

**REVIEW OF ANIMAL HEALTH ANTIBIOTIC  
PRODUCTS AND THEIR POTENTIAL FOR  
CONTRIBUTING TO THE DEVELOPMENT OF  
ANTIBIOTIC RESISTANT STRAINS OF HUMAN  
BACTERIAL PATHOGENS**

**INFORMATION PAPER**

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# **REVIEW OF ANIMAL HEALTH ANTIBIOTIC PRODUCTS AND THEIR POTENTIAL FOR CONTRIBUTING TO THE DEVELOPMENT OF ANTIBIOTIC RESISTANT STRAINS OF HUMAN BACTERIAL PATHOGENS**

## **1 INTRODUCTION**

### **1.1 Purpose of the review**

The purpose of the review of animal health antibiotics is to amend the licences of animal health antibiotic products to:

1. ensure that their use, particularly in food-producing livestock, will not prompt resistance in bacteria that cause diseases in humans, reducing the effectiveness of these antibiotics when used to treat disease;
2. retard the development of antibiotic resistance in bacteria that cause diseases in animals; and
3. foster the prudent use of the full range of animal health antibiotic products.

Changes in licences will manage the hazards and exposure to hazards more effectively and the additional requirements to collect data will pinpoint the nature and significance of those hazards.

### **1.2 Scope**

Apart from the hazards of antibiotic resistance, there are other hazards to the health and welfare of the treated animals, to the health of people using the products and to primary produce trade, that would be affected by any changes to the regulation of animal health antibiotic products. This review focuses specifically on the potential hazards that may contribute to resistance in bacteria that cause diseases in humans and animals.

There are many products that are designed to inhibit micro-organisms. They include disinfectants, antiseptics, anti-fungal agents, anti-viral agents and antibiotics. It is not necessary to review the full range of antimicrobial products at this time. Therefore, the present review is limited to antibiotics (see definitions in section 6 of this paper). There are some antimicrobial agents that are not strictly antibiotics according to the definition, but they are used like antibiotics to control bacterial infections. These agents will be included in the review for completeness and in the medium to long term the resistance assessment rationale will be applied to all antimicrobial agents.

## **2 BACKGROUND**

### **2.1 Situation report**

#### **2.1.1 International concern**

Throughout the developed world there is public and governmental concern about the increasing prevalence of antibiotic resistance in bacteria that cause diseases in humans. There is a worry that many antibiotics currently available to treat human diseases will no longer be effective. This ineffectiveness is expected to lead to difficulties in treating some human infections as well as increasing health costs. There is a parallel concern that the development of resistance among bacteria is being outstripped by the ability of the pharmaceutical industry to develop new antibacterial agents.

The problem of the development of antibiotic resistance in bacteria has been the subject of specially commissioned reports under the auspices of a variety of government and international bodies. Much of the focus of these reports has been upon the use of antibiotics in animals and, in particular, their use as feed additives for the purpose of growth promotion.

The European Commission, on 14 December 1998, voted to ban the use of four antibiotics as growth promotants. These four antibiotics were zinc bacitracin, spiramycin, virginiamycin and tylosin phosphate. The ban was to be reviewed before 30 December 2000. Europe also instigated a surveillance programme to determine the extent and nature of the perceived antibiotic resistance problem as it relates to antibiotic use in animals.

It appears that the main thrust of concern in Europe has come from Scandinavia. Sweden and Finland have had a national prohibition on the use of antibiotics for growth promotion for some years. Both countries, with the support of Denmark and Germany, have been the main sponsors of the extension of the ban throughout the European Union.

The EU had previously (from December 1998) confirmed its ban on the use of avoparcin as an antibiotic growth promotant.

The issue has received considerable attention in the United States as well. The US has established a surveillance system to define the problem and provide technical evidence if possible. The US has also developed a model for addressing the resistance problem and has reviewed licensing of antibiotics used in animals. Australia has followed the same pattern.

The impact of antibiotic-resistant bacteria or resistance genes found in animal isolates on the increasing antibiotic resistance of human pathogenic bacteria have been reviewed and reported on in a number of countries. Some of the reports are listed in the references in section 7 of this paper. Two notable reports were the Australian Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR, 1999), the United Kingdom Ministry of Agriculture, Food and Fisheries (MAFF, 1998) and the Swedish Commission on Antimicrobial Feed Additives (CAFA, 1997). All these reviews showed that there is evidence for direct spread of resistant bacteria from animals to humans and also the possibility, under certain circumstances, for transfer of antibiotic-resistance genes from animal bacteria to human pathogenic bacteria.

Existing antibiotic resistance surveillance programmes in most countries are not able to provide comprehensive data on antibiotic usage and the prevalence of antibiotic resistance among human and veterinary bacteria isolates. Nevertheless, what data is available indicate that the total use of antibiotics is a contributing factor in the development of antibiotic

resistance. It is known that the use of antibiotics in humans is a significant cause of antibiotic resistance in humans. What is not known is whether or not the use of antibiotics in feed animals is a significant factor.

The European Union has found that precipitous action to prohibit the use of certain antibiotics in livestock feed has resulted in serious negative animal health consequences that required immediate action to rectify. This experience has highlighted the need to ensure that any action taken protects both human and animal health.

### **2.1.2 Use of antibiotics in food producing animals in New Zealand**

New Zealand has not imposed general bans on the use of antibiotics. Of the antibiotics that have been banned in Europe, only zinc bacitracin, virginiamycin, and tylosin are licenced in New Zealand with claims for growth promotion. Spiramycin is only licenced for therapeutic use in dogs and cats. Avoparcin is presently registered in New Zealand but the licensee has advised that the antibiotic will be removed from the market.

