



Antibiotic Resistance

Review and update on New Zealand regulatory control of antimicrobial agricultural compounds with regard to antimicrobial resistance

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Contents	Page
Summary	
Background	1
Primary area of concern	2
Expert Panel Review 1999	2
Expert Panel Review 2004	3
Current situation	3
Scope	3
Evidence of antimicrobial resistance	4
International reports on significance of antimicrobial agents	5
World Health Organization (WHO)	5
World Organisation for Animal Health (OIE)	5
Codex Alimentarius Commission (CODEX)	6
New Zealand antimicrobial resistance strategy	7
New Zealand industry and veterinary response	7
Industry	7
Veterinary	8
Review of antibiotic sales in New Zealand (2004-2009)	9
In feed/water administration	9
Parenteral or oral administration	9
Antimicrobial resistance surveillance and monitoring	10
Adjustment in New Zealand regulatory control of antimicrobial agents	11
Intramammary administration to control mastitis	11
Oral administration of antimicrobial agents	11
Adjustment in registration information requirements	12
References	12

Antimicrobial Resistance

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Summary

Early last decade, New Zealand adopted a prudent approach to the potential for antimicrobial resistance developing as a result of the use of antimicrobial products in animals. The New Zealand Food Safety Authority (now MAF):

- removed growth promotion as an acceptable use of critically and highly important antimicrobial active ingredients;
- imposed veterinary authorisation on any active ingredient it considered to be relevant to the antimicrobial resistance; and
- revised the information requirements for registering antimicrobial veterinary medicines to ensure that the potential for resistance was adequately addressed.

Subsequent work done by the World Health Organization (WHO), the World Organisation for Animal Health (OIE) and Codex Alimentarius has reinforced the soundness of New Zealand's approach. From an international perspective, New Zealand's low level of antimicrobial resistance was enviable.

Now, after ten years of prudent management, recent surveys have confirmed that the prevalence of antimicrobial resistance is still quite low, particularly in regard to the antimicrobial active ingredients identified by WHO and OIE as critically and highly important.

During this period the livestock industry sectors have been committed to adjusting management and animal health care practices to reduce dependence on critically and highly important antimicrobial active ingredients.

While minor refinements in regulatory control will be made to address innovations and technological advances, New Zealand's current regulatory control of antimicrobials used in animals is considered to be adequate and consistent with international common best practices.

Background

Antibiotic resistance and reduction in the effectiveness of antibiotics to treat certain bacterial infections in humans has been a growing concern internationally. There has always been consensus that the development of resistance is associated with continued use of antibiotics.

Evidence suggesting that the development of resistance may be facilitated by use of antibiotics in food-producing animals via the transfer of resistant pathogenic bacteria from animals to humans (or via the transfer of some antibiotic resistant non-pathogenic bacteria with subsequent genetic transfer of the resistance to human pathogens) began emerging as more attention was paid to this possibility.

The early evidence was limited, so considerable effort has been taken to gather data needed to put the suggestion into a technically sound perspective. Nevertheless, many countries, including New Zealand, took prudent action to address the possibility of resistance developing.

PRIMARY AREA OF CONCERN

While the Ministry of Health in New Zealand takes the lead in regard to the prudent use of antibiotics in humans¹, MAF is responsible for addressing the issue of antibiotic use in animals. After consultation with experts and interested parties, MAF considered that the primary area of concern was the oral administration of certain types of antibiotics to large groups of food-producing animals such as cattle, pigs and poultry.

After ten years of focused investigation around the world, it is still agreed that if resistance is going to develop and transfer from animals to humans, oral medication of large groups of food-producing animals remains the single most likely pathway. MAF's regulatory attention and control of antibiotics has, predictably, focused on prudent use of antibiotics in food-producing animals, with emphasis on in-feed and in-water administration.

EXPERT PANEL REVIEW 1999

MAF established the Antibiotic Resistance Steering Committee in 1999. That committee has commissioned two expert panel reviews. The first one (1999) examined the existing information on antibiotic resistance and New Zealand's regulatory control of antibiotic products. The steering committee made recommendations to MAF and controls on products via conditions of registration for certain antibiotics were adjusted appropriately. However, even at that time in New Zealand, there was very little oral administration of the antibiotic types that were implicated in the potential transfer of antibiotic resistance. Nevertheless, MAF classified certain antibiotic families on the basis of:

- potential to contribute to resistance;
- potential for human exposure to resistant bacteria; and
- the relative importance of the antibiotic family in human medicine.

