

# ***ANIMAL REMEDIES BOARD***

---

*ASB Bank House, 101 - 103 The Terrace  
P O Box 2526, Wellington, New Zealand*

*Phone 64 4 460 8750  
Fax 64 4 460 8771*

In line with the Animal Remedies Board [Operational Policy - Antibiotic Resistance Review](#) and taking into account previous Board recommendations, products containing Zinc bacitracin and macrolide antibiotics for potential mass medication use have now been reviewed.

This categorisation and review process was endorsed at the 191<sup>st</sup> Meeting of the Animal Remedies Board, on the 14<sup>th</sup> June 2001.

As described in the above policy, the review has been forwarded to registrants for their comment.

## **BACKGROUND**

Antibiotic resistance reviews have been carried out in New Zealand and overseas. The reviews have all emphasised that, while the development of antibiotic resistance is possible (and even likely for particular antibiotics) there is very little factual evidence to:

- clarify the nature and extent of the problem; or
- establish the significance of the use of antibiotics in animals as a source of resistance in human pathogenic bacteria.

In light of the uncertainty surrounding the issue of antibiotic resistance, the Animal Remedies Board considers that the potential for resistance must become a hazard that is addressed when assessing applications for new licence for antibiotic trade name products. The Animal Remedies Board has also directed that the licences of all existing antibiotic trade name products be reviewed with regard to the potential to cause antibiotic resistance.

The term antibiotic is used comprehensively to include other antimicrobial substances, but does not include disinfectants, sanitisers or sterilisers.

### **Purpose of the review**

The purpose of this review is to ensure that antibiotic trade name products are adequately regulated in regard to the development of antibiotic resistance in either:

- pathogenic bacteria; or
- bacteria potentially capable of transferring resistance genes to pathogenic bacteria.

### **Expected outcome**

It is expected that the licences of all antibiotic trade name products will be adjusted to:

- encourage their prudent use; and the prudent use of those antibiotics
- facilitate the collection of information that could clarify the resistance situation.

