria that relate to the safety, efficacy, trade and labelling of these chemicals. Applicants wishing to have active constituents approved and products registered must demonstrate how their proposed active constituents and products satisfy all the relevant statutory criteria. This guideline describes how you may address the safety statutory criteria to register a new antibiotic or to extend the use of an antibiotic that is already registered. The guideline should be read in conjunction with other relevant guidelines and supporting information.

2. Satisfying the statutory criteria

This guideline outlines the types of studies, data and information that are necessary to characterise the potential for the development of antimicrobial resistance associated with the proposed use of antimicrobial products in animals. These studies, data and information cover attributes of the antimicrobial active constituent, the veterinary product, the nature of the resistance, the potential exposure of the gut flora in the target animal species, and risk assessment.

The guideline also describes the antibiotic-resistance data and information that may be submitted in support of applications for the registration of veterinary chemical products that contain antibiotics as active constituents. This information is consistent with the following guidelines and incorporates their requirements for basic information about antimicrobial agents for use in food-producing animals:

- VICH guideline number 27: Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance;
- FDA/CVM guideline #144: Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance, VICH GL27 and
- FDA/CVM guideline #152: Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern.

Although we provide this guideline to support potential applicants to make applications to us, we are willing to consider other approaches that may also satisfy us of the statutory criteria for approving active constituents and registering products. Applications that do not satisfy us of the statutory criteria must be refused. We recommend that if you plan a significant departure from the data or information outlined in this guideline, that you speak to us first to ensure that you will be able to satisfy the criteria.

3. The JETACAR report

The Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) reported to the Australian government in 1999 on various aspects of antimicrobial resistance, including those associated with the use of antibiotics in food-producing animals. The JETACAR report concluded that there was evidence for:

- the emergence of resistant bacteria in humans and animals following antibiotic use
- the spread of resistant animal bacteria to humans
- the transfer of antibiotic-resistance genes from animal bacteria to human pathogens
- resistant strains of animal bacteria causing human disease.

A key recommendation of the JETACAR report, supported by the Australian Government, was that the APVMA would evaluate all new applications for the registration of antibiotics for use in animals, major extensions of use, and any reviews of currently registered antibiotics, using an agreed set of data and information and a risk assessment provided by applicants, as described in the regulatory guidelines. The data, information and risk assessment are independently analysed by the APVMA to ensure that the active constituent and/or proposed product satisfy the statutory criteria.

4. What are the risks of antimicrobial resistance?

The use of antimicrobial agents in humans, animals or plants is likely to select for antimicrobial resistance in both target and non-target microorganisms. Zoonotic organisms can be transferred to humans from animals. Therefore, it follows that antimicrobial-resistant zoonotic and commensal organisms can also be transferred directly to humans.

The transfer of antimicrobial-resistant non-zoonotic bacteria or their genetic material from animals to humans indirectly via the food chain is known to occur. However, there are limited data to demonstrate the magnitude and importance of such transfer and whether such transfer occurs via consumption of contaminated meat or via contamination of water or vegetables with animal excreta.

The transfer of antimicrobial-resistant bacteria or their genetic material from companion animals to humans is also possible, as is the transfer from humans to companion animals and back to humans, as has been demonstrated in the case of methicillin-resistant *Staphylococcus aureus* (Scott et al, 1988; Cefai et al, 1994; Manian, 2003; Weese et al, 2005). Data demonstrating the magnitude and importance of such transfers are limited.

Humans may be exposed to antimicrobial-resistant bacteria from companion animals by the following routes:

- direct contact with animal faeces—dogs and cats defecate in public spaces, home gardens or litter trays within homes
- indirect contact with animal faeces—anal licking during self-cleaning behaviour by dogs and cats may transfer resistant enteric bacteria to other parts of the animal's body, such as the coat and mouth. Humans may then be exposed to the resistant bacteria through grooming or stroking the pet, or when the animal licks a family member
- direct or indirect contact with resistant bacterial pathogens on the animal's skin, nares or in the animal's mouth or urine.

