National Registration Authority
for Agricultural and Veterinary Chemicals

Part 10 of
Veterinary Requirement Series

SUBMISSION TO WORKING PARTY ON ANTIBIOTICS

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Part 10

SPECIAL DATA REQUIREMENTS

Submission to the Working Party on Antibiotics in support of the approval of new antibiotic active constituents and registration of veterinary chemical products containing antibiotic active constituents, and significant variations to such products (new dosage forms, extensions to use)

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10A INTRODUCTION

These instructions describe the general requirements for submitting antibiotic resistance data for the registration of veterinary chemical products that contain antibiotics as active constituents. The NRA will seek advice from the Working Party on Antibiotics (WPA) on the assessment of the public health risk from development of antibiotic resistance in human pathogens. Applicants must submit data, through the NRA, in support of :

a) any proposed use in Australia of a product containing a new antibiotic,
b) any proposed extension of use in Australia of a registered product containing an existing approved antibiotic where the NRA considers 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 NRA considers that 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 (eg. in-feed or in-water dosage forms)
- an extension of use pattern to a major food producing host species (eg chickens to pigs, sheep to cattle; dogs to cattle)
- an extension of use pattern to another major group within the same food-producing species (eg broiler chickens to layers; beef cattle to dairy cattle)

Applicants are encouraged to seek clarification from the NRA on other situations that may be considered a significant increase in the volume of usage, or may pose a public health risk, before submitting data.

The following points should be noted :

- The submission should be in the form of a risk assessment.
- The risk assessment should be based on quantitative scientific data as far as possible. It is recognised that qualitative relevant scientific argument may also be necessary.
- Scientific evidence to support the claims made is required and where there are citations to scientific literature, then copies of these papers are required.
- The ranking of the antibiotic with respect to its importance in human health, and its proposed use in food-producing versus non-food producing animals, may be used as a guide to the need to supply data and/or scientific argument.
- Further questions or requests for data may arise during the review of this submission.
- Applicants are advised to read the glossary before reading the data requirements.

10B DATA REQUIREMENTS

A Part 10 submission should be presented according to the following table of contents. Each item must be addressed by data or relevant scientific argument. However it should be noted that not all requirements may be relevant to all submissions.

10-1 Description of the antibiotic constituent/s of the product

10-1.1 Name and identification of antibiotic

a) Common name
b) Chemical name
c) CAS registry number
d) Chemical structure
e) Manufacturer's code number and/or synonyms

10-1.2 Class of antibiotic

a) Chemical relationship to other members of class and related classes

10-1.3 Antimicrobial activity of the antibiotic

a) Antimicrobial mechanism of action, if known
b) Antimicrobial spectrum
c) Minimum inhibitory concentrations (MICs) for target animal pathogens (as per product label claims), food-borne microorganisms and zoonotic pathogens, where applicable. Overseas and/or Australian data should be supplied where available.
    (i) Determined on relevant clinical isolates and standard laboratory strain
    (ii) Validity of methods including breakpoints
    (ii) MIC frequency tables or histograms
d) Where appropriate, post-antibiotic and other antimicrobial effects.

10-1.4 Proposed MRLs for food-producing species

a) Include European Union CVMP technical reports, other regulatory agency reports or JECFA technical reports, if available and where applicable.
b) 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).

10-2 Description of the product(s)

10-2.1 Distinguishing name(s)
10-2.2 Formulation type(s) / pharmaceutical dosage form(s)
10-2.3 Pack sizes, as per label
10-2.4 Claim(s), as per label
10-2.5 Poisons scheduling
10-2.6 Pharmacokinetic profile of the active constituent after administration of the product(s). Provide appropriate pharmacokinetic information which may include the following:

a) Bioavailability, area under the plasma or serum concentration versus time curve, clearance, volume of distribution, protein binding, concentrations of drug in intestinal contents.
b) Known or predicted plasma (serum) concentrations including peaks, troughs after proposed dosing.
c) Tissue concentrations after proposed dosing including achievable concentrations in target tissue(s) and sites of action where available.
d) Relationship of plasma (serum) and tissue concentrations to MICs for target animal pathogens.