According to the expert panel report (see 2.1.4) commissioned by the Animal Remedies Board, a total of 92.9 tonnes of antibiotics are used each year in New Zealand. Use in animals accounts for about 57%. The remaining 43% is used in human medicine. Ionophores make up 34% of the antibiotic used in animals. If ionophore volumes are excluded from the total, then animal use accounts for 47% of the remaining total 74.9 tonnes of antibiotics used in New Zealand (Expert Panel Review, 1999, pp14-15).

Ionophores have quite a distinct mode of action from other antibiotics and are not used in human medicine at all. Consequently, this family of antibiotics are unlikely to cause antibiotic resistance (see review rationale). The other antibiotic in common use in New Zealand is bacitracin, which is not significant for oral or parenteral use in human health and should not contribute to the antibiotic resistance problem.

Some antibiotic products used in animals in New Zealand are licensed for use as growth promotants. Because of the low stocking density, pastoral farming system used in this country, the use of antibiotics is low. The only industries that use significant volumes of antibiotics are the pig and poultry industries. Diseases can spread more quickly on pig and poultry farms because of the close contact between animals in intensive farming operations. In addition, while ionophores and bacitracin are licensed in New Zealand for growth promotion, both the pork and poultry industries have shown that the products are actually used for disease prevention purposes.

### **2.1.3 Antimicrobial Resistance Surveillance**

New Zealand's surveillance systems like those in the other countries mentioned were not designed to provide the appropriate information to establish whether the use of antibiotics in animals is having any effect on the development of antibiotic resistance. The Ministry of Health has monitored the prevalence of antibiotic resistance among important human pathogens since 1972. Among human pathogens, there has been an increase in the prevalence of methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and antibiotic-resistant gram-negative bacilli. There has also been a small increase in the number of vancomycin-resistant enterococci (VRE) confirmed in New Zealand. To date, nine VRE have been confirmed. The first VRE was isolated in 1996, the second in 1998 and, in the period 1999 till January 2000, seven VRE were confirmed. There is no evidence that use

of antibiotics in animals (either in feed or parenteral) has prompted the resistance in these cases.

The only zoonotic bacteria that has been monitored through this surveillance programme has been *Salmonella* spp. Between 1972 and 1982, every salmonella isolate that was received at ESR was tested for susceptibilities. From 1982, five yearly surveys of the antibiotic susceptibilities of salmonella from human and non-human sources were carried out. The data from this surveillance has shown a low level of antibiotic resistance among salmonella from human and non-human sources. Multiresistant *Salmonella Typhimurium* DT104 has been isolated, albeit infrequently, in New Zealand.

#### **2.1.4 Animal Remedies Board action**

##### *Expert Panel Report*

There are international concerns about the possible association of antibiotics used in animals (in particular the use of antibiotics as growth promotants in animals) and human antibiotic resistance problems. The Animal Remedies Board commissioned an expert panel report to review not only the international situation but also the implications for New Zealand.

After its review of the literature, the panel considered that the information that was available was not sufficiently comprehensive and robust to carry out a meaningful quantitative risk analysis for any of the antibiotics being used for growth promotion in New Zealand. Therefore, the panel decided that the available information on each antibiotic (or group such as the macrolide antibiotics) should be assessed in light of a consistent rationale. The panel's rationale was used as the basis for the one to be used in a review of all antibiotic products used in animals. The rationale is based on the principles that:

- important human uses of antibiotics must be protected; and
- animal health care uses that are not relevant to the antibiotic resistance problem should not be hindered.

The highest priority recommendation of the expert panel was to implement a surveillance programme that would provide more useful information.

The Board accepted in principle all the recommendations of the expert panel with the qualification that, rather than taking immediate action and applying general bans, the rationale should be applied to each trade name product in turn, starting with those that contain the antibiotics of greatest human health significance. The Board considered a prudent response as appropriate to ensure public health was protected and, at the same time, animal welfare problems were not exacerbated unnecessarily. The Animal Remedies Board's decisions were as follows.

1. In recognition of the urgent need for inter-agency co-ordination of activities related to antibiotic resistance in animal and human health, the Board recommended the establishment of a joint ministerial committee to ensure co-operation, co-ordination and ongoing review of policies and criteria for regulatory control of in-feed antibiotics.
2. The Board supported the development of standards, guidelines and codes of practice for the use of agricultural antibiotics by veterinarians and industry, and will provide endorsement of codes considered appropriate to manage antibiotic resistance.

3. The Board considered that the following matters must be addressed in the licensing of new antibiotic products for growth promotion and re-assessment of existing products:
  - the implications for public health of the concurrent use of a functionally related product in human medicine in New Zealand or Australia;
  - the implications for public health of the subsequent introduction of a functionally related product in human medicine in New Zealand or Australia;
  - the implications for public health for products that produce resistance or cross-resistance to systemic antibiotics used in human medicine;
  - product use should be compatible with a zero withholding period;
  - the impact of the product on animal welfare;
  - the impact of the use of the product on the concurrent availability of the same or functionally related product as a therapeutic agent for animal disease;
  - the efficacy of the product; and
  - the impact of the product on international trade in primary produce.
  