Growth promotion (or any other production enhancing claims) was prohibited for products that contained antibiotics in the critical family groups. Production enhancing claims were allowed for those antibiotic families that were not implicated in the antibiotic resistance issue. Prophylactic and therapeutic uses of oral antibiotics were allowed, but additional restrictions were imposed for some of the most critical antibiotics to ensure prudent use.

¹ Use of antibiotics in humans remains the primary mechanism for the development of antibiotic resistance in humans.

MAF imposed a regulatory obligation to report annual sales on all antibiotic products to allow trends in sales (and by implication trends in use) to be monitored. Additional information requirements in line with the VICH Guidance for Industry (Pre-approval information for registration of new veterinary medicine products for food-producing animals with respect to antimicrobial resistance, VICH GL27) were imposed to ensure the potential for resistance to develop was considered and addressed prior to product registration.

EXPERT PANEL REVIEW 2004

The second expert panel review in 2004 updated the 1999 review and examined the adjustment in regulatory control. The panel concluded that New Zealand regulatory policy in 2004 was prudent and conservative, and further restrictions beyond specific recommendations for limited antibiotics were not required. The Antibiotic Resistance Steering Committee reported back to MAF that the commitment of the livestock industry sectors to prudent use of antibiotics and the refined regulatory control were having the intended effect.

The recommendations proposed in the report and progress on their implementation may be viewed on our website.

[Antibiotic resistance recommendations: implementation update](#)

CURRENT SITUATION

Sales of oral antibiotic products containing critical antibiotic family active ingredients have steadily decreased. It is now ten years after the refinement of regulatory control of antibiotics, and the current situation is examined in this paper.

Scope

Internationally, the resistance issue has been put into the broader context of antimicrobial resistance to deal with emerging trends involving a wide range of pathogenic or parasitic organisms. This paper is written in light of the international context and refers to antimicrobial agents.

In New Zealand the antimicrobial resistance issue remains exclusively a matter involving antibiotics that have primarily an antibacterial action. Consequently, this paper does not consider any of the products whose primary antimicrobial action is against prions, viruses, fungi, parasites or any other pathogenic or parasitic organism group.

The paper looks at the body of resistance evidence (international and domestic) that has been generated over the last five years and the international regulatory response to the resistance issue. It examines the New Zealand antibiotic sales statistics over the same period, which coincides with the period immediately after the last review of the conditions of registration for antibiotics. While information on use is still limited, MAF's Agricultural Compounds and Veterinary Medicines (ACVM) Group informally monitored the use pattern of the major livestock industry sectors.

The paper reviews current regulatory control in light of the World Health Organization (WHO) concept of critically important antibiotics as detailed in its report, *Critically Important Antimicrobials for Human Medicine* (Third Edition). This concept was reviewed in tandem with the parallel World Organisation for Animal Health (OIE) report considering antibiotics from an animal health perspective.

Evidence of antimicrobial resistance

Over the last ten years research has refined the definition of the antimicrobial resistance problem as it relates to the use of antimicrobial agents in animals. It has also allowed the risks to be estimated, albeit in a qualitative manner. Internationally, the more focused concept of antibiotic resistance has been expanded to encompass other types of antimicrobial agents to prompt scientific interest in other potential types of resistance.

However, to date the primary and confirmed focus remains on the oral use of antimicrobials with antibacterial activity on large groups of animals producing food for human consumption with the potential to transfer resistant enterobacteriaceae (human or zoonotic pathogens or commensal bacteria that could possibly transfer resistance to human pathogens).

The growing database of survey and trial results is confirming that use of antimicrobial agents with antibacterial action in animals does, in some cases, lead to the development of resistance or resistance determinant factors to those agents. Survey results are also confirming that strains of resistant bacteria apparently originating from animal sources are being found on contaminated animal products and, in some instances, in or on humans. This appears to support the proposition that humans can be exposed to resistant bacteria via meat products from animals that have been treated orally with certain antimicrobial agents.

Both research and scientific modelling support the contention that cross-resistance can develop between similar antimicrobial agents. This underlines the concern that the oral use of an antimicrobial agent potentially jeopardises the future efficacy of other similar agents.

Evidence is still not conclusive that dairy products pose a similar risk. Nor is it conclusive that other routes of administration, such as parenteral injection of the same antimicrobial agents, contribute significantly to the risk of transmitting resistant bacteria.