Overseas and/or Australian data should be supplied where available.

10-3 Registration status in Australia and overseas

This information should be presented in the following format

Country	Animal species	Approved usage patterns	Restrictions on use

10-4 Risk assessment

This section is split into risk assessments for food-producing animals and other animals. Only the relevant part should be addressed.

Risk assessment – Food–producing animals

For antibiotics to be used in food-producing animals, a risk assessment (qualitative, semi-quantitative or quantitative) should be prepared addressing the possible contribution of the proposed use pattern to antibiotic resistance in food-borne microorganisms and human pathogens, and consequent disease in susceptible humans.

With respect to antibiotic resistance, the risk to be assessed is the probability of disease due to infection in susceptible humans 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, is not considered to significantly compromise therapeutic use of antibiotics in humans.

The risk assessment should include consideration of studies or discussion (where relevant to the target animal species) of the following areas:

10-4.1 Summary of the risk profile

Summary of

- the hazard (10-4.2)
- the exposure (10-4.3)
- the impact (10-4.4)
- uncertainty of data used in risk assessment (10-4.5)
- benefit of use of antibiotic in Australian animal health (10-4.6)

- the risk (10-4.7).

10-4.2 Hazard characterization : *antibiotic resistant microorganisms or their resistance plasmids (that have the potential to transfer to humans) within an animal species, arising from the use of an antibiotic in an animal species*

a) List the expected quantity of use of the antibiotic and the expected geographical / farm areas of use within Australia.
b) List relevant microorganisms (target animal pathogens, food-borne microorganisms).
c) Identify the proposed use of the product and the target animal species, using the following table.

Animal species	**Specific examples**
Major food-producing species Mass medication	Cattle, sheep, pigs, poultry, aquaculture (eg. fish, crustacea, molluscs) species
Major food-producing species Individual animal treatment	Cattle, sheep, pigs, poultry, aquaculture (eg. fish, crustacea, molluscs) species
Other food-producing species Mass medication or Individual animal treatment	Buffalo, deer, goat, kangaroo, rabbit, bee and minor species

d) Characterize the hazard with respect to:
    - The known mechanism/s and genetics of resistance pathways in relevant microorganisms.
    - Details of microbial resistance patterns in relevant microorganisms in vitro:
        - MICs of antibiotic against relevant microorganisms. Include overseas and/or Australian data where available.
        - Estimated rate of development 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 microbial resistance patterns in relevant microorganisms which have emerged with the use of the product, the antibiotic or related substances. Overseas and/or Australian data should be supplied where available.

      This would include changes that have been identified in MICs of the antibiotic against isolates of relevant microorganisms collected from clinical cases, field trials or other uses of the antibiotic or related substances following use of the antibiotic or related substances.
e) Evidence of *in vitro* cross-resistance in relevant microorganisms with other antibiotics in:
        - the same antibiotic class
        - other antibiotic classes.

   Overseas and/or Australian data should be supplied. If not available, relevant scientific argument must be supplied.
f) *If the antibiotic (or metabolites) is likely to be present as an active substance in the large intestine of target animal species* :
        - Known or predicted antibiotic concentrations in colonic contents, where available;

- 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, relevant scientific argument must be provided.

g) Describe the hazard that may be expected to arise from the proposed use pattern and the quantities and distribution of use set out above
h) Probability of hazard, when the product is used according to the proposed use pattern (N, L, M, H – see glossary)