4. In addition to the above, the Board considered that the following matters must be addressed in the licensing of new antibiotic products for prophylactic use and re-assessment of existing products:
  - the impact of the use of the drug in animals on the use of a functionally related product in human medicine for the treatment of serious disease in people for which there is no suitable alternative. Such drugs include: fluoroquinolones, glycopeptides, streptogramins and third generation cephalosporins;
  - efficacy of the drug and establishment of optimum dose and treatment duration; and
  - the impact of resistance selection on animal and human health.
  
5. Reassessment of existing growth promotant and prophylactic antibiotic products, requiring the above matters to be addressed for continued licensing, should occur as soon as possible, with priority given to re-assessment of avoparcin products.

Where licensing solely for growth promotion cannot be supported following re-assessment, consideration must be made of the use of that product for disease prevention and treatment purposes to ensure that a product essential for the health and welfare of the animals is not inadvertently and precipitously removed from the market.
  
6. The Board noted the existing oral fluoroquinolone therapeutic animal remedy for food-producing animals. The licence for the product has been suspended. It is not likely to be reactivated, although the licensee is being given the opportunity to justify continued use. Similar products in the future are unlikely to meet the criteria established by the Board for licensing.
  
7. The current moratorium on the licensing of any new antimicrobial growth promotants will continue until appropriate modification of Regulations (ie schedule 2 of the Animal Remedies Act 1967) are able to be made to allow appropriate conditions to be imposed on existing and new products. The moratorium will be reviewed at the next meeting of the decision making body acting on behalf of the Animal Remedies Board. The moratorium is likely to be lifted, because all new products can be assessed under the rationale described in this review (Animal Remedies Board Decisions, 1999).

At the Board meeting of 15 December 1999, policies were confirmed to progress the management of the antibiotic resistance issue. The two principle actions are to:

1. work with the Ministry of Health to establish the terms of reference for a joint antibiotic resistance management strategy, including a joint ministerial committee with an overview of the issue; and
2. progress a managed review of all existing veterinary antibiotic products.

Meetings are being held with the Ministry of Health to complete the first action, but an initial report will be prepared for the Ministers' consideration early in March. The review of antibiotic products has already begun and is described in section 3.

## **2.2 Factors in the review of antibiotic products**

To be comprehensive and appropriate the review of antibiotic products has to recognise that:

- there are different aspects to antibiotic resistance that must be considered separately;
- not all antibiotics are the same in the way they inhibit bacteria or their potential to lose effectiveness due to bacterial resistance;
- not all antibiotics are used for the same purposes;
- there may not be common opportunities for humans to be exposed to resistant bacteria; and
- not all antibiotics are equally important to human health.

### **2.2.1. Nature of antibiotic resistance**

#### ***Evolution of antibiotic resistance***

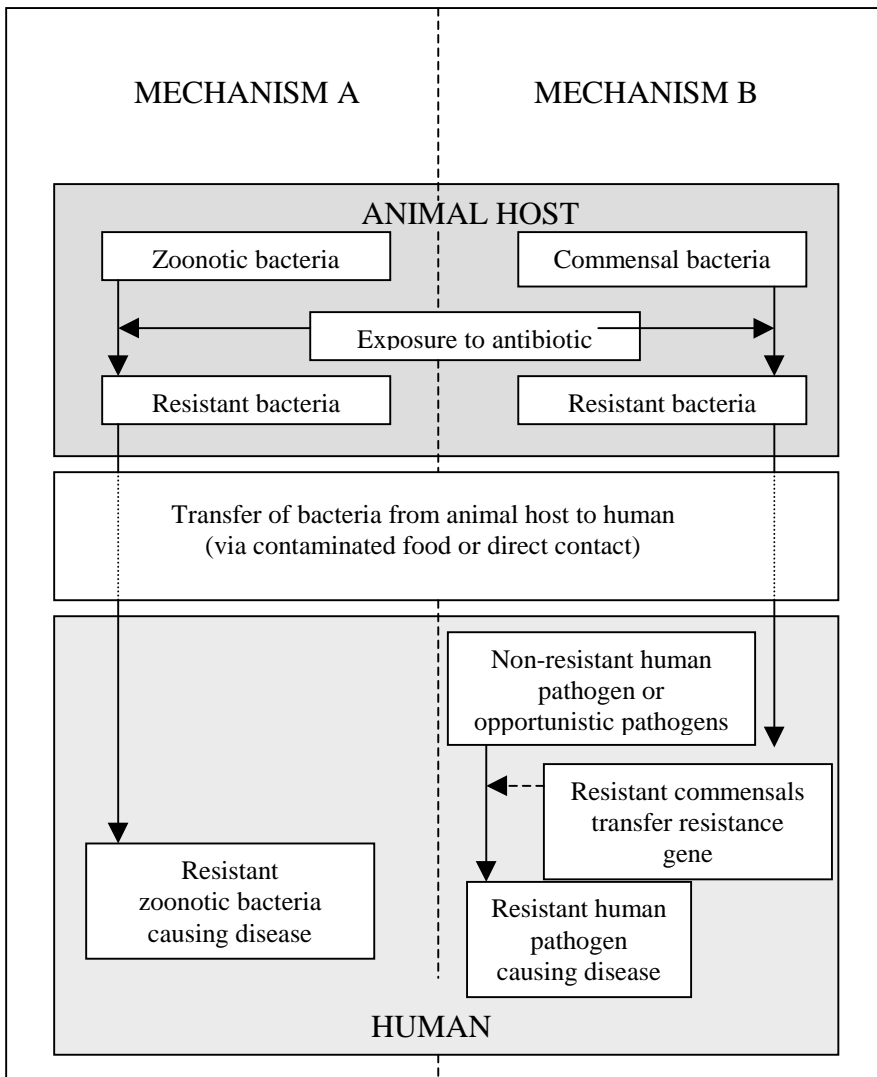
Antibiotic resistance arises as a result of genetic change, which can occur through mutation or by the acquisition of an antibiotic resistance gene. The antibiotic-resistant bacteria are subsequently able to grow in the presence of the antibiotic that is preventing the growth of non-resistant strains. The resistant strain replaces the non-resistant strain and the antibiotic loses its effectiveness.

