

# **REGULATORY CONTROL OF ANTIBIOTICS TO MANAGE ANTIBIOTIC RESISTANCE: PROGRESS REPORT January 2003**

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# 1 INTRODUCTION

As part of the management of antibiotic resistance, the ACVM Group has collected and analysed the statistics on sales of antibiotics during 2001. For the past two years sales information (on an active ingredient basis) was voluntarily provided by the proprietors of antibiotic products. Annual sales statistics for 1999 were also available as part of the expert panel report to the Antibiotic Resistance Steering Committee commissioned by the Animal Remedies Board and MAF. Although data for three years are available, the survey methodology changed over those three years so it would be inappropriate to place too much confidence in the apparent trends to date.

The survey results were provided to the livestock product associations for the major intensive livestock industry sectors for comment. This was to add some confidence to any conclusions that have been drawn about use from the sales statistics. A brief comment has been added where appropriate to describe differences in sales statistics and actual use.

In compiling this report it has come to the ACVM Group's attention that a number of registrant companies and individual products have changed ownership. This appears to have added an additional uncertainty factor in regard to the comprehensive coverage of the sales statistics for antibiotic products.

In addition to the sales survey there have been considerable changes in the regulatory control of antibiotic products. Registrations have been changed to give effect to a more prudent and focused registration policy for antibiotic products. A number of these changes did not become effective until 1 July 2002 so they may not have had an impact on the 2001 sales statistics.

There have also been a few antibiotic active ingredients considered for registration as veterinary medicines.

This report covers the sales survey and provides an update on the regulatory changes for existing products and the registration decisions on the new antibiotic active ingredients.

## 2 ANTIBIOTIC SALES SURVEY

### 2.1 Antibiotic sales report 2001: General comments

In 2001 a survey containing a list of active ingredients (see appendix 2) was sent to registrants. This list was a modified version of the one used in 2000. The sales were to be expressed as kilograms of active ingredient. Because the focus of concern has been mass medication in feed/water, respondents were asked to provide the amount of antibiotic specifically for administration in feed/water as one category and by any route other than feed/water as a separate category. Registrants were also asked to provide the breakdown of amounts of in-feed/water products intended to be used for prophylactic (to prevent disease), therapeutic (to treat clinical disease) or growth promotion purposes.

The statistics were to be provided by species of animal to be treated. The groups were:

- cattle (divided into unspecified age and calves);
- pigs;
- poultry;
- species other than cattle, pigs or poultry <sup>1</sup>.

Many antibiotic products are sold for use on a wide range of species and for multiple purposes. Consequently, it is not possible for a registrant to be certain which species will be treated and for what purpose. A separate category, sales for unspecified species, was included. However, because of the types of products represented in this group it is reasonable to assume that they would not have been used in feed/water and would not have been used for mass medication. It is also reasonable to assume that they would have been used only for therapeutic purposes. Products would have been used on some food-producing animals as well as the full range of non food-producing species (i.e. companion animals). It is not possible for the registrants to know if their products are being used “off-label”, so there is an inherent uncertainty about the actual use of the antibiotics included in table 6 of this report.

In addition, it must be noted that a relatively small amount of human antibiotic products would have been used under veterinary prescription on animals. These sales are not identified in this survey. However, the products would have been used primarily in household pets and are unlikely to figure significantly in the development of antibiotic resistance in human pathogens.

The survey statistics were collated and compared to sales in 2000. While all active ingredients were listed individually in the survey, the statistics were combined into antibiotic family groups for reasons of commercial confidentiality. The family groups were:

- penicillins;
- cephalosporins;
- aminoglycosides;
- macrolides/lincosamides;
- tetracyclines;
- sulphonamides;
- ionophores; and
- ‘others’ (including flavophospholipols, bacitracin, avilamycin, baquiloprim, carbadox, carnidazole, dimetridazole, enrofloxacin, florfenicol, furazolidone, fusidic acid, metronidazole, atamycin, nitrofurazone, novobiocin, orbifloxacin, trimethoprim, virginiamycin).

The survey results are only indicative of use at best. The formal survey has been carried out only for two years during a period of rapid regulatory and industry change. At the same time, use during a particular year is very dependent on the health circumstances during that year. With only two years’ results it is impossible to draw any reliable conclusions based upon variations between the two years. After collecting statistics for a number of years, it may be possible to quantify the impact of yearly variations in health problems.

