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Antibiotics Sales Analysis: 2009-2011

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1 Summary

Antibiotic sales data is compiled yearly by the ACVM Group of MPI by active ingredient to monitor for increases and decreases in the sales of those active ingredients significant to human health. The 2009-2011 Antibiotic Sales Analysis evaluated the sales of antibiotics by active ingredient over the nominated period, and is part of a continuous and ongoing monitoring programme. The data were interpreted based on submissions by industry representatives and practicing veterinarians discussing their experiences of antibiotic use in the field. As with previously reports, these data and interpretations will be re-evaluated in a five-year trend analysis spanning from 2009 to 2014 when all the data for that period have been collected and analysed.

The overall use of antibiotics in veterinary medicine and horticulture has decreased 19% within the 2009 to 2011 reporting period. This overall reduction is primarily being driven by positive changes in the management of production animal health. The industries have reported using more non-antibiotic preventative treatments and changes to on-farm practices to decrease their antibiotic use.

When antibiotics are indicated, there appears to be a move towards multi-active therapies and the extension of dosing intervals to reduce the incidence of sub-therapeutic or ineffective use that could lead to the development of antibiotic resistance. These changes are most clearly demonstrated in the pork industry, where vaccination is being more widely used to prevent disease, and in the dairy industry, where teat sealing and dry cow therapies are being used more often in the management of mastitis.

There are some emerging trends evident in the evaluation of the sales data with input from industry and practicing veterinarians on use that have raised some issues. The main trends of interest revealed in this reporting period have been the increased use of injectable tylosin in cattle, the increased use of third and fourth generation cephalosporins in production and companion animals, and the reported marketing of antibiotics based on convenience and the choice of antibiotics on convenience rather than that antibiotic being the most appropriate therapeutic choice. These trends indicate a need to look at controls around the marketing and use of antibiotic trade name products to confirm whether they remain effective in ensuring the risks associated with antibiotic resistance are effectively managed.

2 Introduction

2.1 BACKGROUND

It is generally accepted that antibiotic resistance in human pathogens is primarily due to the use or misuse of antibiotics in the human population. However, use of antibiotics to treat animals and plants entering the human food chain has also been identified as a potential pathway by which humans might be exposed to resistant bacteria or antibiotic resistance determinants of animal origin. Direct contact between humans and farm and/or companion animals treated with antibiotic products may also represent a potential pathway for human exposure to resistant bacteria or resistance determinants.

As part of the management of antibiotic resistance, registrants of Restricted Veterinary Medicines (RVMs) containing antibiotics must provide an annual report of sales by month to MPI as a condition of product registration. These data are then analysed and summarised to monitor sales trends within different industries to approximate usage trends. This report focuses primarily on the sale of antibiotics for use in food-producing animals. However, due to the close association with owners and their pets and the common use of antibiotics in companion animal medicine, sales data for antibiotics used in companion species are also recorded and analysed for the development of trends that may impact human health.

2.2 SALES DATA COLLATED FOR 2009-2011

This report is a summary of the data collected from 1 April 2009 to 31 March 2011. These data, reported as sales per product per month, include all RVM antibiotics and horticultural antibiotic products sold within the nominated period. Sales data and analysis for the period between 2004 and 2009 were summarised in the last sales report, *Antibiotic Sales and Use Overview 2004-2009*, available on the MPI website at http://www.foodsafety.govt.nz/elibrary/industry/antibiotic-sales-2004-2009.pdf.

Sales data for antibiotics that are not managed as RVMs are not collected or included in this report. These antibiotics, including avilamycin, quinoxalines, and ionophores, are not likely to be used in human medicine and as such are not considered of concern to the development of antibiotic resistance. In addition, there is currently no evidence to suggest that these active ingredients can contribute to antibiotic resistance in humans. There is therefore no regulatory requirement to report sales data for products containing these antibiotics.

2.3 LIMITATIONS OF DATA INTERPRETATION

The use of sales data as an indicator of antibiotic use and thereby antibiotic resistance is inherently limited due to a number of variables. The following should be considered when interpreting the sales data:

- While sales can approximate use over the nominated period, actual use can encompass product sold one or two years prior to and following the nominated period. Because veterinarians can authorise antibiotics for immediate use and to be held for future use, the amount of antibiotic sold within the evaluated time period may not be used within that same time period and therefore is not directly representative of the current use patterns. In addition, sales data do not take into consideration the amount of product lost during administration or transport or non-compliance where owners do not administer the full course. This is especially important when reviewing antibiotics used in feed.

- Sales data can only approximate use with respect to approved use patterns and indications. If it is determined that the currently available veterinary medicines will not be adequate to treat a particular animal or species, veterinarians have the authorisation to employ discretionary use for products not limited to "on label" species, use patterns, dose rates and treatment regimes. Because of this, sales of a particular antibiotic cannot accurately predict all uses of that antibiotic in the field.
- Data are only provided for registered veterinary medicines. The requirement to report sales data is a condition of registration applied to those products classed as Restricted Veterinary Medicines. These data therefore do not take into consideration any veterinary use of human preparations or compounded medicines that may be authorised by a veterinarian in specific cases. This is especially important when considering the impact of antibiotic sales on the emergence of resistance because compounded and non-veterinary medicines are often used when either the veterinary antibiotics fail to cure the infection or the veterinarian determines that multi-modal therapy incorporating non-veterinary medicines is indicated.
- Sales data do not give any indication of the fluctuations of animal numbers within the New Zealand herd or the health of individual animals. Increases and decreases of sales can therefore be representative of population changes just as readily as they can be representative of changes in antibiotic use.
- The data provided is reflective of all sales for a particular active as reported by the registrant(s) of product containing that active. As a condition of the registration of each antibiotic trade name product, registrants are required to report sales data. Because products can sometimes be exported for use overseas, a proportion of the reported sales may include product that was sold but not used in New Zealand.