There is some evidence confirming the presence of resistant strains of bacteria in humans that have also been found in animals in circumstances where exposure would not involve contaminated food. What is not certain in this evidence is the direction in which the transfer occurred (that is, animals to humans or humans to animals). However, it would seem likely that transfer occurred via direct contact and the bacteria could have developed the resistance from use of an antimicrobial agent in either animals or humans.

Confirmed cases of the spread of resistance via genome transfer are still limited.

International reports on significance of antimicrobial agents

WORLD HEALTH ORGANIZATION (WHO)

A WHO working party prepared a report (revised in the third edition referred to in this paper) that addressed the relative importance of antimicrobials to human medicine in light of parallel use of them in animals (focusing almost exclusively on oral administration).

The report formally introduces the concept of antimicrobials critically important (to humans), although the concept has always been fundamental to the consideration of antibiotic resistance. The report places antimicrobial agents into three groups: critically important, highly important and important. This grouping was based on two criteria:

- whether or not the agent is used as sole therapy or one of a few alternatives to treat serious human diseases;
- whether or not the agent was used to treat diseases caused by either organisms:
 - that may be transmitted via non-human sources; or
 - that may acquire resistant genes from non-human sources.

It notes that in setting priorities for development of risk management strategies, the antimicrobials grouped as critically important should take precedence. The report identified the following active ingredient families as **critically important**:

Aminoglycosides

Anamycins

Carbapenems and other penems

Cephalosporins (3rd or 4th generation)

Glycopeptides

Glycylcyclines

Lipopeptides

Macrolides and ketolides

Oxazolidinones

Penicillins (natural, aminopenicillins and antipseudomonal)

Quinolones

Streptogramins

Tetracyclines

Miscellaneous anti-mycobacterial drugs.

The active ingredient agents identified as **highly important** are ones that may meet the criteria in regard to transmission of bacteria from animals to humans but are not of particular importance in human medicine.

WORLD ORGANISATION FOR ANIMAL HEALTH (OIE)

In order to create a balanced perspective between human and animal health, OIE carried out an international survey to identify the antibiotics of importance to animal health. OIE used similar groupings as the WHO report from a veterinary perspective (that is, veterinary critically important antimicrobials, veterinary highly important and veterinary important). Some groups in the OIE list were not present in the WHO list and vice versa, highlighting the fact that some antimicrobial groups are not used to treat both humans and animals.

OIE used two criteria to group the agents:

- more than half the respondents identified the agent as important; and
- the agent is used to treat serious animal diseases with limited alternative antimicrobial agents.

The report of the survey identified the following as **veterinary critically important** antibiotics:

Aminoglycosides

Cephalosporins (all generations represented)

Macrolides

Penicillins

Phenicol

Quinolones

Sulfonimides

Tetracyclines.

The obvious overlaps between the two lists as identified by the Joint FAO/WHO/OIE expert meeting on critically important antimicrobials are:

Aminoglycosides

Cephalosporins (3rd and 4th generation)

Macrolides

Penicillins

Quinolones.

From an international perspective, the priority for these active ingredient families must be to strike a balance between critical animal health needs and preserving the efficacy of particular antimicrobial agents for human use. Collectively, the reports provide a focus of attention for antimicrobial resistance management.

At the same time, examination of the overlaps between critically and highly important antimicrobial agents highlights the animal health importance of antimicrobial agents such as ionophores and polypeptides that are not as important in human health (that is, not used or contraindicated to treat humans). This creates an opportunity to address animal health needs via the preferred use of less important human health antimicrobial agents.

CODEX ALIMENTARIUS COMMISSION (CODEX)

Codex has approached the antimicrobial resistance from another perspective. Recognising that the use of antimicrobials in food-producing animals poses risks of developing resistance, Codex established an ad hoc intergovernmental task force on antimicrobial resistance. The task force is currently refining guidelines for risk analysis of foodborne antimicrobial resistance. The following guidelines are nearing completion and can be read in conjunction with other Codex documents on microbiological risk assessment, risk management and minimising/containing antimicrobial resistance.

- Principles and Guidelines for the Conduct of Microbiological Risk Management (CAC/GL 63-2007)
- Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005)
- Code of Practice on Good Animal Feeding (CAC/RCP 54-2004).

New Zealand antimicrobial resistance strategy

In New Zealand the refinement of regulatory controls of antibiotics anticipated the WHO/OIE outcome.