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<sup>1</sup> In effect this category represents the non-food producing animals because the only significant food-producing animal not represented is sheep. There are no antibiotic products that are specifically intended for use in sheep in a manner that is predictable by the proprietor of the product.

## 2.2 Survey results

### 2.2.1 Cattle

**Table 1: 2001 sales of antibiotics for cattle (age unspecified)**

	<b>In-feed/water (kg of active ingredient)</b>			<b>Other routes (kg of active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed Conversion</b>			
<b>penicillins</b>	0	1060	0	5671	<b>6731</b>	5158
<b>cephalosporins</b>	0	0	0	660	<b>660</b>	674
<b>aminoglycosides</b>	0	0	0	620	<b>620</b>	636
<b>macrolides lincosamides</b>	0	0	0	426	<b>426</b>	303
<b>tetracyclines</b>	0	77	0	390	<b>467</b>	793
<b>sulphonamides</b>	0	0	0	117	<b>117</b>	189
<b>ionophores</b>	29694	0	0	0	<b>29694</b>	20707
<b>others</b>	0	0	0	27	<b>27</b>	67

Table 1 shows the sales of antibiotics that were intended for use in cattle of unspecified age. There was an increase in sales of penicillins and macrolides. There was a decrease in sales of cephalosporins, aminoglycosides, tetracyclines, sulphonimides and 'other' antibiotics. While this may be a trend to more use of antibiotics, it may be only a normal variation in the years recorded.

Most of the changes relate to administration other than in feed/water that is not considered to have much influence on the development of antibiotic resistance. Most antibiotics administered to cattle in New Zealand are given by routes other than in feed or water and they are not used as mass medication. There were no antibiotics sold for growth promotion. The only in-feed/water antibiotics used (for prophylactic purposes) were ionophores, which are considered irrelevant to the potential antibiotic resistance problem. There was a large increase in the sale of ionophores for use in cattle. However, it appears as though there is a significant off-label use of ionophores in pigs (see section 2.2.2 below). Most likely this use has resulted in an overestimate of the use of ionophores in cattle.

There were five kilograms of fluoroquinolones (under veterinary prescription only) sold for use in cattle and no virginiamycin was sold.

**Table 2: 2001 sales of antibiotics for cattle (calves)**

				<b>In-feed/water (kg of active ingredient)</b>	<b>Other routes (kg of active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed conversion</b>				
penicillins	0	0	0	0	<b>0</b>	1	
cephalosporins	0	0	0	0	<b>0</b>	-	
aminoglycosides	0	0	0	33	<b>33</b>	8.5	
macrolides	0	0	0	0	<b>0</b>	-	
lincosamides	0	0	0	0	<b>0</b>	-	
tetracyclines	0	0	0	0	<b>0</b>	-	
sulphonamides	0	0	0	564	<b>564</b>	129	
ionophores	8464	0	0	0	<b>8464</b>	2130	
others	40	0	0	0	<b>40</b>	337	

Table 2, sales for calves, shows an increase in sales of aminoglycosides and sulphonamides. There was a marked decrease in the use of other antibiotics. No virginiamycin or fluoroquinolones were sold for use in calves. There was also a large increase in the sale of ionophores as there was in cattle of unspecified age (see note above on off-label use of ionophores in pigs). There were no other antibiotics sold specifically for use in feed or water for any purpose including growth promotion. These sales statistics could reflect a change in attitude toward the use of important human antibiotics, especially when combined with the sales of zinc bacitracin, which is also an antibiotic considered to be of little significance to the potential antibiotic resistance problem. However, it is too soon to be certain about a trend.

## 2.2.2 Pigs

**Table 3: 2001 sales of antibiotics for pigs**

	<b>In feed/water (kg of active ingredient)</b>			<b>Other routes (kg active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed conversion</b>			
penicillins	0	21	0	0	<b>21</b>	-
cephalosporins	0	0	0	0	<b>0</b>	-
aminoglycosides	0	41	0	0	<b>41</b>	16
macrolides lincosamides	1071	1404	0	0	<b>2475</b>	2463
tetracyclines	30	52	0	0	<b>82</b>	1375
sulphonamides	0	269	0	1	<b>270</b>	413
ionophores	0	0	0	0	<b>0</b>	5
others	280	0	0	0	<b>280</b>	430

Table 3 shows the sales of antibiotics for use in pigs. The statistics indicate that the majority of products sold are for in-feed/water products. While this is consistent with the practicalities of medicating pigs, parenteral administration of antibiotics for therapeutic and metaphylactic (ie treatment in the face of an imminent outbreak of disease) purposes is a relatively common practice. The registrants have advised that there were no antibiotics sold for growth promotion purposes. However, during 2001 over-the-counter antibiotic products were still registered for that purpose.