2.4 DATA ANALYSIS AND PRESENTATION

To help mitigate the limitations of the sales data and to allow for more accurate trending and monitoring of the potential for antibiotic resistance, a new approach was taken for review and analysis of the sales data informing this report. A preliminary summary of the trends noted for the 2009-2011 reporting period was compiled and sent to industry representatives and members of the veterinary profession for comment. These groups were asked to review the data in light of known use patterns within their respective industries, and provide insight on any changes in population, management, or disease factors that may affect the final sales.

The interpretations and conclusions identified in this report are therefore the result of the evaluation of the sales data in conjunction with information submitted from industry and practicing veterinarians on the use of antibiotic trade name products in the field. These submissions have allowed for a better understanding of antibiotic use, and how that use may impact antibiotic resistance. This approach will be continued for all subsequent data analyses to provide a closer approximation of sales and use.

The format of this report is similar to previous reports, using charts and tables to evaluate the data. The data is categorised by antibiotic family and active ingredient, species or species group, and administration route.

Species or Species group categories are defined as:

- **Companion –** cats and/or dogs.
- **Cattle –** dairy and/or beef cattle.
- **Horses/Sheep –** Horses and sheep have been identified as their own group in this report, separate from those classed in the "other" category. This is because although there are few

products registered exclusively for horses, the overall antibiotic mass used in this species is twice as large as that used in companion animals and therefore it is considered that horses should be evaluated separate from the "other" category. Sheep have been included here as they are sufficiently important to New Zealand to be recognised outside of the "other" category, but do not have enough species-specific antibiotic products to warrant their own category.

- Pigs/Poultry – pigs and/or chickens, turkeys and game birds. Where possible, particular classes and active ingredients will be discussed as they pertain to either pigs or poultry.
- Multiple Species – all products registered for use in multiple species including companion animals. This category includes products with claims for deer as there are few examples of antibiotics registered with use claims specific to deer.
- Multiple Production Species – all products registered for use in multiple production animal species. This category has been added to gain some understanding of which products are specifically used in food producing species.
- Other – This category currently includes caged birds, pigeons and ornamental fish.
- Plants - Products registered for use on plants are evaluated as a separate category.

Administration Route categories are defined as:

- **Oral** – tablets, capsules, pastes, powders and suspensions for individual dosing.
- **Injectable –** intravenous, subcutaneous and intramuscular preparations for individual dosing.
- **Feed –** in dedicated animal feed for the mass treatment of animals.
- **Water** – in dedicated animal water supply for the mass treatment of animals.
- **Intramammary** – lactating and "dry" cow products administered via the teat canal for individual dosing.
- **Topical –** superficially applied solutions, gels, ointments, creams and aerosols for individual dosing. These products have been identified as a separate administration route due to number of products represented, many of which contain antibiotics of importance such as aminoglycosides.
- **Other** – products for ophthalmic, intra-aural, intrauterine or spray-on (plant) use, or products for which more than one administration route is possible (e.g. oral and intrauterine administration).

The antibiotic sales were reported in units appropriate to each individual product, and converted to weight in kilograms using the active ingredient concentration expressed on the product label. Overages used in manufacturing and non-active salts are not included in the final mass.

3 Sales Trends and Analysis

3.1 OVERALL

Overall antibiotic sales decreased 19% within the reporting period, from 70,343 kilograms in 2009-2010 to 57,043 kilograms in 2010-2011. Despite this overall reduction, however, sales within certain classes of antibiotics considered important to human health including the macrolides/lincosamides, the cephalosporins and the aminoglycosides increased within the reporting period. Because of the limitations of sales data analysis, increased sales are not necessarily indicative of increased use.

In addition, increases in sales of one antibiotic can sometimes be due to a decrease in sales of another antibiotic within the same class or a different class, representing a shift in therapy rather than an overall increase. However, an increase in sales of certain classes can represent a greater availability of those actives for use and thereby a potentially increased risk of the incidence of antibiotic resistance within those classes. This is especially important when the increase in sales is noted for classes considered critical to human health.

Changes in the availability of some products and shifts in favoured therapies can also greatly influence sales. The 2009 veterinary medicine aminoglycosides review resulted in de-registration of a number of intramammary aminoglycoside products, which led to a substantial decrease in the use of aminoglycoside products in the first year of the reporting period.

The development of innovative combinations of active ingredients and longer acting products are often met with a shift in sales towards those types of products; this has been noted within the reporting period with the increased sales of cloxacillin/ampicillin products and a decrease in cloxacillin-only products. And the shifts away from intrauterine antibiotic administration and towards injectable administration of antibiotics in cattle have greatly influenced the sales of the active ingredients used in those types of products.

Of the 15 new registrations of antibiotic products between April 2009 and February 2011, eight contained antibiotics with a high Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) and Expert Advisory Group on Antibiotic Resistance (EAGAR) classification indicating they are very significant to human medicine. It is noted that the technical assessments of these products for registration were undertaken with advice from the Ministry of Health regarding appropriate restrictions on their use and their associated label warnings, and their subsequent approvals were based on scientific evidence that the benefits of the use of the products in veterinary medicine outweighed the associated risks. This includes the risk to public health with respect to antibiotic resistance.