- The registration information requirements were amended to require antimicrobial resistance data to address the potential for a new veterinary antimicrobial agent.
- All production enhancing claims were prohibited unless the agent was identified as “not relevant to resistance in human pathogens”. Registrations were adjusted to remove existing production enhancing claims for critically important and highly important agents.
- Oral administration to large groups of animals was the target of particular scrutiny, particularly when administered in feed or water.
- An Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 amendment passed in October 2007 enables consideration of hazards in relation to antimicrobial resistance to be made when applying conditions of registration.
- All antibiotics that are considered significant with regard to development of resistance in human pathogens have been classified as restricted veterinary medicines (RVMs) and are therefore available only under veterinary authorisation.
- There is a mandatory requirement to provide annual sales data for all RVMs containing antibiotics. The sales data are analysed and reported every second year.
- Growth promotion claims for antibiotics of concern (in effect the critically important and highly important antibiotics listed by both WHO and OIE, and ones uniquely important in New Zealand such as the polypeptide bacitracin) have been prohibited.
- Label requirements have been updated to manage antibiotic resistance for specific products containing critically important antimicrobial agents in regard to human health.
- Following a recommendation in the 2004 Expert Panel’s report, a review of the registration of products containing aminoglycoside and beta-lactam antibiotics was completed by MAF in 2009. As a result, products containing these antibiotic combinations are no longer registered.

New Zealand industry and veterinary response

Some notable industry and veterinary changes have been made since the first reports on the regulatory control of antibiotics to manage antibiotic resistance were published in 2003.

INDUSTRY

The New Zealand Pork Industry Board (NZPork) has developed guidelines for responsible use of antibiotics in the New Zealand pork industry. These guidelines, developed in consultation with New Zealand pig veterinarians, were not limited to the prudent and responsible use of antibiotics. They also set out good practice principles for animal disease management in order to reduce the need for the use of veterinary medicines in the first instance.

Fonterra, the largest milk producer in the country, now reviews and updates MAF-registered Farms Risk Management Programmes (RMPs) for their milk suppliers. These RMPs manage the quality of raw milk and include requirements to record all antibiotic use.

Similar programmes including Whole Flock Health Schemes exist in the poultry industry. These programmes will be supplemented by specific guidelines for antibiotic use in poultry that were developed by poultry industry veterinarians and completed in 2011. (They are available on the PIANZ website.)

VETERINARY

The New Zealand Veterinary Association (NZVA) has developed draft General Guidelines on the Use of Antibiotics. These guidelines note that in treating animals with antimicrobials, veterinarians should aim to optimise therapeutic efficacy and minimise the potential for development of resistance to antimicrobials, and that particular care should be taken when prescribing antibiotics that could give rise to cross-resistance with drugs used for serious infections in people. Such drugs are to be avoided unless there is a good reason to use them rather than another class of antibiotic. These guidelines supplement the Veterinary Council of New Zealand (VCNZ) Code of Professional Conduct which requires all veterinarians to take due care to ensure that veterinary medicines they use, prescribe or dispense are:

- appropriate for use in a specific circumstance;
- used in accordance with their conditions of registration.

NZVA is also developing and documenting sector-specific best practice guidelines for prudent use of antibiotics. The Society of Dairy Cattle Veterinarians of NZVA has produced a therapeutic formulary that offers a clear indication of the best practice treatment options available and a hierarchy of drug choice for various conditions. Similar guidelines for specific conditions have been developed for companion animal veterinarians. NZVA has also developed guidelines for antimicrobial treatment of respiratory disease in horses.

As noted above, the specialist pig industry veterinarians liaised with NZPork to develop antibiotic guidelines for the pork industry and the poultry industry veterinarians are developing specific guidelines for antibiotic usage in poultry flocks. Note that a limited number of antibiotics of high significance in human medicine are registered for use in these species for therapeutic purposes.

To ensure dry cow intramammary therapy is prescribed appropriately, the VCNZ Code of Professional Conduct defines the consultation requirements for prescription of these treatments in The Dry Cow Therapy Standard.

The above initiatives support and promote the prudent use of antibiotics in animals and help to minimise the potential risk of transfer of antimicrobial resistant pathogens to humans via possible animal pathways.

Review of antibiotic sales in New Zealand (2004-2009)

MAF has reviewed antibiotic sale from 2004/05 to 2008/09. (The sales year is from 1 April to 31 March.) The data and industry comments on the data are presented in the full report, *Antibiotic Sales and Use Overview 2004-2009*, which is available in the eLibrary of our website.