10-4.3 Exposure characterization *the amount and frequency of exposure of susceptible humans to antibiotic-resistant microorganisms (or their plasmids) from animal sources*

a) Routes of exposure
b) Levels of carriage of food-borne microorganisms in populations of the target animal species.
c) Potential for contamination of food commodities on farm (eg. eggs, milk) at abattoirs (eg. meat) or other relevant locations of harvest.
d) Potential for contamination and amplification along the food chain including processing, storage, distribution and preparation.
e) Contamination preventative programs along the food chain including:
    - Effectiveness, reliability of Codes of Practice, HACCP regarding contamination.
    - Effectiveness and reliability of process controls to destroy or inhibit microorganisms.
    - Microorganism survival and potential for growth / reduction / dilution in food along the food chain (processing, storage, distribution and preparation) with respect to temperature, time, pH, water activity, microbial interaction.
f) Intended use of foods and consumption patterns.
g) Probability and extent of human exposure in the general human population (N, L, M, H – see glossary).
h) Demonstrated establishment of antibiotic-resistant microorganisms (of animal origin) in the general human population.
i) 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, distribution).
j) List populations of susceptible humans with respect to relevant microorganisms.
k) Probability of spread to susceptible humans (N, L, M, H –see glossary).
l) Demonstrated establishments of antibiotic-resistant microorganisms (of animal origin) in susceptible humans.
m) Probability and extent of exposure of susceptible humans to resistant microorganisms from animal sources (N, L, M, H –see glossary).

10-4.4 Impact characterization *the evaluation of infections (caused by antibiotic-resistant pathogens of animal origin) in susceptible humans*

a) Rank the antibiotic with regard to the perceived or known clinical importance of the class of antibiotics to humans

Group	Description	Examples
A	Classes of essential antibiotics used in human medicine where there are few or no alternatives for many infections	**Antibacterial**: Anti-pseudomonal penicillins, 3rd generation cephalosporins, carbapenems, monobactams, certain aminoglycosides, certain macrolides, glycopeptides, nitroimidazoles, fluoroquinolones, streptogramins, antimycobacterials, antileprotics **Antifungals**: Polyenes such as nystatin; Allylamines such as terbinafine
B	Classes of antibiotics used in human medicine for which there are other alternatives available but fewer than for Group C; OR there are concerns that use will lead to more chance of resistance in Group A drugs	**Antibacterials**: β-lactamase inhibitors, anti-staphylococcal penicillins, 1st and 2nd generation cephalosporins, certain aminoglycosides, certain macrolides, lincosamides, non-flourinated quinolones, chloramphenicol **Antifungals**: Polyenes such as amphotericin; Imidazoles such as bifonazole, clotrimazole, econazole, isoconazole, ketoconazole, miconazole; Triazoles such as fluconazole; Morpholines such as amorolfine; Griseofulvins
C	Classes of antibiotics used in human medicine for which there are a reasonable number of alternative agents available in different classes to treat most infections	**Antibacterials**: Benzylpenicillin, certain aminoglycosides, tetracyclines, sulphonamide-trimethoprim combinations, certain macrolides, polypeptides **Antifungals**: Thiocarbamates such as tolnaftate
D	Classes of antibiotics with no equivalents in human medicine	Ionophores / polyethers

b) Dose response assessment - 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.
c) Antibiotic-resistant disease severity, morbidity, mortality.
d) Expected numbers of infections and deaths.
e) The impact on human health and quality of life including the range of the susceptible humans expected to be affected.

f) Probability of antibiotic-resistant infection development in susceptible humans (N, L, M, H – see glossary).

10.4.5 Assessment of the uncertainty of the data used in risk assessment

a) Uncertainty due to inherent variability and measurement error.
b) Uncertainty due to lack of information or understanding.

10-4.6 Benefits of use of the antibiotic in Australian animal health

a) Benefits of use of the antibiotic in Australian animal health
b) Groups that benefit from taking the risk
c) Groups that bear the risk and would benefit from risk management
d) Risk – benefit distribution in Australian society including relative importance of the class of antibiotics in animals and humans.