Table 1: Total antibiotic sales by class (in kilograms active ingredient), 2009-2011

Antibiotic Class	2009/10	2010/11	Difference
Zinc Bacitracin	37,125.98	20,476.00	45% decrease
Macrolides/Lincosamides	4,793.61	6,524.07	36% increase
Penicillins	16,521.00	15,682.54	5% decrease
Clavulanic Acid	169.13	192.79	14% increase
Cephalosporins	1,551.22	1,707.30	10% increase
Tetracyclines	4,615.92	6,019.37	30% increase
Sulphonamides/Trimethoprim	4,155.11	4,696.43	13% increase
Aminoglycosides	992.92	1,234.95	24% increase
Fluoroquinolones	37.06	39.67	7% increase
Novobiocin	0	0	Nil
Nitro-imidazoles	57.30	57.24	Nil
Nitrofurans	4.34	0.89	80% decrease
Virginiamycin	12.45	11.38	9% decrease
Fusidic Acid	1.58	0.85	46% decrease
Other	347.72	399.25	15% increase
Total	70,340.04	57,042.73	19% decrease

3.2 VARIATIONS IN PRODUCTION ANIMAL POPULATIONS

The total number of beef cattle in the New Zealand herd decreased over the reporting period, with the 2010/11 herd size (3.95 million) being smaller than it has been since 2000/01 (4.3 million). The average herd size between 2000 and 2010 has been 4.4 million cattle; the herd size in 2009/10 was 4.1 million cattle. Sheep numbers are steady but have also decreased to below the 10-year average of 34.6 million animals: 32.4 million animals were reported for 2009/10 and 32.6 million animals were reported for 2010/11. It was noted that during the reporting period, prices paid for beef and lamb stock were low, leading to a reduction in "non-essential" veterinary intervention and thereby lower sales of products for use in these industries. There were no reported changes in disease challenges or management practices that may impact antibiotic use.

The national pig breeding herd has been in decline since 2002, though total animal numbers were static through the reporting period. The industry has reported an increased use of vaccination in growing pigs against certain diseases like bacterial ileitis which have historically been managed with antibiotic therapy. This allows for the reduction of antibiotic use in young animals. There is still an approximated 1.8% incidence of bacterial arthritis being recognised in animals at abattoirs, with a suggested cause of *Mycoplasma hyosynoviae* on some farms. This incidence has not changed from previous reporting periods.

The New Zealand poultry flock size increased from 83 million to 89 million through the reporting period, with an increasing percentage of birds being farmed free range. The percentage of free range farms has been slowly building from 1-2% to 4-5% through the reporting period. This has a direct impact on the sales of zinc bacitracin, the most commonly used antibiotic in this industry, as free range farms do not administer zinc bacitracin (although other antibiotics may be used when therapeutically indicated). Overall, the industry reports that disease challenges have not changed.

Horse ownership has decreased slightly since the last reporting period, with a 5% decrease in the number of mares being bred and a static to slight decrease in race horse ownership. The industry reports, however, that the pleasure horse population remains relatively static. Disease incidence has not significantly changed through the reporting period.

During the reporting period, the number of dairy herds were stable at 11,691 (2009/10) and 11,735 (2010/11). However, total cow numbers have been steadily climbing since 2001/02 to a high of 4.5 million animals at the end of the reporting period. This increase in animal numbers despite the stable numbers of herds is inevitably leading to increased herd sizes, up to an average of 386 animals per herd in 2010/11. Despite the increasing herd sizes the average cows per hectare have remained the same, indicating that farms are also getting larger to accommodate the larger herds.

This growth has led to changes in farming practices to manage the larger farms, an increase in the number of animals being milked, the need for the prevention of cross-contamination and diseases related to crowding, and a decrease in time available to carry out treatment regimes and individual animal assessments. Dairy farmers are using moredry cow therapy intramammary products in cows and teat sealants in cows and heifers as part of their mastitis management strategies, influencing sales of intramammary treatments. In addition, there is a shift toward injectable products to help decrease the treatment times needed per animal when antibiotics are necessary, and to reduce the expertise needed to use treatment modalities like intramammary products effectively and appropriately as more unskilled labour is utilised on farm.

3.3 SALES ANALYSIS BY ANTIBIOTIC CLASS

3.3.1 Zinc Bacitracin

Zinc bacitracin continues to be the largest selling antibiotic active ingredient, comprising 52% (2009/10) and 36% (2010/11) of total antibiotic sales, and 85% (2009/10) and 69% (2010/11) of all medications administered by feed and/or water. When the two years within the reporting period are reviewed by themselves, it appears that sales of this active ingredient have decreased by 45% between 2009/10 and 2010/11.

However, according to the sales reported between 2004 and 2009, the average sales of zinc bacitracin in pigs and poultry (sales of this active for use in other species are negligible) were 22,176kg per year. The 2009/10 sales of zinc bacitracin, reported at 37,126 kg, therefore represents an increase in sales for that year rather than a significant decrease of sales within the reporting period. When viewed in light of the previous average, the 2010/11 sales total represents a decrease of approximately 8% below the five year average.

It was noted in the last report that the use of zinc bacitracin was predominately in the poultry industry, with the pork industry estimating that less than 5% of sales are used in pigs. This is still the case, with use of zinc bacitracin in the pig industry being reported as “minimal.” The size of the national poultry flock increased from 83 million to 89 million through the reporting period, although a greater proportion of poultry are being farmed free range where zinc bacitracin is not used.

Between 2009 and 2011, the proportion of the national flock being farmed as free range was estimated at up to 5%, continuing to increase rapidly in the years since this reporting period. It can therefore be concluded that the sale and use of zinc bacitracin overall is actually decreasing, primarily due to changes in husbandry practices in the poultry industry, and that the approximated 8% decrease from the average sales appears to be a more accurate representation of the sales of this active than the 45% decrease indicated in the data. The 2009/10 “spike” in sales was investigated with the industries and registrants involved to determine the reason for the sudden increase. From the information provided, it was determined that the increase was due to a change in the commercial availability of a supply of zinc bacitracin, leading to the stockpiling of product for future use.