The risk of exposure to antimicrobial-resistant bacteria from companion animals is negligible for members of the general public. However, this risk is considerably higher for members of a pet-owning family or other specific population groups that are in frequent and often prolonged contact with pets. Young children (less than four to five years of age) may have the highest risk of exposure compared with other family members because they are too young to control their hand-to-mouth actions and may not practise adequate hand hygiene (Schutze et al, 1999; LeJeune & Davis, 2004).

The bacterial flora of both food-producing animals and companion animals, whether healthy or diseased, may act as a reservoir of resistance genes. Humans are also a potential reservoir of antimicrobial-resistant microorganisms. Amplification of antimicrobial resistance may occur in both animal and human reservoirs.

The main risk to be considered by applicants and assessed by the APVMA is the probability of diseases occurring in susceptible humans due to infection with antibiotic-resistant pathogens arising from proposed changes in the use of antibiotics in animals, and the consequences of such disease.

The level of acceptable risk is that which, when weighed against proposed benefits of use in the target animal species, will not significantly compromise therapeutic use of antibiotics in humans.

5. When an assessment of antimicrobial resistance is performed by the APVMA

The APVMA seeks advice from the National Health and Medical Research Council (NH&MRC), on the assessment of public health risk from the development of antibiotic resistance in human pathogens associated with the use of antibiotics in animals. In order to assess this risk, applicants should submit data in support of:

- any proposed use in Australia of a product containing a new antibiotic
- any proposed extension of use in Australia of a registered product containing an existing, approved antibiotic where we consider that there is likely to be a significant increase in the volume of usage, or that there may be an increased risk to public health as a result of the use of that antibiotic.

The following are examples of situations where there is likely to be a significant increase in the volume of antibiotic usage or an increased risk to public health as a result of the use of that antibiotic:

- a change in dosage form or use pattern, from use in individual animals to mass medication (for example, from injectable to in-feed or in-water dosage forms)
- an extension of the use pattern to a new major food-producing host species (for example, chickens to pigs; sheep to cattle; dogs to cattle)
- an extension of the use pattern to another major group within the same food-producing species (for example, broiler chickens to layers; beef cattle to dairy cattle)
- an extension of the use pattern from food-producing animals to dogs or cats for the first time for the antibiotic.

Before submitting data, you are encouraged to seek guidance from us on other situations that may be considered as a significant increase in the volume of usage, or may pose a public health risk. You are encouraged to use the pre-application assistance process offered by the APVMA.

6. Antimicrobial data you may submit to satisfy the APVMA of the statutory criteria

You should submit your submission according to the headings suggested in the template. Each item should be addressed by data or relevant scientific argument. We recommend that you provide a complete set of data and a risk assessment as described in the 'Risk assessment' section below—missing information may result in us being unable to be satisfied against the statutory criteria. Although you may choose to not provide certain information if you believe this will not affect our satisfaction against the statutory criteria, it is recommended that you discuss this different approach with us through the pre-application assistance process.

Please note the following additional points:

- the risk assessment part of the submission should, in the first instance, be a qualitative risk assessment with scientific argument—you also have the option of providing a quantitative risk assessment
- you should provide scientific evidence to support the claims made and, where there are citations to scientific literature, you should provide copies of these papers with the submission to allow us to check the claims made in your application
- further questions or requests for data may arise during our review of the submission
- absence of evidence for antimicrobial resistance is not evidence of its absence.

6.1. Description of the antibiotic constituent(s) of the product

6.1.1. Name and identification of the antibiotic

You should provide the following information about the antibiotic:

- the common name
- the chemical name
- the Chemical Abstract Services (CAS) registry number
- the chemical structure
- the manufacturer's code number and/or synonyms.

6.1.2. Class of antibiotic

You should state the chemical relationship between the antibiotic and other members of the antibiotic's class and related classes.

6.1.3. Mechanism and type of antimicrobial action

You may infer information on the antimicrobial mechanism of action from literature studies, patent information, or from specific mechanism-of-action studies that you undertake. Characterisation as to concentration-dependent or time-dependent bacterial killing and bacteriostatic versus bactericidal action should be included in this section.