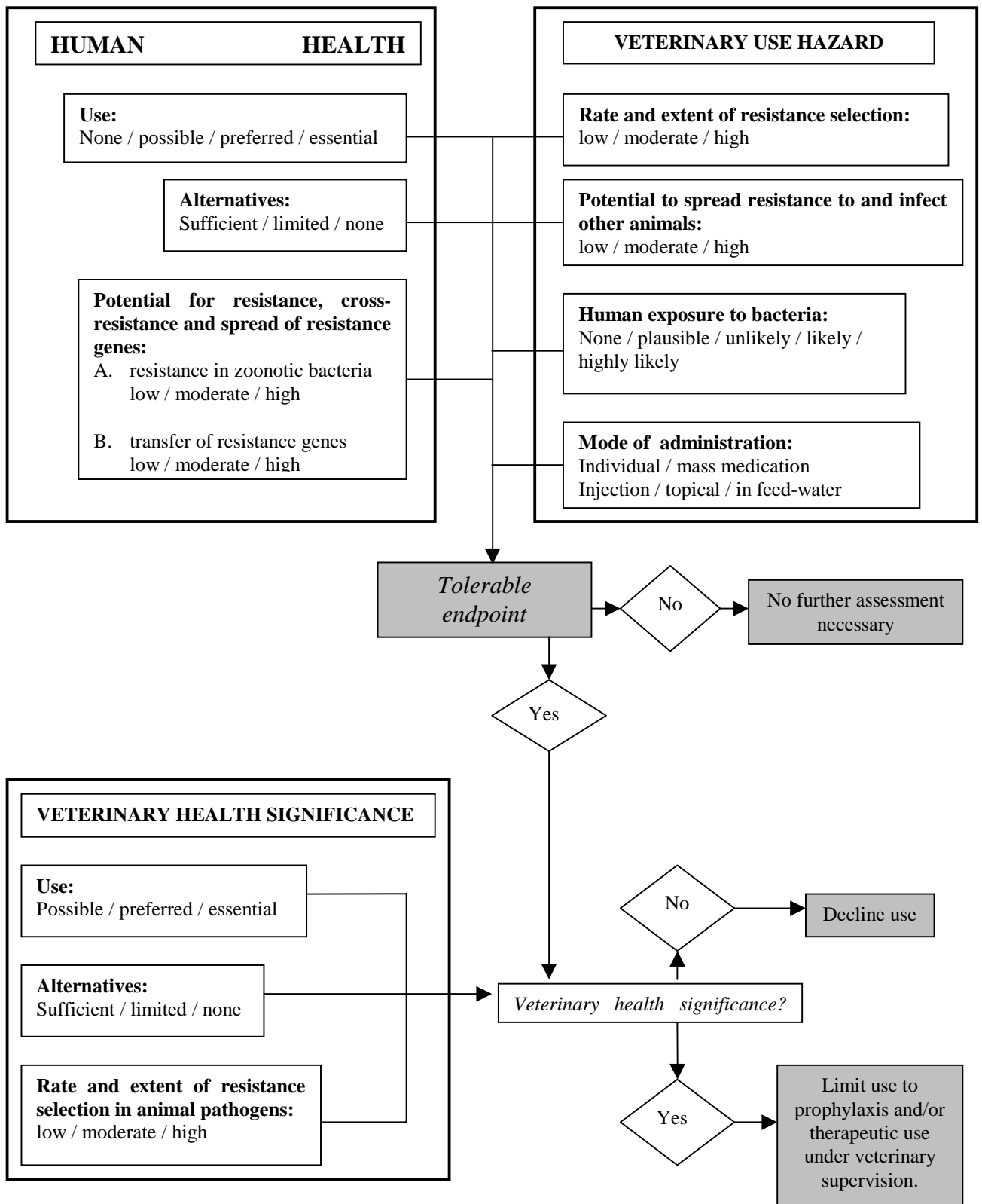
This will mean that some licences will be withdrawn entirely or for specific uses. However, in many cases, it is more likely that either:

- no change in a licence is necessary because the controls on the trade name product are already adequate; or
- a few additional controls will be imposed to achieve the expected outcome.

### **Review rationale**

As stated above, there is only limited information available to address the uncertainty as to whether or not the use of antibiotics in animals is contributing significantly to the development of antibiotic resistance in humans. Therefore, until the essential information is available, the rationale for assessing trade name products must be based on qualitative information, experience and an agreed categorisation of the relative importance of an antibiotic in controlling human and animal infections. The rationale to be used for the categorisation is shown in the following figure:

# ANTIBIOTIC RESISTANCE REVIEW RATIONALE



## Human Health Significance

The Animal Remedies Board and the Agricultural Compounds and Veterinary Medicines Group felt that specific expertise was required, to judge the human health significance of an antibiotic. Therefore, the judgement of the Ministry of Health is used to estimate the significance of an antibiotic in regard to:

- use or expected use in human medicine;
- whether or not alternative antibiotics are readily available and effective; and
- the potential for resistance to develop.

The last criterion is the most complex and subject to considerable uncertainty, particularly in regard to the potential for resistance or cross-resistance to develop in bacteria that might transfer genetic material. There is much more information available about zoonotic pathogenic bacteria such as *Salmonella* and *Campylobacter* species, so they are considered separately.

Since the uncertainty is relatively high in regard to the potential for resistance to develop, the Animal Remedies Board's policy to act in a prudent manner would prompt regulatory control to protect any antibiotic that is essential (or even preferred) to manage human health problems.

## Veterinary Use Hazard

The next consideration is the opportunity for the use of antibiotics in animals to prompt the development of antibiotic resistance in human pathogens. This would require:

- a significant level of use of the antibiotic in animals in a manner that would prompt resistance to develop in animal bacteria and for the resistant bacteria to spread; and
- circumstances in which people would be exposed to the resistant bacteria.