#### ***Spread of antibiotic-resistant bacteria and genes***

Spread of antibiotic resistance can occur by two mechanisms:

- A. transfer of resistant disease-causing bacteria (pathogenic bacteria) from one host to another; and
- B. transfer of antibiotic resistant bacteria that do not cause disease (commensal bacteria) and subsequent transfer of resistance genes from the animal host commensal bacteria to pathogenic (to humans) bacteria or commensal bacteria that can become pathogenic under certain circumstances.

Resistant bacteria can be transferred from one person to another, from animals to people, or even from people to animals. However, this paper is concerned with the transfer of antibiotic resistant bacteria from animals to people. These bacteria are zoonotic, which means they are maintained in animals but can be transferred to humans and, subsequently, cause disease. The following figure shows the difference between mechanisms A and B.



### **Development of antibiotic resistance in zoonotic bacteria**

While resistance mechanism B can be involved, mechanism A is usually the cause of resistance in zoonotic bacteria. The bacteria are exposed to the antibiotic while they are in the animal. The bacteria are already resistant when they are transferred to people. The most common diseases involved are the food-borne gastro-intestinal diseases caused by *Salmonella* and *Champylobacter* but can involve other pathogenic bacteria. It is unknown how much the use of antibiotics in animals contributes to the development of antibiotic resistance in humans. However, the development of multi-resistant *Salmonella Typhimurium* DT104 suggests a link between antibiotics used in animals and resistance patterns emerging in zoonotic pathogens.

### **Transfer of resistance genes**

The development of resistance via mechanism B is more complicated. Commensal bacteria in animals exposed to an antibiotic can develop resistance to that antibiotic. The bacteria can be transferred to a person via either direct contact or contaminated food. The commensal bacteria do not cause disease in that person but, they may be able to transfer the antibiotic resistance gene to pathogenic bacteria that are already present in that person.

Resistance genes are often carried on genetic elements, which frequently carry more than one resistance gene. Genetic transfer of the genetic elements frequently results in the transfer of all the different resistance genes.

Mechanisms A and B are distinctly different. The significance of mechanism A is fairly well known as a result of existing surveillance programmes, but the significance of mechanism B is still uncertain.

Mechanism A is dependent on:

- the presence of the zoonotic bacteria in animals;
- exposure of the bacteria to the antibiotic and mutation to a resistant strain;
- exposure of people to the resistant strain; and
- susceptibility of people to the zoonotic bacteria.

Mechanism B is dependent on:

- the presence of commensal bacteria in animals;
- exposure of the bacteria to the antibiotic and mutation to a resistant strain;
- exposure of people to the resistant strain of commensal bacteria;
- the presence at the same time of a non-resistant strain of pathogenic bacteria in people;
- the opportunity and mechanism for transferring resistance genes from the commensal bacteria to the pathogenic bacteria; and
- susceptibility of people to the pathogenic bacteria.

### ***Cross-resistance***

Many antibiotic resistance genes confer resistance to many or all members of an antibiotic group (e.g. the *erm* genes confer resistance to macrolides, lincosamides and streptogramins B).

## **2.2.2 Antibiotic product differences**

### ***Differences in antibiotics***

There are a number of different antibiotic families. Different antibiotics and antibiotic families have been developed to provide effective alternatives to treat different kinds of bacteria. The antibiotic families differ chemically and in the way they inhibit bacteria. Different species of bacteria respond differently to different types of antibiotics. Not all bacteria develop the same level and type of resistance to all the antibiotic families. Some oral antibiotics stay in the digestive tract and inhibit only gut bacteria, while others are absorbed and act on bacteria in other parts of the body. Some antibiotics are sufficiently similar to other types of antibiotics that resistance to one may result in resistance to others. Consequently, general statements and, in particular, precipitous and non-specific bans on antibiotic use, are seldom appropriate and often result in serious negative animal health consequences.

### ***Differences in uses***

Some antibiotics are used in human and animal health, while others are used only in animal health. Particular antibiotic families are the preferred choice for treating specific bacterial infections in humans. The relative importance of a particular antibiotic in human medicines is a primary consideration in this review. The development of resistance to an antibiotic that has no use in human medicines (and does not contribute to cross-resistance to any antibiotic that does have a use in human medicines) is not significant. Conversely, the development of resistance to an antibiotic that is essential in human medicines requires immediate and effective regulatory action to protect that use. However, since circumstances can change, it is essential to be prepared to reassess the relative significance of an antibiotic.

Antibiotics are also used for different purposes in animals and humans. In humans they are most often used therapeutically to treat clinical cases of bacterial infection. They may also be used prophylactically where apparently healthy people have been exposed (or are likely to be exposed) to diseases such as bacterial meningitis. Human antibiotic products, with the exception of a few skin preparations, can be obtained only under the prescription of a medical practitioner.

In animals, antibiotics are primarily used therapeutically to treat clinical cases of bacterial infection. They are usually given by injection to individual animals rather than mass medication. Protecting the effectiveness of antibiotics for use as therapeutic agents for both human and animal use is the primary driver for minimising antibiotic resistance.