These excess sales were subsequently countered by a decrease in sales in the first half of 2011 while farms used the zinc bacitracin they already had on hand. This increase in sales is therefore not directly correlated to an increased in use of zinc bacitracin within the reporting year, but is due to fluctuations in disease incidence and the demand for readily available product.

3.3.2 Macrolides/Lincosamides

The sales of antibiotics in this class have increased 36% within the reporting period, from 4,794kg in 2009/10 to 6,524kg in 2010/11. Like zinc bacitracin, however, it appears from the data that the 36% increase evident between the 2009/10 and 2010/11 reporting years is actually an exaggeration of the overall trend in macrolide sales: sales in this class have historically been reported at an average of 5,351kg per year between 2004 and 2009, indicating that the 2009/10 total actually represents a decrease in sales for that year. While the increase is still substantial within the reporting period, the 2010/11 sales represent a less dramatic 22% increase above the average sales for this class.

The majority of sales within this class can be attributed to the active ingredient tylosin, used in the pig and poultry industries primarily in feed or water, and in the production animal industries primarily in injectable products. In-feed and in-water tylosin sales for use in the pig and poultry industries have increased by 118%. Pig industry representatives report a small percentage of pigs presenting at abattoirs noted to be affected with arthritis. The suggested cause, infection with *mycoplasma hyosynoviae*, would require treatment with macrolides such as tylosin or tiamulin. They did note, however, that the disease prevalence is similar to previous years and is not increasing so there was no real change in overall macrolide use in the management of this disease. It was also noted that there was a decline in the use of some antibiotics including tylosin in growing pigs due to the shift within industry from reactive antibiotic treatment to proactive vaccination.

Poultry industry representatives have reported a small increase in macrolide use in poultry flocks but it is not significant enough to drive the increased sales indicated by the data. Based on the information received from industry, it is expected that the sales of tylosin are a reflection of forecasting and purchases in anticipation of use rather than an indicator of the actual use of this antibiotic on farm. Like zinc bacitracin, the supposed increase in in-feed and in-water tylosin sales within the reporting period does not correlate to the reported use of the active in the field, making overall trending over time the better indicator of use. The sales of in-feed and in-water tylosin will be monitored in subsequent reports to determine if it corresponds to a genuine increase in macrolide use.

Tylosin sales in products approved for use in multiple production animal species have also increased 26% within the reporting period, with injectable products specifically increasing by 14%. The multiple species oral products are approved for use in pigs, chicken and beef cattle, making the interpretation of the increase in sales difficult due to the propensity for purchasing product in anticipation of use to manage disease outbreaks and the problems correlating that to use. This is especially relevant as the pig and poultry industries have reported minor changes in tylosin use within the reporting period and the beef cattle industry reported that tylosin is not widely used in New Zealand beef cattle.

However, the increase in sales of multiple species injectable products represents an actual increasing trend in tylosin use: veterinarians within the dairy industry report a growing and “significant” use of injectable tylosin in dairy cattle for the treatment of mastitis. It is reported that this increased use of tylosin is often because of its convenience as a once-daily injectable treatment, and not because tylosin is the most appropriate therapeutic choice.

Tylosin is classed by JETACAR as a Category C antibiotic, which means there are a reasonable number of alternative agents in different classes available to treat most infections. In the 2005 Expert Panel Review, it is noted that the Ministry of Health preferred the use of tylosin was reserved for the treatment of significant infections insensitive or unresponsive to other antibiotics due to the potential for tylosin to confer cross-resistance to other macrolides, lincosamides and streptogramins, and the importance of the macrolide group to human medicine. The use of tylosin as a convenience drug is therefore unacceptable and may require review of the approved uses of injectable tylosin products.

With the exception of tilmicosin sales for use in pigs, which have decreased 20%, and the nil sales reported for pirlimycin and erythromycin, the sales of all other antibiotics in this class have also increased within the reporting period. However, the combined total kilograms sold of all seven antibiotics in this class other than tylosin are 7% and 6% of the total macrolide/lincosamide sales in 2009/10 and 2010/11, respectively. Though these sales are not insignificant, the greatest risk to antibiotic resistance continues to be the sales and use of tylosin within the production animal industries.

3.3.3 Penicillins

Sales of penicillins appear to be relatively stable, with average sales of 15,071 kilograms per year in 2004 to 2009, and sales of 16,521 kilograms reported in 2009-2010 and 15,683 kilograms in 2010-2011.

Amoxycillin sales have decreased 24% during the reporting period, primarily due to a significant decline in the sales of amoxicillin for use in production animals: sales of cattle-only products have decreased by 79% as a result of decreased sales of injectable products, and pig and poultry products have decreased to nil. Sales of companion animal and multiple- species amoxycillin-based products have increased 14% and 12% respectively over the reporting period despite the overall decrease. These changes are likely to be the result of shifting therapy from one antibiotic to another or from one class to another rather than true changes in use patterns for this active ingredient.

All antibiotics containing clavulanic acid are amoxycillin-based products. These are mostly oral companion animal products, but also include multiple-species injectable products, multiple-species oral products, and intramammary preparations. Clavulanic acid sales have increased 14% within the reporting period, with the most significant increases attributable to the sales of oral products for use in dogs, cats, and calves. This correlates to the increases noted in amoxycillin sales for companion animal and multiple-species products.

Overall cloxacillin sales have also decreased 14%, apparently due to a decrease in sales of lactating cow intramammary preparations. However, it is evident from the sales of different types of cloxacillin products that there is a shift from single-active cloxacillin products to dual-active products containing cloxacillin and other actives. This is most clearly demonstrated when concurrently evaluating the 16% increase in the sales of ampicillin-based products, all of which are ampicillin/cloxacillin combinations and most of which are dry cow intramammary preparations.