## Veterinary Health Significance

The relative significance of an antibiotic in the management of infections in animals helps determine what controls would be necessary and sufficient to protect the use of the antibiotic in humans and, at the same time, allow uses in animals that are essential for their health and welfare.

While emphasis has been placed on the consequential development of antibiotic resistance in human pathogens, the potential for resistance to develop in animal pathogens is also noted.

The following is the antibiotic resistance tolerable endpoint that would prompt regulatory action in regard to the licensing of antibiotic products:

- use of the antibiotic or a related antibiotic in human medicine is at least preferred; and
- there are limited alternative antibiotics for use in human medicine (possibly for a particular purpose); and
- there is at least a plausible mechanism for direct resistance to the antibiotic to develop and the exposure of humans to the resistant bacteria is at least likely; or
- there is at least a plausible mechanism for genomic transfer of resistance to the antibiotic to occur and the exposure of humans to the resistant bacteria is at least likely; and
- the mode of administration of the antibiotic to animals is such that it would increase the probability of resistance developing in a critical mass of the animal population (i.e. mass medication in feed or water exposing whole flocks/herds to the antibiotic); or
- unique circumstances would make exposure of individual people to resistant pathogens likely.

## **Presentation of the conclusions of the review for specific antibiotics**

This document describes the categorisation of the two antimicrobial groups reviewed, namely the macrolides, and the polypeptides in the form of Zinc Bacitracin. The Ministry of Health has provided input concerning the human health significance of these substances, and the Animal Remedies Board has addressed the veterinary use hazards and the veterinary health significance, thereby providing the qualitative information needed to apply the review rationale.

A summary statement is made about each antibiotic in regard to each of the factors in the rationale. The factors have been provided in tabular form as well. The human health significance is a general estimation independent of medicine type or route of administration. The veterinary use hazard and veterinary health significance are estimated relative to the type and use of the product because the risks are significantly different from one type/use to another.

**The summary is followed by a statement of the regulatory action to be taken in regard to the licences of trade name products containing the antibiotic.**

## **Presentation of the conclusions of the review for Zinc Bacitracin**

### **Zinc Bacitracin and the Polypeptides**

The polypeptide group of anti-bacterial agents used in animal health is limited to use of zinc bacitracin. The substance is registered and used as a growth promoter as well as for the treatment and prevention of necrotic enteritis in pigs and poultry. In companion animals, polypeptide anti-bacterial products including polymyxin, and gramicidin are used in the eyes and ears of animals. Similar products are also marketed for human use. These products are available under veterinary prescription.

### **Human Health significance and use**

There are no human products currently available in New Zealand that contains zinc bacitracin. A few agents have been registered for topical use in the past; however, newer agents have superseded them. The polypeptide group of anti-bacterials include: bacitracin, gramicidin, polymyxin and colistin. Due to their parenteral toxicity these agents are largely only available in combination with other agents for local treatment of infections in the ears, nose or eyes caused by a range of bacteria (and fungi). All of these agents are classified as human prescription medicines. Colistin is available as an intravenous treatment for gram-negative infections caused by species other than *Proteus* and *Neisseria*. Parenteral use of colistin is limited to specialists treating patients with either renal disease or cystic fibrosis.

### **Alternatives**

Colistin has activity against *Pseudomonas* spp and though its toxicity limits its usefulness, the emergence of multi-resistant pseudomonas infections may lead to clinicians having to use this product again. Colistin should therefore be considered as an essential antibiotic for human health. In addition, bacitracin has activity against *S. aureus*, and its use to reduce carriage of MRSA, (along with mupirocin, has been advocated by some authors. The absence of bacitracin from the New Zealand market may increase the potential value of this product against MRSA.