Antibiotics may also be used in animals prophylactically (ie to prevent disease). For this purpose they are usually given orally in feed or water to livestock and usually on a flock/herd basis. Some diseases (such as necrotic enteritis or coccidiosis in chickens) are so common that the antibiotic is included in the feed for the whole production period. Other diseases occur at a particular stage of production, such as at weaning in pigs. For these diseases the antibiotic is added to the feed just before or at the time when the disease challenge is most likely to occur. However, in all cases, administration is closely tied to a diagnosis or clinical history of the disease and use is limited to what is necessary and sufficient to prevent the disease.

The effectiveness of antibiotics used either therapeutically or prophylactically is measured on the farm by the elimination or absence of clinical signs of the particular disease. In the laboratory, effectiveness is measured by testing the minimum inhibitory concentration (MIC),

which is the smallest amount of the antibiotic that inhibits the disease-causing bacteria. The antibiotic is always used at dosages that exceed the MIC to ensure maximum biocidal effect.

Antibiotics may also be administered to animals for a growth promotant purpose (ie increased production). They are always given orally (mixed into feed or water). While they modify the mix of bacteria in the digestive tract, their effectiveness is measured in production gains (increase weight, growth, milk or egg production, etc) rather than by the effect on the bacteria. Since biocidal effect is not the specific outcome, dosages may be less than is required to maintain the MIC for that antibiotic. This may mean that disease-causing bacteria are exposed to growth promotant antibiotics for long periods of time at concentrations too low to inhibit them but at sufficiently high concentrations to prompt the selection of strains of bacteria that are progressively more resistant to the bacteria. It is this long-term exposure that brings the use of antibiotics solely for growth promotion into question.

Internationally, the use of certain antibiotics for growth or performance enhancement has in the past been common practice in intensively reared livestock operations. This was the case in New Zealand in the formative years of intensive livestock farming. In the past decade antibiotic use in feed for poultry and pigs was common practice, but the purpose was to prevent specific diseases. Growth or performance gains are secondary benefits. Nevertheless, antibiotic products are still licensed solely for growth promotion and information was not provided at the time the products were licensed that specified the most appropriate use of the product to prevent specific diseases. Recommendations for disease prevention have subsequently been developed by the livestock industries using the products for this purpose.

All therapeutic animal health antibiotic products that are licensed in New Zealand can be obtained only under the prescription of a registered veterinarian. Products registered for growth promotion can be purchased by anyone without a prescription. This may seem like inadequate regulatory control and may encourage the development of antibiotic resistance. However, the only two livestock industries (pig and poultry industries) that use in-feed antibiotics depend for the most part on specialist veterinarians rather than general practitioners for advice on disease prevention. Those industries discourage the use of the products for growth promotion. Therefore, use of the products in those industries is under veterinary supervision but not on an individual veterinary prescription/farm basis. Nevertheless, unrestricted access and distant veterinary supervision may not provide sufficient control to prevent or stop imprudent use of the antibiotics, or ensure that emerging resistance problems would be identified in a timely manner.

### **1.2.3 Potential for exposure to resistant bacteria**

Antibiotic resistance due to use of antibiotic in animals can occur only if people become exposed to the resistant bacteria. Most therapeutic uses of antibiotics in animals do not result in situations in which people would come into contact with the resistant bacteria. However, the situations in which significant human exposure can occur (eg food-borne diseases and direct contact with animals, particularly with air and fluid discharges) will have to be kept in mind during the review.

### **2.2.4 Significance of antibiotics to human health**

Not all antibiotics are used on humans. Some antibiotics are so toxic to humans that they will never have any practical use in human medicine. For example, the ionophore family of antibiotics is not used to treat humans. While bacitracin has been incorporated into some human products (topical antibacterial preparation), its adverse side effects and ineffectiveness severely limit its practical use in internal medicine. Despite this limited use, bacitracin, as a

growth promotant, was banned in Europe so that it could be saved for use against bacteria resistant to vancomycin. This is unlikely because some of the bacteria that it might be used against are inherently resistant to bacitracin.

In New Zealand the most commonly used in-feed antibiotics are ionophores and bacitracin. The former is used to prevent coccidiosis and the later to prevent necrotic enteritis. Neither antibiotic poses a threat in regard to antibiotic resistance.

There are antibiotics of significant importance in human health care used in animal health care, but there is no evidence that their use in animals is contributing to the antibiotic resistance problem in human health. Nevertheless, their use should be allowed ONLY when that use is essential to the health and welfare of the animals, and the risks of developing antibiotic resistance can be managed adequately.

Some antibiotics are essential for treating specific human diseases, and for a number of these there are no practical alternatives. The fluoroquinolone family of antibiotics is a good example. Two other important families of antibiotics are the glycopeptides such as vancomycin and macrolides, such as tylosin. The use of these families of antibiotics in human health must be protected.

The expert panel report noted that, in New Zealand, erythromycin and roxithromycin are the most frequently used antibiotics from the macrolide family, used to treat lower respiratory infections suspected due to *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. In addition, clarithromycin and azithromycin are new antibiotics from the macrolide family used in the treatment of *Helicobacter pylori* and chlamydial disease respectively. The expert group noted the importance of ensuring that the efficacy of these drugs be maintained for the treatment of human disease for as long as possible (Expert Panel Report, 1999, p23).