There was a small increase in the sale of penicillins, aminoglycosides and macrolides for therapeutic and prophylactic purposes, but the increases were too slight to be significant. This would indicate that there was no shift from growth promotion use to therapeutic or prophylactic use as some parties feared. There was a decrease in the sale of tetracyclines, sulphonamides and 'other' antibiotics. No fluoroquinolones or virginiamycin were sold. The sales statistics indicated that the only antibiotic in the 'other' category was zinc bacitracin, making up the full 280 kgs.

Discussion with the Pork Industry Board identified a difference in the sales statistics and actual use practices. Use of tetracyclines is considered to be approximately the same level as for 2000. This discrepancy appears to be related to a change in ownership of some of the products, resulting in inadvertent under-reporting of sales. The industry advises that the sales figures for parenterally administered products would lead to a conclusion that underestimates the actual use of such products. This could mean that a significant (but not quantifiable) amount of parenterally administered products included in table 6 below was probably used to treat pigs. Having said this, the use would have been restricted to therapeutic or prophylactic uses under veterinary prescription and would not have included a growth promotion use.

The sales statistics identified only zinc bacitracin in the 'other' antibiotic group. Industry has advised that a significant amount of carbadox (a quinoxiline antibiotic) was used even though that use was not reflected in the sales statistics. There is no obvious explanation for this

discrepancy. It may be related to the change of ownership of the products during the year, but it may be that the use is subsumed into table 6 statistics. Products containing carbadox are registered with growth promotant claims and are not subject to veterinary prescription. The ACVM Group has not changed the registration conditions for quinoxaline antibiotics because they are not used in human medicines and there was no suspicion from the expert panel or evidence that they could contribute to the antibiotic resistance problem.

The pig producing industry uses a significant amount of ionophores off-label. This means that the level used in cattle is probably overstated because an amount (once again not quantifiable) is used in pigs. However, this use is not significant in regard to antibiotic resistance because ionophores are not used in human medicines and are not known to cause cross-resistance to any antibiotic that is.

The most significant discrepancy between the sales statistics in 2001 and actual use relates to the macrolide family of antibiotics. The registrants for such products reported they did not sell any product for growth promotion during the year. However, there were products in the marketplace during 2001 that were registered for growth promotion use and not subject to veterinary prescription. It can be assumed that the products were used for that purpose. The registrations of those products have since been altered to remove growth promotion as an approved claim and to make them prescription only products. The registrants have been behaving for some time as if the changes have already been made. The pig producing industry has advised that all growth promotion use has stopped from 1 July 2002 and the products are now used only for therapeutic or prophylactic purposes under veterinary prescription.

### 2.2.3 Poultry

**Table 4: 2001 sales of antibiotics for poultry**

	<b>In feed/water (kg of active ingredient)</b>			<b>Other routes (kg active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed conversion</b>			
<b>penicillins</b>	0	10	0	0	<b>10</b>	1.6
<b>cephalosporins</b>	0	0	0	0	<b>0</b>	-
<b>aminoglycosides</b>	0	58	0	0	<b>58</b>	30
<b>macrolides lincosamides</b>	2137	45	0	0	<b>2182</b>	3592
<b>tetracyclines</b>	0	0	0	0	<b>0</b>	-
<b>sulphonamides</b>	0	0	0	0	<b>0</b>	-
<b>ionophores</b>	12011	0	0	0	<b>12011</b>	13373
<b>others</b>	24089	0	0	0	<b>24089</b>	14342

Table 4 shows the sales of antibiotics for use in poultry. No antibiotics were sold specifically for parenteral administration to poultry. There were no antibiotics sold for growth promotion use. There was no marked increase in sales of important human antibiotics for either prophylactic or therapeutic purposes that would indicate a shift from growth promotion. There were minor increases in the sales of aminoglycosides and penicillins for therapeutic purposes but the total amounts were very small (28 and 8.4 kilograms respectively). There was a

marked decrease in the sales of macrolides. There was a decrease in ionophores and a marked increase in the sales of antibiotics in the 'other' category. However, those sales were predominantly zinc bacitracin, which is considered to be of little significance in regard to the potential antibiotic resistance problem. There were also significant sales of avilamycin, which has been assessed to date as not relevant to the potential antibiotic resistance problem. These changes appear to be a reflection of the industry's adjustment in preferred products and treatment regimes in light of the outcome of the antibiotic resistance review. There were no sales of fluoroquinolones or virginiamycin.