The data reviewed do not include sales figures for antibiotics that are not managed as RVMs, such as ionophores, avilamycin or quinoxalines. These products are not likely to be used in human medicine and there is no evidence to suggest that they could contribute to antibiotic resistance in humans.

These data provide approximate information regarding annual sales of restricted veterinary antibiotics. This summary focuses on antibiotics used in food-producing animals.

IN FEED/WATER ADMINISTRATION

For the most part antibiotic products designed to be administered in feed or water are registered primarily for use in pigs or poultry (and other avian species). Individual oral or parenteral administration is usually more appropriate for other species. Therefore, it can be assumed that the majority of the sales of in-feed and in-water products will be used in the poultry and pig industries. A limited number of antibiotic families identified by the WHO as critically or highly important in human medicine are registered for administration via these routes. These include the aminoglycosides, macrolides/lincosamides, and streptogramins.

Sales of aminoglycosides have declined 65% to 71kg in 2008/09 from a peak in 2006/07 of 204kg. Sales of macrolides/lincosamides have also decreased 28% to 3,299kgs from 4,564kgs recorded in 2004/05. No virginiamycin (streptogramin) has been sold for use in poultry over the survey period.

The percentage decrease in sales is greater than the corresponding decrease in the pig and poultry populations recorded between 2006/07 and 2008/09. These trends suggest that the pig and poultry industries are using these antibiotics prudently with the desired outcome of reducing dependence on active ingredients of high human health significance.

PARENTERAL OR ORAL ADMINISTRATION

Antibiotics registered for parenteral or oral administration in food-producing animals that have been identified by WHO as critically or highly important in human medicine include the aminoglycosides, 3rd and 4th generation cephalosporins, fluoroquinolones, macrolides, anti-mycobacterial antimicrobials and the streptogramins. These same active ingredients are also registered for use in companion animals and many of the products are registered for both groups of animals. This complicates the analysis of sales data.

Sales of aminoglycosides have declined following a MAF review of combination aminoglycoside/beta-lactam products, and sales are expected to fall further in subsequent reports as the product supply is exhausted.

Sales of cephalosporins have increased 26% between 2004/05 and 2008/09, possibly because of new product registrations and increased dairy cattle numbers. Sales of 4th generation cephalosporins were very low in 2008/09.

Sales data for injectable fluoroquinolones, which have specific label restrictions to manage antibiotic resistance, have increased 114% between 2004/05 and 2008/09 but total sales mass is still very low at 22kgs reported in 2008/09. Oral sales of marbofloxacin registered for use in calves were very low between 2006/07 and 2008/09.

Parenteral and oral macrolide sales have increased by 81%, primarily because of increased sales of injectable tylosin. Injectable tylosin is likely to be used most frequently in dairy cattle. Dairy cattle numbers have increased significantly over the survey period. Tylosin may also be used in pigs and some limited use may occur in sheep and goats.

Sales of the anti-mycobacterial antibiotic streptomycin have remained relatively static over the survey period. Sales will decline significantly in subsequent reports as this aminoglycoside was in aminoglycoside/beta-lactam combination scour products that are no longer registered following the 2009 review. An injectable product containing streptomycin has specific and limited use indications.

The streptogramin virginiamycin is registered for restricted use in horses with laminitis. The sales mass remains very small. A small number of horses are processed for export but there is no New Zealand market for horse meat.

In light of the reported sales figures, it is concluded that there are no reported trends that would suggest antibiotics are not being used as intended or outside their registration conditions.

Antimicrobial resistance surveillance and monitoring

The New Zealand Ministry of Health monitors both outbreaks of diseases and the occurrence of antibiotic resistant strains of certain human pathogens. Judging from the latest Ministry of Health annual report, *Notifiable and other diseases in New Zealand 2009*, and the annual surveillance report in April 2010, there were no obvious linkages between outbreaks of disease, the presence of resistant strains of bacterial and epidemiologically likely animal sources of the pathogens or antibiotic resistance in the relevant human or zoonotic pathogens.