6.1.4. Antimicrobial activity of the antibiotic

6.1.4.1. Antimicrobial spectrum

In order to determine the overall spectrum of activity, you should provide information that includes data from minimum inhibitory concentration (MIC) tests on a wide variety of microorganisms, or from literature studies. Where MICs are determined by you, you should indicate the source of the isolates. MICs may be sourced from culture collections, diagnostic laboratories or other repositories.

Where possible, MIC values should be determined with a validated and controlled method, such as those described by the Clinical and Laboratory Standards Institute (CLSI—formerly known as NCCLS) in documents such as:

- CLSI VET01-A4 and VET01-S2, Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; Approved standard—fourth edition and supplement, and
- CLSI VET02-A3, Development of *in vitro* susceptibility testing criteria and quality control parameters for veterinary antimicrobial agents; Approved guideline—third edition.

Contemporary Australian data should be provided where available and should include:

- relevant clinical isolates and standard laboratory strains
- validity of methods, including breakpoints
- MIC frequency tables or histograms.

6.1.4.2. Post-antibiotic and other antimicrobial effects (where appropriate)

If relevant, describe any additional effects such as first-exposure effects, post-antibiotic effects and sub-MIC effects.

6.1.4.3. Minimum inhibitory concentrations of target animal pathogens

Include MICs for target animal pathogens (as per the product label claims).

6.1.4.4. Minimum inhibitory concentrations of zoonotic pathogens, food-borne pathogens and commensal organisms

You should present data to show MICs of relevant zoonotic pathogens, food-borne pathogens, and commensal organisms. This information may be based on published data or on studies that you have done.

Depending on the spectrum of activity, appropriate food-borne organisms may include *Salmonella enterica* serovars, *Campylobacter* species particularly *C. jejuni* and *C. coli*, *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus faecium* and *Klebsiella* species.

Wherever possible, the strains included should be selected according to the following guidelines:

- strains of relevant bacterial species or serotypes should be isolated from the proposed target animal species; when the product is intended for use in a broad range of animal species, the strains should be from the main food-producing species (for example, cattle, pigs and poultry)
- the strain collection should include recent isolates (that is, within the last two years)
- information on the tested strains should include

- identification at least to the species level
- the origin, source and date of isolation.

This information may be used as a source of background data for surveillance studies of changes in patterns of antimicrobial resistance.

6.1.5. Antimicrobial resistance mechanisms and genetics

You should provide information on the resistance mechanisms and the molecular genetic basis of resistance to the antimicrobial agent. This information may come from literature or from studies that you have done. Information from analogues or the antibiotic class may be provided in the absence of data on the antimicrobial agent itself. The information should include:

- known mechanisms of resistance in animal and human pathogens (for example, antimicrobial inactivation, alteration of the target, reduced uptake, efflux of the antimicrobial agent)
- location of resistance determinants (for example, plasmid-mediated versus chromosomal; present on transposon, integron, or phage).

6.1.6. Occurrence and rate of transfer of antimicrobial resistance genes

You should provide information on the occurrence, or absence, of transfer and the rate of transfer of resistance genes. This information may come from literature or from studies that you have done.

Specific studies to evaluate the occurrence of genetic transfer may follow a protocol such as that found in *Antibiotics in laboratory medicine* (Lorian 2005) Lippincott, Williams and Wilkins, Philadelphia, PA. Relevant issues include:

- whether resistance determinants can be transferred among bacteria by transformation, transduction, conjugation or transposition
- if resistance determinants can be transferred, the rate of transfer
- if resistance occurs by point mutation, the rate at which the point mutations occur.

You may consider including data on target animal pathogens, relevant food-borne pathogens, and relevant commensal organisms. In the absence of data on the antimicrobial agent, information from analogues may be provided.

6.1.7. Occurrence of cross-resistance

You should provide information on cross-resistance to the antimicrobial agent. This information may come from literature or studies that you have done. The information should include a phenotypic description and, if available, a genotypic description.