Discussion with the Poultry Industry Association of New Zealand indicated that use patterns closely paralleled sales patterns. There was no significant off-label use of antimicrobial products as was identified in the pig producing sector. This was probably due to the fact that there is a sufficient range of products registered specifically for poultry to minimise the need to use products off-label.

#### 2.2.4 Other species

**Table 5: 2001 sales of antibiotics for animals other than poultry, pigs, calves and cattle**

				<b>In feed/water (kg of active ingredient)</b>	<b>Other routes (kg active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed conversion</b>				
<b>penicillins</b>	0	173	0	235	<b>408</b>	265	
<b>cephalosporins</b>	0	0	0	45	<b>45</b>	15	
<b>aminoglycosides</b>	0	0	0	67	<b>67</b>	77	
<b>macrolides lincosamides</b>	0	0	0	33	<b>33</b>	-	
<b>tetracyclines</b>	0	63	0	0	<b>63</b>	42	
<b>sulphonamides</b>	0	70	0	1108	<b>1178</b>	1380	
<b>ionophores</b>	0	0	0	0	<b>0</b>	-	
<b>others</b>	0	0	0	263	<b>263</b>	46	

Table 5 shows the sales of antibiotics for use in animals other than cattle, pigs and poultry. This category includes household pets and other companion animals, aquarium fish and aviary birds. It could also include sheep, goats, camelids, horses, etc.

The food-producing animals included are likely to make up a small proportion of the total sales. When considering the amounts of in-feed/water products sold across all the species, there appears to be virtually no mass medications of food animals.

Most of the antibiotics were sold for parenteral administration. Oral medication would most likely be confined to individual administration rather than in feed or water except for groups of aviary birds or aquarium fish. It is unlikely that any food animals would have been given any feed/water medications.

Penicillins, tetracyclines and sulphonamides were sold as in-feed/water preparations for therapeutic purposes (all under veterinary prescription). No antibiotics were sold for growth

promotion purposes. While there were minor variations (ups and downs) in all the antibiotic families, the only marked changes in sales between 2001 and 2000 were in penicillins and the category of 'other' antibiotics. No conclusion could be drawn to explain the increase in sales of penicillin or if the difference is a trend.

The sales in the 'other' category were made up of 4 kgs of zinc bacitracin, 15 kgs of fluoroquinolones and 221 kg of trimethoprim. Trimethoprim is primarily used to treat dogs. None of the products were for in-feed/water administration. No virginiamycin was sold.

### 2.2.5 Unspecified species

**Table 6: 2001 sales of antibiotics for animal species unspecified**

	<b>In feed/water (kg of active ingredient)</b>			<b>Other routes (kg active ingredient)</b>	<b>Total 2001</b>	<b>Total 2000</b>
<b>Antibiotic group</b>	<b>Prophylactic use</b>	<b>Therapeutic use</b>	<b>Growth/feed conversion</b>			
penicillins	0	0	0	6577	<b>6577</b>	4997
cephalosporins	0	0	0	174	<b>174</b>	150
aminoglycosides	0	46	0	1252	<b>1298</b>	1355
macrolides lincosamides	0	23	0	144	<b>167</b>	243
tetracyclines	0	63	0	2228	<b>2228</b>	957
sulphonamides	0	0	0	3801	<b>3801</b>	3460
ionophores	0	0	0	0	<b>0</b>	-
others	0	0	0	87	<b>314</b>	239

Table 6 shows the sales of antibiotics for unspecified animals. This is composed of the sales of antibiotic products that are registered to be used on a wide range of animals and for multiple purposes. They are administered orally or parenterally but only for therapeutic purposes. There are a few aminoglycoside, macrolide and tetracycline products that could be used in feed/water but the total amounts sold (46, 23 and 63 kgs) were small. There were no antibiotics sold for growth promotion or prophylactic purposes. Some antibiotics could have been used in cattle, pigs, or poultry, raising the actual use figures above the sales figures in earlier tables. However, even if the total amounts of in-feed/water products were used in food animals the statistic would not be altered significantly.