Dairy cattle veterinarians have reported an increased use of dry (non-lactating) cow therapy in general, specifically noting an increased use of cloxacillin products to achieve longer treatment periods and thereby reduce the use of shorter, less effective courses and repeat treatments that pose a greater risk of antibiotic resistance. This change in dairy cattle management, although increasing sales and use of cloxacillin, is a positive change in the use of antibiotic such that the overall risk of antibiotic resistance associated with intramammary dry cow preparations can more appropriately managed.

There was a 3% net increase in the sales of products containing penicillin G procaine, with a 34% decrease in sales of the intramammary products and a 10% increase in injectable products. Based on comments from industry and veterinarians, it can be concluded that this trend towards injectable products can be attributed at least in part to farmers wanting to use injectable products rather than intramammary products as a more convenient means of treating mastitis within the herd. Sales of products containing penicillin G benzathine and penethamate hydriodide have remained stable through the reporting period. Sales of products containing penicillin G potassium, which are injectable products approved for use in production animals, have decreased 90% through the reporting period.

All registered products containing penicillin G potassium are injectables for use in production animals with 30 or 91 day meat withholding periods. Based on the information provided from veterinarians, it is expected that the decrease in sales of penicillin G potassium products is related to the use of other injectable antibiotics with much shorter withholding periods in this and other classes that have similar claims and indications. Sales of products containing nafcillin have decreased to nil as this active was included only in aminoglycoside/penicillin intramammary products which were de-registered after the 2009 veterinary medicines aminoglycoside review.

3.3.4 Cephalosporins

The overall sales of cephalosporin-based products have increased 10%, a relatively small increase compared to some of the other antibiotic classes. However, given the importance of the class to human medicine, the trends noted in the sales data with respect to third and fourth generation cephalosporins and practicing veterinarians' comments on use indicate that there are potential issues with the sales of products within this class.

Cephalosporins are generally categorised in two groups, with the first and second generation cephalosporins attracting a JETACAR classification of Category B drugs, and third and fourth generation cephalosporins classed as Category A drugs. Classification as a Category B drug means that the drugs are important to human medicine but there are other alternatives available, or there are concerns that use will lead to a greater risk of resistance in Category A drugs. Category A drugs are considered essential for the treatment of human infections where there are few or no alternative treatments. These classifications mean that all cephalosporins are important to human medicine, though third and fourth generation cephalosporins are considered critical and therefore should be reserved for use only when absolutely necessary.

The 2005 Expert Panel stated that first and second generation cephalosporins should be used based on bacterial identification and testing to determine the most appropriate therapeutic treatment (bacterial culture and sensitivity testing), and third and fourth generation cephalosporins should be available for use only in life-threatening conditions in individual animals where bacterial culture and sensitivity testing "provides evidence of their unique clinical value". The Panel also recommended that the registration of third and fourth generation cephalosporins for intramammary use should be reconsidered because of their importance to human medicine.

When sales are evaluated by active ingredient, some striking patterns begin to emerge. Sales of all first generation cephalosporins are declining, while sales of second, third, and fourth generation cephalosporins are all increasing. Third generation cephalosporin sales are increasing particularly quickly, with sales of the active ingredient ceftiofur increasing 118% within the reporting period.

Although presenting as an overall decrease, cephapirin sales are actually divided with a 49% increase in intramammary product sales and a 55% decrease in intrauterine product sales. The decrease is more likely to be contributed to a shift away from the use of intrauterine treatments rather than a decreased use of the active ingredient itself. Sales of cephalexin based products are also divided despite an overall net decrease: sales of companion animal products have decreased 10% and intramammary products have decreased 21%, but sales of injectable cephalexin products have increased 66% during the reporting period. The sales of all ceftiofur products have increased dramatically between 6% and more than 300%. It is noted that all third and fourth generation cephalosporins bear a prudent use statement on their product labels advising end users to only use these products when absolutely necessary and after using culture and sensitivity to ensure the most appropriate antibiotic is administered.

Table 2: Changes in cephalosporin sales by active ingredient, 2009-2011

Family	Active Ingredient	Percent Change	Primary Use and Route(s)
FIRST GENERATION	Cephapirin	25% decrease	Cattle intramammary and intrauterine therapy
	Cephalexin	5% decrease	Companion animal oral; multiple species injectable; lactating cow
			intramammary
	Cephalonium	3% decrease	Dry cow intramammary
SECOND GENERATION	Cefuroxime	20% increase	Lactating cow intramammary
THIRD GENERATION	Cefovecin	26% increase	Companion animal injectable
	Ceftiofur	118% increase	Production animal injectable (horses, cattle and pigs)
	Cefpodoxime	100% increase (product was not available until 2010/11)	Companion animal oral
FOURTH GENERATION	Cefquinome	13% increase	Production animal injectable (cattle and swine); lactating cow intramammary

While it is generally considered that the risk of antibiotic resistance is lower with respect to companion animals when compared to production animals, this increase in the use of third and fourth generation cephalosporins could result in significant exposure and the development of antibiotic resistance long term.

Companion animal veterinarians identified an issue with the increased use of later generation cephalosporins, and substitution of first and second generation cephalosporins with third and fourth generation actives where use of an older active would have been an appropriate treatment. The veterinarians consulted cited marketing on the basis of "convenience, customer compliance, and simplicity" as the primary reasons for choosing the later generation cephalosporins instead of other active ingredients. This is especially important given a recent paper on the incidence of antibiotic resistant bacteria in companion animals in New Zealand, indicating an emerging issue of resistance in animal pathogens and the potential for the transfer of resistant bacteria or resistance determinants to humans from companion animal sources.