### **Potential for resistance, cross resistance and spread of resistance genes**

Very little data is available for bacitracin with respect to the risk of either developing resistant pathogens or transfer of resistance from species to species. Resistance to bacitracin in soil and animal bacteria has been documented but appears stable. Due to its narrow spectrum bacitracin has no activity against enterococci and so resistance against this index species for transmission of resistance is not an issue.

The possibility of resistance to bacitracin conferring cross-resistance to vancomycin is raised in a small number of documents, but no clear data appears available as to whether this cross-resistance actually occurs.

### **Veterinary use hazard**

Zinc bacitracin is used for growth promotion purposes and is administered by mass medication. In addition it is available without prescription over-the-counter. The potential for resistance development is likely therefore to be greater than for use in individual animals.

Before bacitracin was replaced by safer drugs for systemic use in humans, no significant resistance occurred.

### **Veterinary health significance**

Zinc Bacitracin has become increasingly important in poultry production, mainly as a result of the antimicrobial resistance review, and the response of industry to move away from antimicrobials that

are very important to human health. As a result, removal would leave the poultry industry in particular, with an inability to control clostridial diseases especially necrotic enteritis. This could result in disease outbreaks with a resultant increase in antibiotic use to bring such outbreaks under control. In addition the well- regulated and relatively disease-free New Zealand poultry flock could be severely harmed. To maintain supplies of chicken meat if decreased due to disease outbreaks, chicken meat might then be imported from countries that are further behind New Zealand in their antimicrobial resistance review. This could result in more product being consumed which has been treated with various antimicrobials, over which we have no control. This paradoxical potential would benefit neither human health or agriculture of New Zealand.

### Zinc Bacitracin

<b>HUMAN HEALTH SIGNIFICANCE</b>	
<b>Influencing factor</b>	<b>Estimation</b>
Use	Possible
Alternatives	Sufficient
Potential to spread resistant organisms	Low - Moderate
Potential for cross-resistance:	
Resistance in zoonotic bacteria	low
Transfer of resistance genes	low
<b>VETERINARY USE HAZARD</b>	
	<b>Oral in feed/water</b>
Rate and extent of resistance selection	Low-moderate
Potential to spread resistance to and infect other animals	Low - Moderate
Human exposure to bacteria	Low - Moderate
Mode of administration	Mass medication
<b>Tolerable endpoint</b>	<b>exceeded</b>
<b>VETERINARY HEALTH SIGNIFICANCE</b>	
Use	essential
Alternatives	limited
Rate and extent of resistance selection in animal pathogens	low
Veterinary Health Significant	Yes (therapeutic and prophylactic use)

### Conclusion

The Ministry of Health concludes that:

- Zinc bacitracin and the other polypeptide anti-bacterials should be considered important human medicines for the treatment of resistant bacteria; and
- Use of the polypeptide group should be limited to treatment of diseases in individual animals under the supervision of a veterinarian i.e. prescription animal remedies.

Currently Zinc bacitracin is used for growth promotion purposes and is available over the counter. Clearly in the light of the categorisation process, it appears that that Zinc bacitracin use is essential for animal health and welfare. It appears that the most logical categorisation is restriction of use under veterinary prescription.

As the product has become so important to the poultry industry, and taking into account the potential for unintended consequences should it be removed, it appears that the product should be used for prophylactic and therapeutic use only.

In addition, the potential remains that mass medication formulations will become future technical barriers to trade. These types of issues further underscore the improved and prudent use of antimicrobials.