There was a marked increase in the sales of penicillins and tetracyclines. There was a less marked increase in cephalosporins, sulphonamides and others. The 'other' category was made up of sales of fluoroquinolones (1.5 kg), virginiamycin (15 kg), furazolidone (173 kg), dimetridazole (54 kg) and trimethoprim (70 kg). There was a minor decrease in the sales of aminoglycosides and macrolides.

## 2.2.6 Sale of aminoglycosides for use in horticulture

**Table 7: 2001 sales of streptomycin for horticultural use**

<b>Crop</b>	<b>Quantity sold (kg active ingredient)</b>
<b>Pip or stone fruit</b>	374
<b>Seedling tomatoes</b>	17
<b>Total 2001</b>	391

Table 7 shows the sales of streptomycin for use in the horticultural industry to control some bacterial infestations such as fireblight on apples. At the time the antibiotic resistance review was carried out in 1999, it was estimated that 1200 kgs of streptomycin were being used by the horticultural industry. There were no sales statistics requested for 2000.

## 2.2.7 Total antibiotic sales

**Table 8A: Total 2001 sales for all species (kg of active ingredient)\***

Antibiotic group	Cattle	Calves	Pigs	Poultry	Other animals	Cattle, pigs poultry total	Total
Penicillins	6731	0	21	10	408	6762	<b>7170</b>
cephalosporins	660	0	0	0	45	660	<b>705</b>
aminoglycosides	620	33	41	58	67	752	<b>819</b>
macrolides lincosamides	426	0	2475	2182	33	5083	<b>5116</b>
Tetracyclines	467	0	82	0	63	549	<b>612</b>
sulphonamides	117	564	270	0	1178	951	<b>2129</b>
Ionophores	29694	8464	0	12011	0	50169	<b>50169</b>
Others	27	40	280	24089	263	24436	<b>24699</b>

Total 2001	38742	9101	3169	38350	2057	89362	91419
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<b>Total 2000</b>	<b>28527</b>	<b>2605</b>	<b>4702</b>	<b>31339</b>	<b>1825</b>	<b>67218</b>	<b>69043</b>
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\* These statistics do not include the antibiotics that were sold where the use could not be attributed to a specific animal group.

**Table 8B: Total 2001 sales for all species (kg of active ingredient)**

Antibiotic group	Other animals	Cattle, pigs poultry	Total	Unspecified animals	Total 2001	Total 2000
penicillins	408	6762	<b>7170</b>	6577	<b>13747</b>	10423
cephalosporins	45	660	<b>705</b>	174	<b>879</b>	839
aminoglycosides	67	752	<b>819</b>	873	<b>1692</b>	2122
macrolides lincosamides	33	5083	<b>5116</b>	177	<b>5293</b>	6601
tetracyclines	63	549	<b>612</b>	2228	<b>2840</b>	3167
sulphonamides	1178	951	<b>2129</b>	3801	<b>5930</b>	5571
ionophores	0	50169	<b>50169</b>	0	<b>50169</b>	36215
others	263	24436	<b>24699</b>	314	<b>25013</b>	15461

<b>Total 2001</b>	<b>2057</b>	<b>89362</b>	<b>91419</b>	<b>14144</b>	<b>105563</b>	<b>80399</b>
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Tables 8A and 8B are composites of the first 6 tables and look at the totals from different perspectives. For comparison, table 8C shows the sales in 2000.

**Table 8C: Total 2000 sales for all species (kg of active ingredient)**

Antibiotic group	Non-food animals	Food animals	Total	Unspecified animals	Total 2001	Total 2000
penicillins	265	5161	<b>5426</b>	4997	13747	<b>10423</b>
cephalosporins	15	674	<b>689</b>	150	879	<b>839</b>
aminoglycosides	77	690	<b>767</b>	1355	1692	<b>2122</b>
macrolides lincosamides	-	6358	<b>6358</b>	243	5293	<b>6601</b>
tetracyclines	42	2168	<b>2210</b>	957	2840	<b>3167</b>
sulphonamides	1380	731	<b>2111</b>	3460	5930	<b>5571</b>
ionophores	-	36215	<b>36215</b>	-	50169	<b>36215</b>
others	46	15176	<b>15222</b>	239	25013	<b>15461</b>
<b>Totals</b>	<b>1825</b>	<b>67173</b>	<b>68998</b>	<b>11401</b>	105563	<b>80399</b>