Dairy cattle veterinarians identified a similar trend, stating that the increased use of ceftiofur is likely to be related to both ease of use and the financial incentive of using a product with a shorter withholding period. The veterinarians report that with more intensive farming practices becoming more prevalent in New Zealand, and growing farms having less time and fewer skilled labourers available for individual animal management, longer acting injectable products are becoming the preferred method of treatment for infectious disease. This, compounded by short withholding times for these actives and direct marketing to farmers based on convenience, has driven a demand for veterinarians to supply more antibiotics critical to human health despite the presence of prudent use warnings. It is noted, however, that dairy veterinarians reported that the increased use of cefquinome, the only fourth generation cephalosporin used in veterinary medicine, is more likely to be related to the development of a greater incidence of coliform mastitis during the reporting period and the need for aggressive therapy with cefquinome to treat infection.

Based on the trends noted in the sales data and the feedback from industry, a review of the use of cephalosporins in companion animal and dairy medicine appears to be necessary to determine the best way forward. It is important to retain the availability of the cephalosporins to veterinary medicine as there is a real need to have these treatment options available. This is most clearly evident in the need for cefquinome to combat the increasing incidence of coliform mastitis. However, given the importance of this class to human health, especially with respect to third and fourth generation cephalosporins, more restrictive controls in accordance with Ministry of Health and Expert Panel recommendations may be required to ensure their continued availability for serious and life-threatening veterinary diseases.

3.3.5 Tetracyclines

The sales of tetracycline-containing products have increased 30% between 2009 and 2011. Prior to this reporting period, tetracycline sales averaged 4,301 kilograms per year; the 2009/10 sales totalled 4,616 kilograms, with an increase to 6,019 kilograms in 2010/11. Increases in sales are noted across nearly all administration routes within the reporting period, most notably for the in-water (58%), injectable (32%) and in-feed (19%) preparations. Oxytetracycline-containing products dominated the sales within this class, with the active accounting for 76% of 2009/10 sales and 69% of 2010/11 sales. Sales of oxytetracycline have increased 71.5% within the reporting period, with the most significant increase being in injectable (33%) and in-water (43%) products. These types of products are indicated for use in pigs, poultry, horses, cattle and companion animals, with a small mass being sold for use in caged birds and pigeons. It is noted however that the in-water use of tetracyclines is uncommon in the poultry industry as treatment is difficult to manage. As with tylosin, the pig industry has reported that the use of tetracyclines in grower pigs has declined due to increased use of vaccination. Some in-water tetracycline products are indicated for use in calves, and therefore some of the increase in sales may have been due to the salmonellosis outbreaks in 2010-2011.

Similarly, equine veterinarians report a low but persistent incidence of *Lawsonia* infections in weanling foals for which in-water and injectable products are indicated, though they note there is no evidence of tetracycline resistance in equine medicine to date. The poultry industry has reported no increase in industry usage to date, although there could be an increase in sales and use noted with changes in farming practices.

The increase in injectable oxytetracycline has been attributed to a number of different causes, including the treatment of diseases like salmonellosis and *Lawsonia* infections when in-water administration is not practical, the use of oxytetracycline in horses where trimethoprim/sulfa products are not effective, a preference for oxytetracycline instead of penicillin G procaine in performance horses due to procaine being a prohibited substance in racing, and an increasing propensity towards parenteral antibiotic treatment in cattle.

However, industry representatives and veterinarians have indicated that, like tylosin, some of the increasing sales and use of injectable oxytetracycline can be attributed to the convenience of its use rather than by the determination of the active as the best treatment choice. This is especially significant for long-acting injectable oxytetracycline products for use in dairy cattle. A review of the approved use patterns of these products may also be required if the issue of use for convenience rather than therapeutic indication continues to be reported.

Sales of chlortetracycline, indicated for use in pigs and poultry though reportedly not used in the poultry industry, have increased 73% despite reports from these industries that the use of tetracyclines is either similar or decreased. Given this, and the fact that all chlortetracycline sales are for in-feed products, it is likely that this apparent increase is once again due at least in part to the variability in correlating in-feed product sales and their use. It was noted in the 2004-2009 Antibiotic Sales and Use Overview that pig and poultry producers reported greater tetracycline use to meet prescribed therapeutic levels for diseases managed by in-feed formulations such as mycoplasma arthritis and pleuropneumonia. The increase noted in the 2009 to 2011 reporting period may therefore also represent the continuation of that change in practice, as well as the purchase of a greater amount of product with the expectation that the use of in-feed tetracyclines would continue to increase.

Doxycycline sales have decreased 9% across all products, including those approved for use in cattle, birds and companion animals. Sales of the active ingredient tetracycline have also decreased to nil within the reporting period with the withdrawal of products containing that active.

3.3.6 Sulphonamides

Sulphonamide product sales have historically been very stable, with the 2004 to 2009 sales averaging 4,995 kilograms per year. The sales reported in the 2009/10 reporting year decreased 17% from this average, and then increased 13% to a total sale of 4,696 kilograms in 2010/11. The only notable increase within this class is for the injectable products, which increased in sales by 155% within the reporting period. This increase has been noted by veterinarians and industry, citing the use of sulphonamides in the equine industry as an alternative to antibiotics with longer withholding periods, in the dairy industry for the management of salmonellosis outbreaks within the reporting period, and overall due to preference for the use of injectable products over other administration methods.