A study published in 2010 in the *New Zealand Veterinary Journal* provides baseline data on the levels and patterns of antibacterial drug resistance expressed by Gram-negative bacteria isolated from poultry carcasses in New Zealand. The authors conclude that the levels of resistance shown by Gram-negative bacteria isolated from chicken carcasses in New Zealand are among the lowest reported around the world. No resistance to extended-spectrum cephalosporin drugs was detected in *E. coli*, suggesting that CTX-M and AmpC beta-lactamases are rare or absent. *Salmonella* species were rarely isolated from poultry carcasses during routine testing in New Zealand, and the isolates identified during this study were fully susceptible to the drugs tested. A panel of *Campylobacter jejuni* isolates originating from retail poultry carcasses were susceptible to first-line and second-line antibacterial drugs. These results are significant considering the high rates of foodborne enteritis in New Zealand compared to other developed countries.

In its 2011 report (A baseline survey of antimicrobial resistance in bacteria from selected New Zealand foods 2009-2010) the Antibiotic Reference Laboratory, Institute of Environmental Science and Research reported on a year long survey of animal product produce (freshly dressed carcasses of very young calves, pigs and broiler poultry as part of the National Microbiological Database [NMD] programme). The report confirmed that

the prevalence of resistance among bacteria from food animals and fresh produce included in the survey was usually less than that reported for human isolates of the same bacteria species isolated in New Zealand in 2009, especially for the antibiotics of most importance as human medicines. Moreover, comparison of the results from this survey with the limited data available from earlier New Zealand studies does not suggest a trend of increasing resistance among bacteria from animals in New Zealand. (p v)

Adjustment in New Zealand regulatory control of antimicrobial agents

For the most part, the level of regulatory control imposed on antibiotics used in animals in New Zealand continues to be appropriate to minimise the risk of animals being the source of:

- human or zoonotic pathogens resistant to critically important or highly important antimicrobial agents
- commensal bacteria that could potentially transfer resistance to human pathogens.

The New Zealand initiatives for managing antimicrobial resistance are consistent with both the human health perspective of the WHO report on antimicrobial resistance and the animal health perspective of the OIE. Surveillance intelligence within New Zealand supports the view that antibiotics are being used in animals in New Zealand in a prudent manner.

Livestock industry, biosecurity and disease management initiatives have concentrated on reducing animal health reliance on antimicrobial agents that are critically or highly important for human health.

Registrations for antibacterial agents have been adjusted to place their use under veterinary supervision, and the veterinary profession in New Zealand has established (or is developing) guidelines for veterinary practitioners for prudent use of antibiotics.

In light of the apparent effectiveness of antibiotic resistance management in New Zealand, trade name products containing antibacterial agents will, in the main, continue to be regulated using current controls. The focus of attention will remain on in-feed and in-water administration of antibacterial agents that are critically or highly important to human health.

However, some areas of control, including the following, could benefit from refinement.

INTRAMAMMARY ADMINISTRATION TO CONTROL MASTITIS

Because of the types of products used and the management of the milk produced, it is considered that the therapeutic use of intramammary antimicrobial preparations is not likely to be a significant cause of antimicrobial resistance in humans. First and second generation cephalosporins are used in intramammary products, but there are no specific antimicrobial resistance requirements imposed. Some of the products are approved for dry cow therapy to eliminate subclinical mastitis infections (treatment of apparently healthy cows) before the next lactation period.

Some therapeutic intramammary products contain specific third generation cephalosporin active ingredients. These products have antimicrobial warnings on the label and restrictions on use to ensure that they are used only in technically justifiable circumstances. Because third and fourth generation cephalosporins have been identified as critically important, intramammary products containing such actives will not be approved for dry cow therapy unless there is compelling evidence confirming that they will not cause resistance.

While there has been some debate, New Zealand considers cefiofur to be a third generation cephalosporin. MAF will review current registrations and ensure that they are dealt with according to the rules that apply to all third and fourth generation cephalosporins.

ORAL ADMINISTRATION OF ANTIMICROBIAL AGENTS

The oral administration route (via feed or water) is considered to be of most concern, particularly in regard to animals slaughtered for human consumption. The WHO and OIE lists of critically and highly important antimicrobials will be the point of reference when

considering registration for antimicrobial agents to be administered in-feed or in-water. Such products will not be approved if they contain critically or highly important antimicrobial agents unless there is compelling evidence that they will not cause resistance.

ADJUSTMENT IN REGISTRATION INFORMATION REQUIREMENTS

Currently New Zealand refers to the VICH guidelines. While these guidelines have been a satisfactory point of reference to guide registration applicants, the guidelines will be reviewed to see if they are sufficiently explicit and focused on the New Zealand situation. Guidance documents issued by parallel regulators, along with guidance from WHO, OIE, VICH and Codex will be used as points of reference in the review.

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