The tables show an overall increase in the total sales of antibiotics across all species categories except pigs, which showed a decrease in sales. However, there was a marked decrease in sales of those antibiotics that were assessed as significant for use in humans (i.e. aminoglycosides and macrolides/lincosamides) and that were administered in feed/water. At the same time there was a marked increase in the sales of antibiotics assessed to date as not relevant to the potential antibiotic resistance problem (i.e. ionophores, zinc bacitracin and avilamycin).

There was also a decrease in sales of in-feed/water tetracyclines. There were increases in sales of parenteral penicillins, cephalosporins and sulphonamides.

At the time the antibiotic review was carried out in 1999, the ACVM Group asked for the first time for sales figures. At that point the following totals in kilograms were calculated:

Penicillins	8476
Cephalosporins	763
Aminoglycosides	2207
Macrolides	6082
Tetracyclines	2311
Suphonamides	2066
Ionophores	18032

Amounts were received for other antibiotic families but it is not certain that these combined families would be equivalent to the 'other' category in the present survey, so the totals cannot be compared reliably.

### 2.3 Antibiotic sales survey 2002

Unfortunately, the methodology for collecting and categorising sales information will change again for sales in 2002. The registrations of all prescription antibiotic products will include an obligation to provide an annual report of sales by month. These reports will be used to generate the sales statistics (still based on the family groups in the present survey). A similar reporting obligation will not be placed on over-the-counter antibiotic products (i.e. the ones that do not have a potential to contribute to the antibiotic resistance problem). The registrants will continue to be asked to provide sales statistics voluntarily. The ACVM Group will

discuss the form the obligatory and voluntary reports should take to make the two streams of information as compatible as possible for future use.

It is expected that the reliability of the sales statistics will remain uncertain for at least 12 months after the full effect of the new conditions on registration have been achieved.

### **3 CONSIDERATION OF ANIMAL POPULATIONS AND SURVEILLANCE**

#### **3.1 Livestock population numbers**

**Table 9: Population statistics (millions)**

<b>Species</b>	<b>1998</b>	<b>2000</b>	<b>2001</b>
Dairy cattle	4.4	-	-
Beef cattle	4.2	-	-
Pigs	0.41	0.38*	0.36*
Poultry	63.4	71.2	73.5

\* Total herd size (breeding, weaning and fattening) at any point in time but approximate 0.7 animals slaughtered each year).

There are no statistics on companion animal numbers to indicate a shift in populations that would help to put antibiotic use into better perspective.

Total cattle numbers are uncertain but believed to be increasing. The increase is mainly in dairy cattle. This is a group for which significant antibiotics could be used so increase in antibiotic use in cattle may be partially offset by the increasing size of the national dairy herd.

Because of the extensive farming practices used for beef cattle (as with sheep), use of antibiotics is low and largely restricted to therapeutic use under veterinary prescription. It is reasonably presumed that in beef cattle the use of antibiotics is closely linked to disease prevalence during the year.

Pig numbers have reduced as has the overall use of antibiotics in pigs. Poultry numbers have increased as has the overall use of antibiotics. As could be expected, it would appear that antibiotic use parallels population levels. With the level of uncertainty about the accuracy of the sales statistics, it is not possible to say how closely antibiotic use parallels population changes. There are likely to be other factors equally or more influential.

It would be possible to combine the sales statistics and stock numbers to generate a 'grams per stock unit per year' statistic for each antibiotic family and animal type. However, the ACVM Group sees no value in such a statistic with the inherent uncertainty of the sales statistics. Such a statistic could actually be misleading.

#### **3.2 Surveillance for antibiotic resistance in animals**

In 2000 the Animal Remedies Board recommended that there be a review of the surveillance programme for zoonotic animal pathogens and commensal bacteria that may contribute to the potential antibiotic resistance problem. Initial meetings were held between the Ministry of

Health (MoH) and the MAF to examine existing surveillance programmes and determine what specification should be set for a programme that would provide useful information about the development of antibiotic resistance in animals. It was noted that little surveillance was being carried out that would shed light on the role of animal to human transfer of resistance. While there is extensive microbiological monitoring of specific pathogens in food-producing animals, the programmes are not designed to gather information specific to antibiotic resistance. There is still insufficient justification to modify the monitoring to provide relevant data.