Overall sales within this class are relatively small and appear to be stable and consistent with the average over time. Because of this, and because sulphonamides are generally considered to be of low concern to public health, it is not expected that this trend will result in an increased risk of antibiotic resistance. The sales of injectable sulphonamides will

continue to be noted in subsequent sales analyses to determine if further investigation is required.
The increase in sales of oral formulations within this class is similar across all registered products, indicating that this increase is most likely associated with variations in product availability and seasonality rather than any significant changes in use. As previously reported, sales of sulphonamide based products are approximately divided equally between oral products registered for use in horses and oral "scour" products used primarily in calves, with a small proportion of products indicted for oral and intrauterine use in production animals.

3.3.7 Aminoglycosides

The ACVM Veterinary Medicines Aminoglycosides Review was completed during the 2009/10 reporting year, with the report finalised and recommendations actioned in August of 2009. The review was performed in response to the recommendations of the Expert Panel and on the advice of the Antimicrobial Resistance Steering Group, and evaluated all aminoglycoside products to ensure claims and indications were in accordance with the Panel's recommendations and continued use was justified. The decrease in aminoglycoside sales in 2009/10 was due to a number of products being de-registered and phased out of the market as a result of that review.

Since then, however, the overall sales of aminoglycosides have returned to near pre-review levels. The average sales for aminoglycoside during the 2004-2009 reporting interval were 1,540 kilograms per year, with the 2007/8 total reported at 1,253 kilograms and the 2008/9 total reported at 1,217 kilograms. After an 18.5% decrease in sales in the 2009/10 review year to 993 kilograms, sales increased 24% to 1,235 kilograms in 2010/11. The 2010/11 increase in sales occurred despite de-registration of seven products within this class. This indicates that while fewer products are available on the New Zealand market, sales may be shifting to other aminoglycoside products rather than seeking alternative treatments. It is noted that injectable and topical (including intra-aural) products were not included in the review except for injectable combinations of aminoglycosides with β lactam antimicrobials.

One of the active ingredients to be significantly affected by the review was dihydrostreptomycin. Seven products containing this active were registered in 2009/10 with all but one of the injectable products de-registered by 2010/11. One of the intramammary products and one of the injectable products cancelled in 2009 as a result of the review still reported a very small amount of sales for 2010/11 due to the one year sales grace period allowed after cancellation. This grace period ended in August of 2010. As would be expected, overall reported sales of dihydrostreptomycin products decreased significantly (41%) through the reporting period, with the one remaining injectable product (a dihydrostreptomycin/streptomycin product) reporting an increase in sales of 34%. This increase would be the result of being the only remaining dihydrostreptomycin product still available for use in production animals.
Gentamycin sales decreased 45% within the reporting period. The majority of sales of this active ingredient are from three injectable products for use in multiple species, and one companion animal product contributing a very small portion of the overall total. One of the injectable gentamycin products reported a 37% increase in sales, but was coupled with significant decreases in sales for the other products resulting in a net decrease of gentamycin sales. Again, the increase sales for this product are likely to be due to limited availability of aminoglycoside based alternatives in general, and gentamycin based products specifically.

This trend of a decrease in the sales of production animal products is also reflected in other aminoglycoside active ingredients. Sales of framycetin reduced significantly due to de-registration of the intramammary framycetin product as part of the review; companion animal framycetin product sales remained unchanged. Sales of apramycin-containing products, which are used exclusively in the pig and poultry industries, declined 33% in the reporting period. And sales of spectinomycin, indicated for use in pigs, poultry, and sheep for the treatment of respiratory and gastrointestinal disease, remained constant despite reports of steady pig and sheep populations and no use of this active in the poultry industry.

Sales of the active ingredient neomycin however have gone against this trend, increasing 36% overall. This increase is mostly due to increased sales of oral products (53% increase) for multiple species and intramammary products (15% increase). The increased sales of these products are likely to be due at least in part to the decreased availability or de- registration of other aminoglycoside products indicated for the same uses in the same species: other neomycin/streptomycin-containing oral products for use in multiple species, and all other aminoglycoside-containing intramammary products were cancelled post-review. Dairy cattle veterinarians also report an increase in the use of neomycin-containing products as a result of the use of oxytetracycline/neomycin combination products.

The sales of streptomycin-containing veterinary medicines have also increased during the reporting period, with a 34% increase of injectable products and a 24% increase of oral products. Different streptomycin-containing products are indicated for use in cats, dogs and all non-poultry production animals. The increase in sales of injectable products is due to increased sales of the dual active streptomycin/dihydrostreptomycin product, and is likely to be related to the use of this product for the treatment of infections for which dihydrostreptomycin is indicated after the de- registration of the other products containing that active. Likewise, the increase in the oral product’s sales is likely due to withdrawal of other aminoglycoside products indicated for the same use.

Streptomycin is also the only antibiotic currently approved for use in horticulture, and sales are monitored and reported for that use as they are for veterinary medicines. Throughout the 2009 to 2011 reporting period, horticultural streptomycin sales increased 14.6%, contributing to the overall increase in aminoglycoside sales. This increase is similar to fluctuations of sales in previous years, attributable to the natural variation in disease incidence and environmental changes. Horticultural industry representatives reported no significant changes or disease challenges during the reporting period.

Because of the fluctuations in product availability and sales seen in this class as a result of the 2008 horticultural aminoglycosides review and the 2009 veterinary medicine aminoglycosides review, it is difficult to determine the significance of sales data for this class at this stage. Future reviews will be more informative about the impact these reviews may have had on the use of aminoglycosides and the aminoglycoside-related risk of antibiotic resistance.