### **Regulatory action**

**All claims and use for growth promotion of Zinc bacitracin will be revoked. All use should be under veterinary prescription, and should be limited to prophylactic and therapeutic use under the veterinary code of practice.**

## Presentation of the conclusions of the review for the macrolides

<i>Human Health Significance</i>				
<b>Influencing factor</b>	<b>Estimation</b>			
Use	Essential			
Alternatives	Limited-none			
Potential to spread resistant organisms	Moderate			
Potential for cross- resistance:				
Resistance in zoonotic bacteria	Moderate - high			
Transfer of resistance genes	Low- Moderate			
<i>Veterinary Use Hazard</i>				
	<b>Oral in feed/water</b>	<b>Injectable</b>	<b>Tablet</b>	<b>Topical</b>
Rate and extent of resistance selection	Moderate - high	Moderate - high	Moderate - high	Moderate - high
Potential to spread resistance to and infect other animals	Moderate - high	Low-moderate	Low-moderate	Moderate - high
Human exposure to bacteria	Likely	Unlikely	Unlikely	Unlikely
Mode of administration	Mass medication	Individual	Individual	Individual
<b>Tolerable endpoint</b>	<b>Exceeded</b>	<b>Exceeded</b>	<b>Exceeded</b>	<b>Exceeded</b>
<i>Veterinary Health Significance</i>				
Use	Probable	Probable	Possible	Probable
Alternatives	Limited	Limited	Limited	Sufficient
Rate and extent of resistance selection in animal pathogens	Moderate	Moderate	Moderate	Moderate
Veterinary Health Significant	Yes	Yes	Yes	Yes

### Human Health Significance and Use

A wide range of macrolide antibiotics are available for human use in oral, parenteral and topical dose forms. The macrolides available for human use includes erythromycin, roxithromycin, azithromycin, and clarithromycin. All macrolide products are classified as prescription medicines.

As intermediate spectrum antibiotics, macrolides are active against mainly gram-positive organisms, however, macrolides also express activity against a number of atypical bacteria. The macrolide group of antibiotics are used to treat a range of infections including common respiratory infections, atypical infections in immunocompromised hosts, and use in multi-resistant sexually transmissible infections.

Macrolides are the treatments of first choice in the management of atypical respiratory infections such as infections with *Mycoplasma*, and *Chlamydia*, and a number of zoonotic infections (such as *Rickettsia*).

Azithromycin is the current treatment of choice of resistant gonorrhoea and chlamydial infections and its use is limited to specialists only. Clarithromycin and azithromycin are also first line treatment for life threatening infections such as atypical *Mycobacterium avium* complex infections in immunocompromised hosts, such as patients with HIV.

## **Alternatives**

While a number of alternative agents are available for the treatment of simple gram-positive infections are available, increasing levels of resistance to commonly used antibiotics, such as penicillin, increase the use of the macrolides to treat community acquired pneumonia. For atypical infections, and some resistant bacteria, the macrolide group are essential treatments and access to these agents is currently limited to specialist prescribers.

## **Potential for resistance, cross resistance and spread of resistance genes**

The JETACAR, and other, international reports have documented resistance to macrolides developing in pathogens and commensal organisms in both animals and humans. Enterococci resistance to macrolides is well documented in animal species, as is evidence of spread of resistance from animals to humans and horizontal transfer of resistance into human pathogens. Increasing rates of resistance to macrolides is of particular concern as cross-resistance to both the lincosamide and streptogramin B antibiotics is associated with macrolide resistance. As indicated in earlier reports the Lincosamides and Streptogramins are essential antibiotics for human health and are used almost exclusively for treatment of infections in humans caused by multi-resistant bacteria.

## **Veterinary use hazard**

Macrolides, specifically in the form of tylosin are used to a considerable extent by the intensive farming industries. Formulations of tylosin registered in New Zealand make many and varied claims, from growth promotion, to therapeutic, often in various combinations. In addition, some of the products are available over-the-counter. Tylosin is used in mass medication form, so the exposure potential is considerable.

It is clear then that the concerns surrounding the use of tylosin are not being currently addressed, but that the product remains an important part of the veterinarians' therapeutic armoury.

The mode of administration is also a significant factor. Parenteral (i.e. injectable) administration to individual animals is not likely to result in the spread of resistant bacteria, while oral mass administration to groups of food producing is likely to pose a significant threat of spread. The oral administration of tablets to individual animals to treat systemic infections is not likely to pose a significant threat. Topical administration to ears and eyes is also not likely to pose a significant hazard. Macrolides used in companion animals, e.g. cats and dogs are used under veterinary prescription.