ESR, with cooperation from the previously government-owned veterinary laboratories and the MAF National Centre for Disease Investigation, has carried out an informal monitoring of antimicrobial resistance among animal pathogens (Ref: Surveillance of antimicrobial resistance among animal pathogens in New Zealand, Helen Heffernan, July 2002 ESR). The monitoring has been limited to two pathogens (*E. coli* and *S. aureus*). The samples available to ESR were few and predominantly from clinical cases involving companion animals. ESR has advised the limitations in the results and recommended that the surveillance programme be reviewed and priority areas for surveillance be established.

One study (Dr Gregory M Cook) has isolated a vancomycin-resistant enterococci from poultry in New Zealand treated with avoparcin (an antibiotic which is no longer used in New Zealand). The study also indicated that there may be a close association between resistance genes so that use of another antibiotic may facilitate the retention of resistance to other antibiotics via co-selection rather than actual cross-resistance.

A study on antimicrobial resistance in surface water carried out in Southland (Marc Schallenberg and Amy Krebsbach, Department of Zoology, University of Otago, 2002) indicated that use of antibiotics in livestock may be a cause of resistance developing in bacteria in surface water.

There were also bacterial isolates from miscellaneous samples (Green Party press release).

While these studies add to the overall picture in a fragmented manner, it is considered insufficient definition of the possible role of animals in the transfer of resistance to humans to provide a basis for specifying revised surveillance parameters. It is insufficient justification to institute any changes in the existing surveillance programmes. Nevertheless, discussions between MoH and the ACVM Group are in progress to try to address the surveillance recommendations of the Animal Remedies Board and the Antibiotic Resistance Advisory Group.

## **4 REGULATORY CHANGES**

### **4.1 Progress on review of antibiotic product registrations**

It was intended that the registrations for antibiotic products would be reissued with the conditions designed to manage the antibiotic resistance problem before the commencement of the ACVM (Transitional Provisions) Regulations 2002. In almost all cases this was achieved. However, there were a few products for which the reissuing of registrations has been delayed because of unrelated matters. For example, the registration of some macrolide products has been delayed to resolve a residue issue. This has delayed the removal of the approved growth promotant use and the application of prescription only status. When the registrations of these few products are updated, all antibiotics of significance to the antibiotic resistance problem

will be prescription only. They will also have the appropriate stratified PAR I level applied to facilitate the management of the problem. The effects of the changes should begin to appear in the 2002 statistics.

## **5 OTHER INITIATIVES**

### **5.1 Standard for veterinary prescription writing**

The ACVM Group is considering a code of practice lodged by the New Zealand Veterinary Association for approval under section 28 of the ACVM Act. This will give statutory recognition to standards for veterinary prescription writing that are equivalent to those that must be met by medical practitioners when writing prescriptions. Although the proposed code of practice is not necessarily intended to reduce the use of veterinary antibiotics, it should ensure that they are prescribed in a professional and consistent manner. While the code of practice has not been approved yet, it has already been adopted by the NZVA and incorporated into their members' manual.

### **5.2 Standard for the promotion of prescription animal remedies**

The NZVA, Veterinary Council of New Zealand and the veterinary pharmaceutical industry have endorsed a standard for the promotion of prescription products, including antibiotics. This standard discourages the promotion of products that encourage or put pressure on veterinarians to prescribe antibiotics unnecessarily.

## **6 CONCLUSION**

It must be noted that the collection of the survey information is still undergoing refinement. Recording and reporting information is improving. This means that with only two years' of data over a period of such marked regulatory and industry change, the variations in amounts must be taken as indicative at best. Analysis of the data is also hampered by variations in animal health challenges from one year to the next. It is expected to take a number of years before this compounding factor can be addressed in any meaningful analysis.

It must also be noted that the sales during 2001 were based on the regulatory requirements at the time. The changes in the conditions of registrations that will give effect to:

- the prohibition on using certain antibiotics of concern for growth promotion;
  - the introduction of the stratified prescription animal remedy classification for antibiotics; and
  - the mandatory requirements to provide calendarised annual sales of antibiotics
- have not yet influenced the pattern of sales.