### **3 PROCESS OF REVIEW**

#### **3.1 Review rationale**

Given the previous description of the matters that have to be considered, the review of animal antibiotic products has to be based on a line of inquiry that can put the findings into proper perspective. The first step in the review is to categorise the antibiotic or antibiotic family in regard to its significance to human health and the likelihood that antibiotic resistance will develop. This assessment will be done in a generic fashion because the categorisation is not affected by the animal health use of the antibiotic. Expert parties will be asked to comment on the use of the antibiotic in human health. They will also be asked for information on whether or not and why they consider that use is likely to be in jeopardy. It is expected that proprietors of both human and animal health products as well as human health specialists would participate in the categorisation.

Once an antibiotic or antibiotic family has been categorised as significant to human health, individual trade name products that contain that antibiotic or any antibiotic that might cause cross-resistance will be reviewed in regard to the particular antibiotic resistance hazards they pose. If those hazards are significant then the conditions on their licence will be amended to manage the risks by either reducing the magnitude of the hazards or reducing the exposure to the hazards.

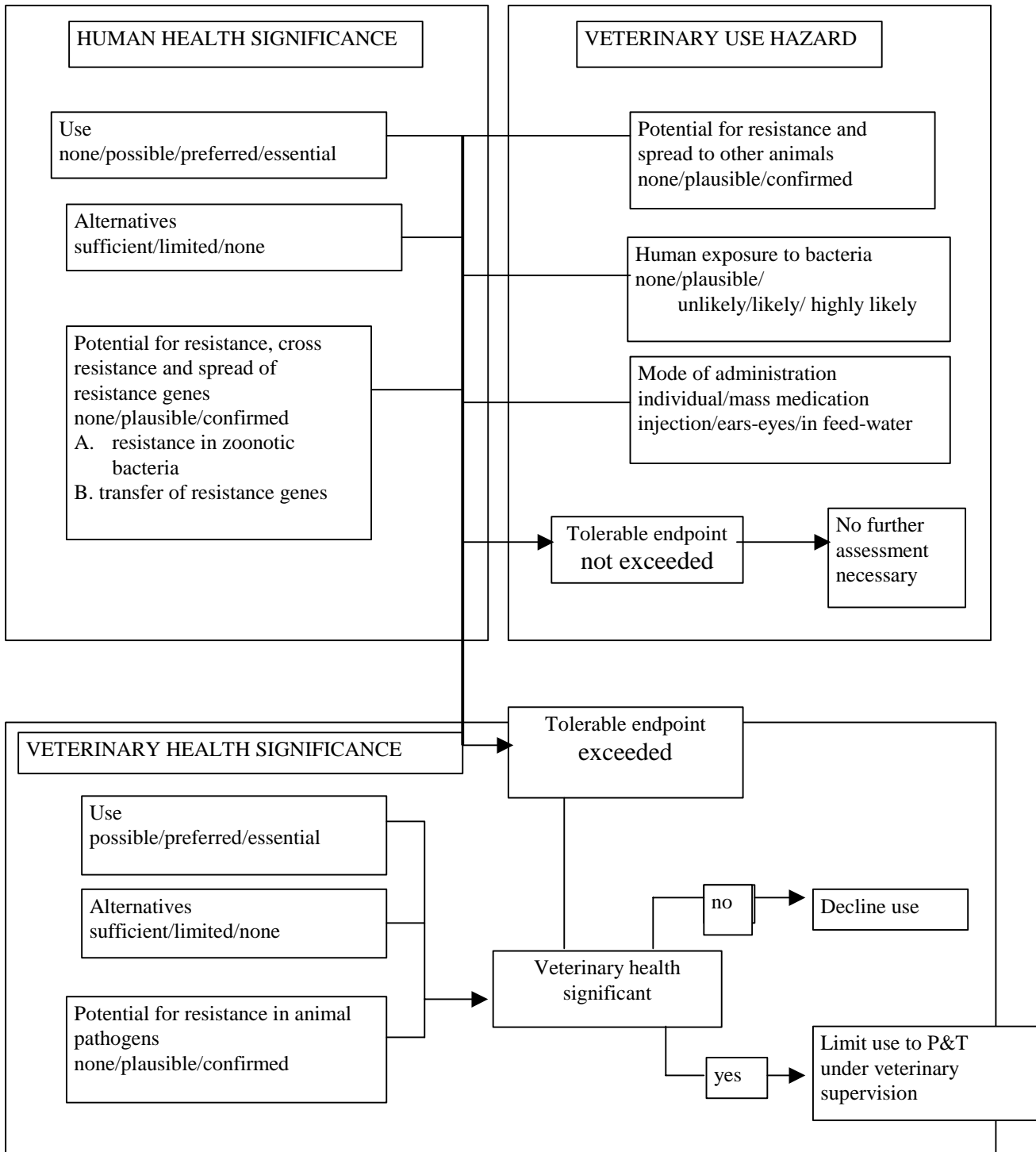
This rationale creates the following order of priority for the areas of interest.

1. human health significance and potential for resistance;
2. veterinary use and exposure hazards; and
3. veterinary use significance.

Obviously the highest priority matter is to establish how important the antibiotic is to human health. Products will be subjected to the full line of inquiry to develop a comprehensive picture. However, if the antibiotic in a product is not important to human health and it does not cause cross-resistance with any antibiotic that is important in human health, then antibiotic resistance in the context of this review is irrelevant.

The following figure shows the factors in each area of interest that will be reviewed. The line of inquiry begins with the categorisation of the antibiotic (or family) then reviews the hazards posed by animal health trade name products containing that antibiotic. If licences must be amended, then the significance of the product to animal health will be reviewed to ensure that antibiotic resistance is managed without compromising the health and welfare of animals that would suffer if an essential product was precipitously withdrawn from the market.