## **Veterinary health significance**

Tylosin remains very important to the intensive farming industries, and the removal thereof could result in an increased potential for disease outbreaks, with a resultant increase in antibiotic use to bring such outbreaks under control. In addition, disease outbreaks could impact negatively on two major risk areas that the ACVMG is required to control, namely animal welfare and agricultural security.

## **Conclusion**

The Ministry of Health considers the development of antibiotic resistance as a major public health

problem and recommends that:

- The macrolide group of antibiotics should be considered to be “essential antibiotics”;
- Use of macrolides is limited to treatment of diseases in individual animals under the supervision of a veterinarian i.e. prescription animal remedies;

In order to best address the overall risks, it is felt that the additional concerns of animal welfare and agricultural security should be factored into the decision, and that the realities of farming should allow for individual groups of animals to be treated.

### **Regulatory action**

**All claims and use for growth promotion of macrolides will be revoked. All use should be under veterinary prescription, and should be limited to prophylactic and therapeutic use under the veterinary code of practice.**

# ACVM GROUP OPERATIONAL POLICY

## ANTIBIOTIC RESISTANCE REVIEW

### 1 BACKGROUND

The purpose of this policy is to clarify the process of review of antibiotics in relation to antibiotic resistance, particularly in in-feed antibiotics used on animals in New Zealand.

In-feed antibiotics have been subjected to stringent review by the lay and scientific communities nationally and internationally. The issue of antibiotic use in general, in both humans and animals, is an area of increasing public concern, and is being addressed by both the agricultural and human health sectors.

The Animal Remedies Board has set out policies to be followed in this review (see references). The review process is based on these.

### 2 POLICY

- 2.1 The review should involve co-operation between the Animal Remedies Board, the Ministry of Health, licensees of affected products, industry and agriculture, and should be conducted in a transparent, scientific and consistent manner.
- 2.2 The review should proceed as expeditiously as practicable in order to address public concerns in a timely manner while still maintaining the animal health status of New Zealand.
- 2.3 The review should take account of lessons learned from similar reviews in countries where this process has been undertaken, particularly in relation to the potential negative consequences of withdrawal of antibiotics, e.g.
  - the potential for outbreaks of disease in animals and the consequential increase in use of therapeutic antibiotics to bring these under control;
  - potential local production losses that could result in increased importation of products from countries that are slower in addressing the use of antibiotic growth promotants in animal feed and the consequential risk of importing resistant pathogens not established in New Zealand, e.g. *Salmonella typhimurium* DT 104.
- 2.4 The process of review will comprise three major activities, namely:
  - categorisation (see [Figure 1](#));
  - trade name product review;
  - ongoing management.

## 2.5 Categorisation

- 2.5.1 The process of categorisation should be undertaken separately from the process of licence review of specific trade name products. Where possible and appropriate, categorisation should be undertaken for antibiotics by class.
- 2.5.2 Categorisation for each class will be in terms of:
- human health significance;
  - veterinary use pattern (and exposure); and
  - veterinary health significance;
- of the antibiotic class under review. This will be based on the process outlined in [Figure 1](#).
- 2.5.3 Parties to categorisation will be:
- the Animal Remedies Board;
  - the Ministry of Health – regarding the issue of human health significance; and
  - licence-holders of the products under review.
- 2.5.4 Categorisation will initially be undertaken by the Animal Remedies Board and the Ministry of Health, who will provide inputs on issues of human health significance. The result will be given to the licence-holder for review.
- 2.5.5 After discussion of the categorisation with the licence-holder, the review of trade name products will continue.
- 2.5.6 It is recognised that the process of categorisation may, at times, be dependent upon interpretation as the process cannot always be reduced to simple ‘yes’ or ‘no’ answers. However, the process will be scientifically rigorous and evidence-based.
- 2.5.7 The process shown in [Figure 1](#) shows that a ‘tolerable endpoint’ is the threshold for making a decision for categorisation.