10-4.7 Risk characterization *Probability of disease due to infection in susceptible humans after exposure of humans to antibiotic-resistant microorganisms (and genetic material) of animal origin* ***and*** *the severity of the impact of exposure on susceptible human*s

a) Characterize the risk with justification

10-4.8 Summary of the risk assessment

a) Summarize the risk profile, including this 3 x 4 matrix.

	Negligible	Low	Medium	High
Hazard				
Exposure				
Impact				

b) Separate risk summaries may be necessary for different bacterial species.

10.5 Recommendation

a) Present a recommendation in support of the proposed use pattern, providing suggestions for risk management, including mitigation and minimization

Risk assessment – Other animals

For antibiotics to be used in non-food-producing animals, a risk assessment for possible contribution to antibiotic resistance in zoonotic microorganisms should be prepared. 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, where relevant, to those required above for

food-producing animals. The risk assessment is more likely to be based on qualitative argument than quantitative data. Overseas and/or Australian data should be supplied where available. The following points should be noted :

- identification of relevant microorganisms of zoonotic potential (see glossary)
- consideration of horses as potential food-producing animals.

10C GLOSSARY

The definitions in this glossary should be read only in the context of potential antibiotic resistance transfer from animals to humans.

Antibiotic

A chemical agent that will selectively kill or inhibit the growth of susceptible microorganisms on direct application to living tissue or by oral or parenteral administration.

This definition *includes* antibacterial agents (including ionophores / polyethers), anti-fungal agents, anti-viral agents, and anti-coccidials with antibacterial activity. Antiseptics and antiparasitics with antibacterial activity may be considered on a case-by-case basis.

This definition *excludes* disinfectants, anti-neoplastics, immunologicals, direct-fed microbials and enzyme substances.

Breakpoint

- microbiological breakpoint

the antibiotic concentration above which organisms are known or very likely to harbour a resistance mechanism.

- susceptible breakpoint

the antibiotic concentration, at the site of action within the target species, at which organisms, whose MICs are at or below this concentration, are highly likely to respond to treatment with that antibiotic.

- resistant breakpoint

the antibiotic concentration, at the site of action within the target species, at which organisms, whose MICs are above this concentration, are unlikely to respond to treatment with that antibiotic.

Note: For some antibiotic/organism combinations, the susceptible and resistant breakpoints are identical. For other antibiotic/organism combinations, organism strains whose MICs fall between the susceptible and resistant breakpoint, or are equal to the resistant breakpoint, are likely to respond to higher doses of the antibiotic or at anatomical sites where the antibiotic is more concentrated. These strains are categorised as intermediate.

- disc diffusion test breakpoints

zone diameters of disc diffusion tests that are determined by calibration against clinical or microbiological breakpoints in the target animal species.

Cross resistance

Resistance to more than one antibiotic or antibiotic class determined by a single mechanism of resistance.

Dose / response assessment (in risk assessment)

The relationship between the magnitude of exposure (dose) to a hazard and the severity and/or frequency of the impact (response) (adapted from Anon 1997).

Exposure characterization (in risk assessment)

The qualitative and/or quantitative description and evaluation of the likely exposure of susceptible humans to a hazard (adapted from Anon 1997).

Exposure (in risk assessment)

How much and how often humans are exposed to a hazard in a manner which may produce an impact. With respect to antibiotic resistance, this is the amount and frequency of exposure of susceptible humans to resistant microorganisms (or their plasmids) from animal sources.

Food-borne microorganisms

Microorganisms carried on or in food commodities, that may be potential human pathogens, that may be resistant to antibiotics or that may carry resistance plasmids, including *Salmonella enterica* serovars, *Campylobacter* species particularly *C. jejuni* and *C. coli*, *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus faecium* and *Klebsiella* species.

HACCP program

Hazard Analysis Critical Control Points program, commonly part of industry QA programs.

Hazard

A biological, chemical or physical agent with the potential to cause an adverse effect on human health (adapted from Anon 1997). With respect to antibiotic resistance, the hazards are antibiotic resistant microorganisms or their resistance plasmids (that have the potential to transfer to humans) within an animal species, arising from the use of an antibiotic in an animal species.