While overall sales of antibiotics increased during 2001, there has been a shift away from the use of antibiotics considered important in human medicines to ones that have been assessed as not relevant to the potential antibiotic resistance problem. There were no sales of antibiotics for growth promotion purposes during the year. Of equal significance, there was not a marked rise in the sale of the relevant antibiotics for prophylactic or therapeutic purposes that would indicate a superficial shift from growth promotion to prophylactic or therapeutic uses as some parties feared.

The regulatory changes have progressed as intended and the effects of the changes should begin to have an impact on use and sales in the near future.

## Appendix 1: Antibiotic PAR Amendment Summary

This document summarises actions taken on specific products additional to those actions arising directly out of the antibiotic resistance review of in-feed antibiotics. These actions are taken as a result of the review and/or as a result of consultation with the Ministry of Health. Products marked \* have been updated to the ACVM Act.

As a direct action arising from the antibiotic resistance review the following occurred:

- Bacitracin:** All products have become Class I Prescription Animal Remedies. All growth promotion claims have been removed. As a result a large number of products have removed bacitracin as an active ingredient. Depending on use situation, additional label advice is required on products as they are updated to the ACVM Act.
- Virginiamycin:** All products have become Class I Prescription Animal Remedies. Additional risk management applied depending on use situation.
- Macrolides:** All products have become Class I Prescription Animal Remedies. Growth promotion claims have been removed. Additional risk management applied depending on use situation.

In addition all antibiotics other than those identified as suitable for over-the-counter (OTC) use by the review are now classified as PAR I. As a result penicillin injectable products previously permitted for OTC sale have had PAR I conditions applied.

The label requirements and conditions of all antibiotics are being reviewed as the licences are updated to ACVM registrations.

### Tylosin

**Tylan Soluble A00086\* Tylan 100 A00080\* Tylan AF 250 A5804\***

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Label statements:

The prophylactic and therapeutic use of this product should be only for the minimum period needed to meet the clinical objective.

Indiscriminate use of this product could contribute to antibiotic resistance. The product should be used only after consideration of the alternative therapeutic and preventative measures.

### Virginiamycin

**STAFAC 500 A02848**

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label requirements:

- Stafac 500 is to be used only where the probability of necrotic enteritis occurring is sufficient to warrant the planned use of virginiamycin in anticipation of an outbreak.
- After each prescription for Stafac 500 the prescribing veterinarian must report the following to the ACVM Group (PO Box 2835, Wellington): quantity prescribed, number of chickens to be treated, length of treatment and location of flock to be treated.
- This product must be used only after appropriate bacteriological and antimicrobial sensitivity investigation has shown other antibiotics to be ineffective.

## **Marbofloxacin**

**Marbocyl 10% - A08161\***    **Marbocyl 2% - A08204\***

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label requirements:

Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.

The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivity tests have shown that it is the only alternative that is likely to be effective.

## **Cefquinome**

**Cobactan 2.5% A08163\***

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label requirements:

Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.

The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivity tests have shown that it is the only alternative that is likely to be effective.

**Cobactan MC A08116\***

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label requirements:

Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.

The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivity tests have shown that it is the only alternative that is likely to be effective.

The prescribing veterinarian must notify the ACVM Group of every case the antibiotic is prescribed, giving date, species prescribed for and condition treated.

## **Enrofloxacin**

### **Baytril Otic A7958**

Relevant conditions:

- Class I Prescription Animal Remedy
- This product must be used only to treat severe refractory cases of otitis externa
- This product must be used only after appropriate bacteriological and antimicrobial sensitivity investigation.

## **Pirlimycin**

### **Pirsue Sterile Solution 007430\***

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label statements:

Indiscriminate use of the product could contribute to the development of antibiotic resistance. The product should be used only in individual cases of serious infections that are not likely to respond to any other antibiotic.

The product must not be used to treat groups of food-producing animals unless bacteriology has confirmed the diagnosis and sensitivity tests have shown that it is the only alternative that is likely to be effective.

## **Zinc Bacitracin**

### **Albac G A6736**

Relevant conditions:

- Class I Prescription Animal Remedy
- An annual report of sales by month must be supplied to the ACVM Group.

Product specific label statements:

Indiscriminate use may increase the risk of the development of antibiotic resistance. Duration of use should be limited to risk periods when possible.