Antibiotic resistance tolerable endpoints that are likely to prompt regulatory action in regard to the licensing of antibiotic products may include the following:

- the degree of importance of the use of the antibiotic or a related antibiotic in human medicine;
  - the existence of limited alternatives for use in human medicine;
  - the plausible and likely development of resistance in zoonotic bacteria or the transfer of resistance genes, or the exposure of humans to the resistant bacteria;
  - the mode of administration of the antibiotic to animals is such that it would increase the probability of resistance developing in large numbers of animals (i.e. mass medication in feed or water exposing whole flocks/herds to the antibiotic), or unusually high risk of personal exposure.
- 2.5.8 There are likely to be three major outcomes from categorisation:
- no further assessment of the antibiotic or class of antibiotics required;
  - decline use of the antibiotic or class of antibiotics;
  - limited use of the antibiotic or class of antibiotics subject to conditions, such as prophylaxis and/or therapeutic use.

The first and second outcomes will result in straightforward treatment of the products involved. The third outcome will lead the products into the trade name product review.

## **2.6 Trade name product review**

- 2.6.1 Where categorisation has resulted in an outcome of ‘limited use subject to conditions’, the licence-holder should make an application to vary the licence held for the affected product according to the limited use allowed. This application will be processed in the same manner as other applications to vary licences. Conditions will be applied according to the hazards associated with the use of the product.
- 2.6.2 Data will be required to support amended claims. Data requirements will be the same as those currently required for licence variations. Data supplied will ideally be original trial data; however, appropriate peer-reviewed literature will be acceptable. Duplication of data already available should be avoided in order to minimise the use of animals where possible.
- 2.6.3 The review will be progressed in a group-wise fashion, according to antibiotic class where appropriate.
- 2.6.4 Once the review of an antibiotic class is complete, a cut-off date for implementation of amended claims and conditions will be scheduled. Amended licences will be issued on that date for those products for which variations have been approved. Licences for products for which variations have not been approved will be suspended as at the cut-off date.

## **2.7 Ongoing management**

### **2.7.1 Surveillance**

A national surveillance system is currently being set up in conjunction with the Ministry of Health in parallel with the regulatory review of antibiotics. The system will be harmonised with international surveillance systems, which are also currently being developed. It is envisaged that one of the requirements for registration for certain of the antibiotics will be participation in this surveillance system once it is implemented. It is likely that the surveillance system will initially be involved with pathogens resulting in foodborne disease.

### **2.7.2 Consultation**

The framework for review is being developed in consultation between the Animal Remedies Board, the Ministry of Health, and the licence-holders. Once consultation is complete, the public will be kept informed, mainly via the ACVM Group website (<http://www.maf.govt.nz/ACVM/>).

### **2.7.3 Liaison with affected groups**

In parallel with wider consultation, liaison with representatives of the intensive farming industries will occur to encourage the adoption of prudent use guidelines to best manage the withdrawal of antibiotics should this result from the review process, and to minimise

any negative consequences such withdrawal might have on animal welfare and disease status of their farming operations. The industry will be consulted in order to monitor the progress and impact of any changing antibiotic use patterns.

The following issues will be addressed:

- animal welfare;
- animal disease;
- economic strategies and management methods;
- trade issues;
- compliance and phasing out.

### **3 REFERENCES**

This document should be read in conjunction with:

- *Review of Animal Health Antibiotic Products and their Potential for Contributing to the Development of Antibiotic Resistant Strains of Human Bacterial Pathogens.*
- Animal Remedies Board policy decisions on antibiotic resistance – 20 October 1999  
(Both available on <http://www.maf.govt.nz/ACVM/>)

Figure 1

# ANTIBIOTIC RESISTANCE REVIEW RATIONALE