6.1.8. Occurrence of co-resistance or co-selection

You should provide information on co-resistance and co-selection of the antimicrobial agent in question with other antimicrobial agents by way of literature information or studies that you have done. This should include a phenotypic description and, if available, a genotypic description.

6.1.9. *In vitro* mutation frequency studies

You may provide *in vitro* mutation frequency studies involving test organisms. This information may come from the literature or from studies that you have done. These studies may follow a protocol such as found in *Antibiotics in laboratory medicine* (Lorian 2005) Lippincott, Williams and Wilkins, Philadelphia, PA.

6.1.10. Other animal studies

If available, you may include information from other animal studies to help characterise the rate and extent of resistance development associated with the proposed use of the antimicrobial product. This may include data from clinical studies conducted in support of other aspects of the application, or other relevant studies published in the scientific literature.

6.2. Description of the product(s)

6.2.1. General

You should describe the following attributes of the product:

- distinguishing name(s)
- formulation type(s) or pharmaceutical dosage form(s)
- pack sizes, as per the label particulars
- claims, as per the label particulars
- poisons scheduling
- label particulars—you should include a copy of the draft relevant label particulars.

6.2.2. Pharmacokinetic or pharmacodynamic profile of the active constituent after administration of the product(s)

You should provide pharmacokinetic or pharmacodynamic information, which may include the following:

- serum or plasma concentrations versus time data
- maximum concentration (C_{max})
- time of maximum concentration (T_{max})
- volume of distribution (VD)
- clearance (Cl)
- area under the concentration–time curve (AUC)
- bioavailability
- protein binding
- known or predicted plasma (serum) concentrations, especially peaks and troughs after proposed dosing.
- pharmacokinetic or pharmacodynamic determinant of efficacy (time above MIC, AUC/MIC ratio or peak/MIC ratio), determined either specifically or from what is known for the antibiotic class, and the magnitude of that parameter, determined using free drug concentrations, which results in bacteriostasis and near maximum killing over 24 hours *in vivo*
- relationship of plasma (serum) and tissue concentrations to MICs for target animal pathogens and indicator bacteria (for example, *Escherichia coli*, *Enterococcus* species).

Overseas data, Australian data, or both, should be supplied where available.

6.2.3. Antimicrobial agent activity in the intestinal tract

Where available, you may provide details on the concentrations of the microbiologically-active compound within the intestinal tract contents or the faeces of the target animal(s) when the antimicrobial product is administered according to the proposed directions for use. The activity in question may be due to the parent antimicrobial agent, or to active metabolites.

Where such data are not available, details may be provided by metabolism studies relevant to the intestinal tract.

6.2.4. Registration status in Australia and overseas

Information on the registration status in Australia and in overseas countries of the product, or products containing the same antimicrobial active constituent, should be presented in the format shown in Table 1.

Table 1: Format for presenting registration status

Country	Animal species	Approved use patterns	Restrictions on use

6.3. Proposed maximum residue limits for food-producing species

Antimicrobial agent residues present in food from food-producing animals may adversely affect the intestinal microflora of consumers. In the case of antimicrobials for use in food-producing animals, you may propose maximum residue limits and a microbiological acceptable daily intake (ADI). In this case, you should:

- include European Union Committee for Medicinal Products for Veterinary Use (CVMP) technical reports, other regulatory agency reports or Joint FAO/WHO Expert Committee on Food Additives (JECFA) technical reports, if available and where applicable
- refer to VICH guideline number 36: Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI
- FDA/CVM guideline #159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI: VICH GL36(R)
- address the risk of susceptible humans developing antibiotic-resistant infections as a result of exposure to antibiotic residues in food commodities (as distinct from transferred microorganisms or genetic material).

6.4. Risk assessment

You should provide a risk assessment for either food-producing animals or non-food-producing animals, depending on the nature of the proposal. We will assess each risk assessment independently before seeking advice either from the NH&MRC, another equivalent advisory body or to an expert advisor.