# ANTIBIOTIC RESISTANCE REVIEW RATIONALE



The criteria of significance in human health are:

- use and importance of the antibiotic;
- whether or not there are alternative antibiotic products; and
- the potential for resistance, cross-resistance and spread of resistance genes from resistant bacteria.

The second area of interest is the veterinary use and exposure hazards. The factors that will be reviewed are:

- potential for resistance to develop in the bacteria in the animals treated and spread to other animals;
- the potential for human exposure to the bacteria that may be resistant; and
- the mode of administration of the antibiotic.

Veterinary use will highlight how prevalent a resistant strain might be and how much human exposure might occur as a result of the veterinary use. It will also address those few cases in which a non-feed use of an antibiotic may result significant opportunities for human exposure.

The third area of interest will highlight the significance of an antibiotic in maintaining animal health. This should expose any negative animal health consequences that might occur as a result of altering present regulatory controls.

The combination of human health significance and veterinary use and exposure hazards establishes a tolerable endpoint (estimate of significance in regard to antibiotic resistance) at which a decision must be made whether or not a particular antibiotic/use combination should be allowed. The antibiotic resistance tolerable endpoint that is likely to prompt regulatory action in regard to the licensing of animal health antibiotic products to prevent resistance may include the following:

- the use of the antibiotic or a related antibiotic in human medicine is important for the treatment of human disease;
- there are limited alternatives for use in human medicine;
- there is a plausible potential for the development of resistance in zoonotic bacteria or the transfer of resistance genes, or the exposure of humans to the resistant bacteria is likely;
- 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 (ie mass medication in feed or water exposing whole flocks/herds to the antibiotic, or unusually high risk of personal exposure to infected material), thus increasing the likelihood of human exposure to resistant bacteria.

If the tolerable endpoint does not apply, then trade name products containing that antibiotic will not be reviewed further and no action will be taken to amend product licences.

If it is decided that the tolerable endpoint does apply, then regulatory action in regard to the licensing of trade name products containing that antibiotic will be reassessed and amended accordingly. The types of action that will be taken may be any one or a combination of the following:

- prohibit all uses of that antibiotic in animal health (veterinary) products;
- prohibit a particular practice (ie mass-administration orally to food producing animals);
- prohibit a particular use (ie use as a growth promotant);

- restrict access to particular persons (ie use only under registered veterinarian's prescription).

Where there is a clear and present danger, trade name product licences will be suspended immediately (as has already been done for the only in-feed fluoroquinolone product) until the review of that product has been completed and appropriate action taken. Otherwise, the sale and use of the products will be allowed during the review.

### **3.2 Anticipated outcome and timeframe**

The Animal Remedies Board expects that the review of antibiotic products will result in changes in the conditions of licences for products containing antibiotics for which the tolerable endpoint is exceeded. In most cases the likely action will be to restrict mass administration to food-producing animals (if necessary) and to make over-the-counter antibiotic products prescription animal remedies. It is also likely that any use other than treatment of disease will not be allowed. These modifications in licences will minimise the opportunity for antibiotic resistance (both human and animal) to develop, and increase the professional supervision over such products.

All animal health antibiotic products that contain antibiotics of human health significance are likely to be made prescription animal remedies with a requirement to specify their use for disease treatment or prevention. These products will not be approved for use as growth promotants. Other products (eg mass medication preparations of fluoroquinolones, avoparcin, virginiamycin and avilamycin) are likely to be considered to be a risk for antibiotic resistance and of limited significance to animal health, and the licences are likely to be revoked.

Most animal health antibiotic products are already prescription animal remedies that are used only to treat individual animals. The licences of these products are likely to remain as they are unless the antibiotic is too significant to human health to warrant the *status quo*.

The review of all animal health antibiotic products should be completed by January 2001. However, it is intended to address, as soon as possible, those antibiotics for which the tolerable endpoint is already known to be exceeded. This includes:

- fluoroquinolones;
- avoparcin;
- avilamycin;
- virginiamycin.

The trade name products containing these antibiotics will be reviewed and licences amended before July 2000. As stated earlier, the licence of the only mass medication fluoroquinolone product has already been suspended and is likely to be revoked. Mass medication products containing avoparcin are likely to be dealt with the same way, although the sole manufacturer of avoparcin has advised MAF that they are stopping production.

Because of the significance of the macrolide family of antibiotics (eg tylosin and tiamulin) in human health, they will be addressed next. The potential for resistance to macrolide antibiotics has been noted and licences must be amended accordingly. In addition, there are new antibiotics being developed in the macrolide family and resistance to tylosin generally confers cross-resistance to other macrolides, lincosamides and streptograms. It has not been confirmed as to whether or not there are sufficient alternatives that could be used in animal health. The veterinary use and exposure hazards must be reviewed.

The macrolide family is too important to jeopardise its effectiveness in either human or animal health. No matter what the outcome of the review of veterinary use or exposure hazards, it is likely that growth promotion use of macrolides will not be allowed. Disease treatment or prevention will be allowed. It is also likely that the products will have to be reclassified as prescription animal remedies to ensure there is adequate diagnosis of disease and antibiotic sensitivity monitoring. Proprietors will have to provide information on the appropriate treatment or prevention use for products that are licensed solely for growth promotion, if they wish to keep the products licensed.