Hazard characterization

The qualitative and/or quantitative description and evaluation of a hazard.

Human pathogens

Microorganisms that have the potential to cause disease in humans.

Impact

One or more adverse effects resulting from exposure to a hazard. With respect to antibiotic resistance, the impact is a disease resulting from infection caused by antibiotic-resistant pathogens in susceptible humans.

Impact characterization

The qualitative and/or quantitative description and evaluation of the nature of the adverse effects on human health from exposure to a hazard.

Major food-producing species :

Cattle (meat and milk), sheep, pigs, poultry (meat or egg – producing), aquaculture (eg. fish, crustacea, molluscs) species.

Minimum inhibitory concentration (MIC)
The lowest antibiotic concentration that visibly inhibits growth of microorganisms after *in vitro* incubation, at a time when an untreated culture becomes readily visible in or on culture medium. The MIC is usually expressed in terms of results for 90 % (MIC_{90}) or 50% (MIC_{50}) of the isolates tested.

Non-food producing animal species
Horse, dog, cat, ornamental fish and others

Other food-producing species (with minor contribution to human diets)
Buffalo, deer, goat, kangaroo, rabbit, bee and others

Post-antibiotic effect
Inhibitory effects on microorganism growth that occur after removal of certain antibiotics present at or above MICs.

Probability
The likelihood or chance that an effect will follow, when an event occurs. In qualitative terms, probability can be categorised (adapted from OMAFRA 1996) as either:

Negligible – probability is extremely low or negligible
Low – probability is low but clearly possible
Medium – probability is likely
High – probability is very likely or certain.

Qualitative analysis
Use of a narrative form or descriptive scales to describe the characteristics of, and likelihood of, each event arising and its consequences.

Quantitative analysis
Use of numerical data to describe the characteristics of, and likelihood of, each event arising and its consequences.

Risk
The probability of an adverse effect and the impact of that effect, consequential to exposure to a hazard (adapted from Anon 1997). With respect to antibiotic resistance, the risk being assessed is the probability of disease due to infection of susceptible humans with antibiotic resistant pathogens arising from the use of antibiotics in animals **and** the consequences of infections caused by such pathogens in susceptible humans.

Risk analysis
A process consisting of three components: risk assessment, risk management and risk communication (Anon 1997).

Risk assessment
The scientific basis for risk analysis, generally consisting of the following steps (adapted from Anon 1997):

i) hazard identification,
ii) hazard characterization,
iii) exposure characterization,
iv) impact characterization and
v) risk characterization.

Risk characterization
The qualitative and/or quantitative evaluation, including attendant uncertainties, of the probability of exposure and the severity of the impact of exposure of susceptible humans to the hazard (adapted from Anon 1997).

Risk communication
The interactive exchange of information and opinions concerning risk among risk assessors, risk managers, consumers and other interested parties (Anon 1997).

Risk management
The process of weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures (Anon 1997)

Susceptible humans
Those humans most likely to succumb to an infection caused by a relevant microorganism eg. food-borne salmonella infections may occur in the general human population but enterococcal infections are more likely to occur in hospitalised or immunocompromised human patients.

Zoonotic
Transferable from animals to humans. Relevant zoonotic microorganisms include *Salmonella enterica* serovars, and *Campylobacter* species particularly *C. jejuni* and *C. coli*. Microorganisms that are potentially zoonotic include *Escherichia coli*, and *Klebsiella* spp. *Enterococcus faecalis* and *Enterococcus faecium* of animal origin are generally considered commensal organisms that are host specific.

10D REFERENCES
Australian/ New Zealand Standard *Risk Management* AS/NZS 4360:1995 (Amendment 2, amended Jan 1998).

Anon. Codex Alimentarius Commission Procedural Manual (10th edition). Joint FAO / WHO Food Standards Programme, Rome 1997.

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.