6.4.1. Risk assessment for food-producing animals

If your application relates to use of an antibiotic in food-producing animals, you should prepare a qualitative risk assessment addressing the possible contribution of the proposed use pattern to antibiotic resistance in food-borne microorganisms and human pathogens, and risk of consequent disease in susceptible humans.

With respect to antibiotic resistance, the main risk to be assessed is the probability of disease due to susceptible humans being infected with antibiotic-resistant pathogens arising from the proposed use of antibiotics in animals, and the consequences of such disease.

The level of acceptable risk is that which, when weighed against proposed benefits of use in the target animal species, will not significantly compromise the therapeutic use of antibiotics in humans.

The risk assessment should include consideration of studies or discussion (where relevant to the target animal species) using the headings in the risk assessment template as a guide.

6.4.2. Risk assessment for non-food-producing animals

For antibiotics to be used in non-food-producing animals, a risk assessment should address risks associated with the potential transfer of antimicrobial-resistant bacteria or their genetic material from non-food-producing animals, such as companion animals, to humans.

For such animals, a risk assessment based on food-borne microorganisms is not relevant. The risk assessment for antibiotic use in non-food-producing animals will consequently be less detailed, but should follow similar headings to the template, where relevant, to those described for food-producing animals.

Template for preparing a risk assessment for non-food-producing animals

7. References

Antibiotics in laboratory medicine , 5th ed., V. Lorian, ed. 2005. Lippincott, Williams and Wilkins, Philadelphia, PA.

Australian/New Zealand standard risk management AS/NZS 4360:1995 (Amendment 2, amended January 1998).

Cefai C, Ashurst S and Owens C (1994). Human carriage of methicillin-resistant *Staphylococcus aureus* linked with pet dog. Lancet 344: 539–540.

CLSI VET01-A4 and VET01-S2, Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; Approved standard—fourth edition and supplement, Available at techstreet.com/products/1860403

CLSI VET02-A3, Development of *in vitro* susceptibility testing criteria and quality control parameters for veterinary antimicrobial agents; Approved guideline—third edition. Available at techstreet.com/products/1860404

Codex Alimentarius Commission procedural manual (15th edition). Joint FAO/WHO Food Standards Programme, Rome 2005.

Commonwealth Department of Health and Aged Care and the Commonwealth Department of Agriculture, Fisheries and Forestry – Australia. The use of antibiotics in food-producing animals: Antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). September 1999. Available at health.gov.au

FDA/CVM guideline #144: Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance, VICH GL27

FDA/CVM guideline #152: Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern.

FDA/CVM guideline #159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI: VICH GL36(R)

LeJeune JT, Davis MA (2004). Outbreaks of zoonotic enteric disease associated with animal exhibits. Journal of the American Veterinary Medical Association 224: 1440–1445.

Manian FA (2003). Asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. Clinical Infectious Diseases 36: e26–28.

OMAFRA (Ontario Ministry of Agriculture Food and Rural Affairs). Risk assessment models of the Ontario Ministry of Agriculture, Food and Rural Affairs. Document 2 – A general model for food safety risk assessment April 1996.

Schutze GE, Sikes JD, Stefanova R and Cave MD (1999). The home environment and salmonellosis in children. Pediatrics 103: E1.

Scott GM, Thomson R, Malone-Lee J, Ridgway GJ (1988). Cross infection between animals and man: possible transmission of *Staphylococcus aureus* infection in humans? Journal of Hospital Infection 12: 29 –34.

VICH guideline number 27: Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance.

VICH guideline number 36: Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI

Weese JS, Archambault M, Willey BM, Dick H, Hearn P, Kreiswirth BN, Said-Salim B, McGeer A, Likhoshvay Y, Prescott JF and Low DE. (2005). Methicillin-resistant *Staphylococcus aureus* in horses and horse personnel, 2000–2002. Emerging Infectious Diseases 11: 430–435

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The Australian Pesticides and Veterinary Medicines Authority acknowledges the traditional owners and custodians of country throughout Australia and acknowledges their continuing connection to land, sea and community. We pay our respects to the people, the cultures and the elders past, present and emerging.