Ionophores, flavophospholipols and bacitracin are unlikely to be of human health significance in New Zealand and they do not compromise the use of other antibiotics. Licensees of products containing these antibiotics will be advised before July 2000 that their licences will not have to be changed in regard to antibiotic resistance developing in bacteria causing disease in humans. However, they will be encouraged to remove growth promotion as a primary use, on the grounds that the use may jeopardise the effectiveness of the antibiotics for disease prevention and treatment in animals. MAF has been advised that the products, presently licensed for growth promotion, are being used to prevent particular diseases not growth promotion.

All new antibiotic products will be subject to the same rationale as applications are received. Conditions on licensing for new antibiotic products will be consistent with the new conditions proposed for existing licensed products. It must be noted that knowledge about antibiotic resistance is constantly changing with new insights being gained almost on a weekly basis. Therefore, no assessment and judgement on an antibiotic or antibiotic family will be permanent. The Animal Remedies Board and, in the future, MAF retains the right to review a licence when new information becomes available. It is intended that licences of all antibiotic products will be reviewed every five years, due to the rapidly changing state of knowledge.

## **4 CHANGE IN LEGISLATION**

The Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 may be implemented while this review is in progress. Under the ACVM Act 1997, the licensing of animal health antibiotics will become the responsibility of the MAF Food Assurance Authority, rather than the Animal Remedies Board. While the change will cause some disruption, the Animal Remedies Board's intended outcome for the review will still be appropriate under the ACVM Act. MAF considers that the review can progress even with a change in governing legislation, as the Animal Remedies Act 1967 cannot give full effect to Government's intention to manage relevant risks without significant amendment.

## **5 PARALLEL PROJECTS**

### **5.1 Joint Ministry of Health/Ministry of Agriculture and Forestry antibiotic resistance strategy**

The Ministry of Health and Ministry of Agriculture and Forestry are discussing the development of an antibiotic resistance management strategy. Within the context of that strategy they are considering the terms of reference and make-up of a joint ministerial committee to take an overview on the management of antibiotic resistance. After brief consideration, the two Ministries have agreed that the role of such a committee should at least include:

- improving co-ordination between the health and agricultural sectors to promote the best use of antimicrobials in animal and human health;
- advising on the terms of reference and components of the resistance management strategy that would be necessary and sufficient (both from a technical and resource management perspective) to define the definition of and monitor the resistance problem in New Zealand;
- considering the analysis of information generated from surveillance programmes; and
- providing advice on the implementation of control measures considered necessary in light of analysis of surveillance findings.

However, there are a number of technical resource management issues that still need to be addressed.

MAF and the Ministry of Health agree that the role of the Ministerial committee and the nature of the resistance management strategy must be clarified before the matter can be presented to Ministers and a committee with the appropriate expertise and experience can be established.

The Ministries intend to have a proposal for the resistance management strategy at a stage of development that can be considered by Ministers by March 2000. In the meantime, MAF will progress with the review of licensed veterinary antibiotic products according to the Animal Remedies Board direction. The Ministry of Health will continue to promote responsible use of antibiotics by the medical profession. Both agencies will determine the nature and extent of surveillance that would allow a better definition of the problem and provide evidence of antibiotic resistance trends.

## **5.2 Development of maximum residue limits based on microbiological parameters**

There are no indications that residues of antibiotics in food products are causing any direct resistance to develop. Presently, there are no domestic or international standards that provide guidance as to the significance of microbiological factors in establishing maximum residue limits for antibiotics in foods. There are international working parties addressing the issue.

MAF and the Ministry of Health are reviewing the process by which maximum residue limits are established in New Zealand. They are also contributing to the development of international standards for microbiological measures, which will be used to set maximum residue limits of antibiotics in food.

## **5.3 Codes for prudent use of antibiotics**

MAF is working with the NZ Veterinary Association, NZ Veterinary Council, NZ Feed Manufacturers Association and the pharmaceutical industry to develop codes of practice for the prudent use of antibiotics. The codes will cover the full range of antibiotic products, not just in-feed products.

## 6 DEFINITIONS

### **Antibiotic**

A chemically complex antimicrobial substance, derived from microbial fermentation or synthetic structural derivatives thereof, and that is antagonistic to microbial growth in very low concentration.

### **Commensal bacteria**

Bacteria that are normally present and are nourished by the host and do not normally cause disease.

### **Growth promotant (promoter) use**

To administer antibiotics orally to large numbers of healthy food animals for long periods at low concentrations, which are below the minimum inhibitory concentration (MIC) for most pathogens, to increase the rate and efficiency of growth.

### **Minimum inhibitory concentration**

The minimum concentration of an antibiotic that effectively inhibits the growth of bacteria.

### **Pathogenic bacteria**

Bacteria that are known to cause disease.

### **Prophylactic use**

To administer antibiotics for a limited period to large or small groups of healthy animals deemed to be at risk of disease caused by pathogens susceptible to the drugs.

### **Therapeutic use**

To administer antibiotics for a limited period to individual animals showing signs of disease.

### **Tolerable endpoint**

The antibiotic resistance tolerable endpoints are those that, when exceeded, are likely to prompt regulatory action in regard to the licensing of antibiotic products.

### **Zoonotic bacteria**

Bacteria that is capable of transmitting disease from animals to humans.

## **7 REFERENCES**

Animal Remedies Board decisions on review of antibiotic products, October 20 1999 and December 15 1999.

CAFA Report. *Antimicrobial Feed Additives*. Report from the Commission on Antimicrobial Feed Additives, Sweden, 1997.

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