3.3.8 Fluoroquinolones

Between 2009 and 2011, sales of products containing fluoroquinolones increased 7%. Although this is a relatively small increase compared to some of the other classes, there were some notable changes occurring that could impact future sales and use. Four new products were introduced during this period, three companion animal products and one cattle product, which may result in an increase in fluoroquinolone sales after 2011. As has historically been the case, most of the products registered in this class are companion animal products with only five products approved for use in either production animals or cattle only. When viewed by target species, it is noted that there was a 1.7% decrease in companion animal fluoroquinolone sales despite the introduction of three new products, two of which reported sales within the period. However, companion animal veterinarians have noted that fluoroquinolone use still remains too high for a class with such importance to human medicine, stating that fluoroquinolones are used in practice when actives with lower EAGAR ratings would suffice. The veterinarians cite ease and/or convenience in dosing, and the marketing of products as such despite the requirement for prudent use, as the primary drivers of a fluoroquinolone preference.

Sales of fluoroquinolones for use in cattle and swine have increased 13%, for both enrofloxacin and marbofloxacin injectable products. Dairy veterinarians have identified fluoroquinolones as another class of antibiotics that is being used more for convenience of use and, like the companion animal products, are being marketed as such.

Equine veterinarians have also reported an increased use of fluoroquinolones, specifically the use of intravenous marbofloxacin for conditions not responsive to other antibiotics. As none of the fluoroquinolone injectable products are approved for use in horses, this represents a potential significant cause of increased sales that would not otherwise have been identified. Although it is not clear from the comments provided whether this use is following bacterial culture and sensitivity testing to determine the most appropriate treatment or following the failure of other treatments (and thereby signalling potential resistance), it has been indicated that these products are not being used as first-choice treatments and therefore it can be assumed that a degree of prudent use is being employed.

Use of these products in both companion and production species is still limited to the management of disease in individual animals by oral or injectable administration and products all bear specific label statements regarding antibiotic resistance. The off-label use of the products in equine medicine is subject to the discretion of the veterinarian managing the case, and would still be limited to the treatment of individual animals. None of the injectable fluoroquinolones are restricted to on-label use.

3.3.9 Nitro-imidazoles

Nitro-imidazole product sales remain unchanged over the reporting period with an overall decrease in sales of 0.1%, easily attributable to fluctuations in sales from year to year. Products in this class are approved for use in pigs and poultry, pigeons and companion animals, and sales of these products have remained consistent over the last six years.

3.3.10 Nitrofurans

There are two nitrofuran active ingredients used in veterinary medicine: nitrofurazone and furazolidone. Overall sales within this class have decreased 80% since 2009 due to decreased sales of both nitrofurazone (55% decrease) and furazolidone (99% decrease). Sales of the two largest selling products, one for use in pigs and poultry and one for use in aquarium fish, have markedly reduced during the reporting period. These decreases can account for the entire decrease in the class, with the decreased use of furazolidone in pigs and poultry and the temporary withdrawal of the aquarium product from the market. Sales of the remaining products in this class were stable throughout the reporting period.

3.3.11 Virginiamycin

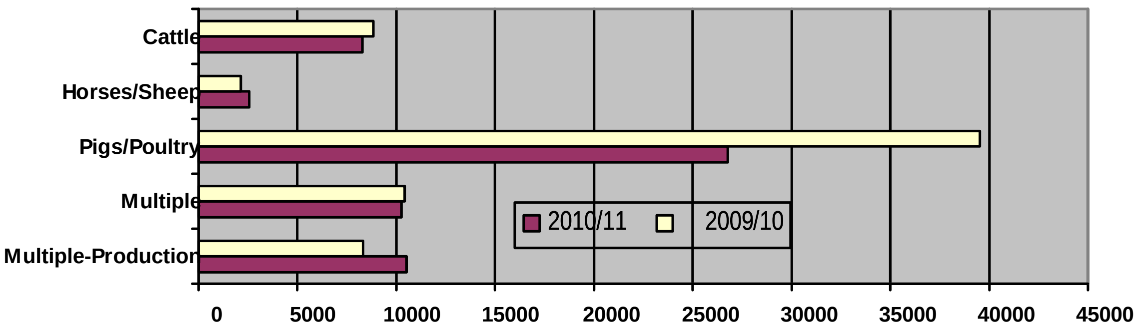
Virginiamycin is not commonly used in veterinary medicine. There are currently only two registered veterinary products in New Zealand, with the sales within this class attributed to the use of virginiamycin in horses. The sales trend within this reporting period is consistent with that of the last report, with a 9% decrease between 2009 and 2011. Equine veterinarians report that virginiamycin use has remained consistently low due to the use of more non-antibiotic therapeutic management strategies for laminitis, and the use of other antibiotic classes in the treatment of diseases previously treated with virginiamycin.

3.3.12 Other

This category contains antimicrobials that cannot be attributed to any other large class, such as carbadox, florfenicol and polymyxin. Sales within this category have increased 15% through the reporting period due to a 15% increase in the sales of the active ingredient carbadox and a 40% increase in the sales of florfenicol. Carbadox is used in-feed for the treatment of salmonellosis, diarrhoea, and gastrointestinal parasites in pigs. As with other antibiotics administered in feed, the increase in sales may be more related to the bulk purchase and storage of in-feed medications in anticipation of use rather than an actual increase in use considering the pig industry have reported no real change in disease prevalence.

Florfenicol is used in production animals primarily for the treatment of respiratory infections in young cattle. While considered by JETACAR to be a Category B antimicrobial, florfenicol is not used in human medicine and has attracted a low EAGAR rating with respect to the risk of antibiotic resistance. It is also noted that all sales within this class accounted for only 0.7% of all antibiotic sales in the 2010/11 reporting year. Sales of other products with active ingredients in this class have remained constant throughout the reporting period.

Figure 1: Total antibiotic sales by species (in kilograms), 2009-2011



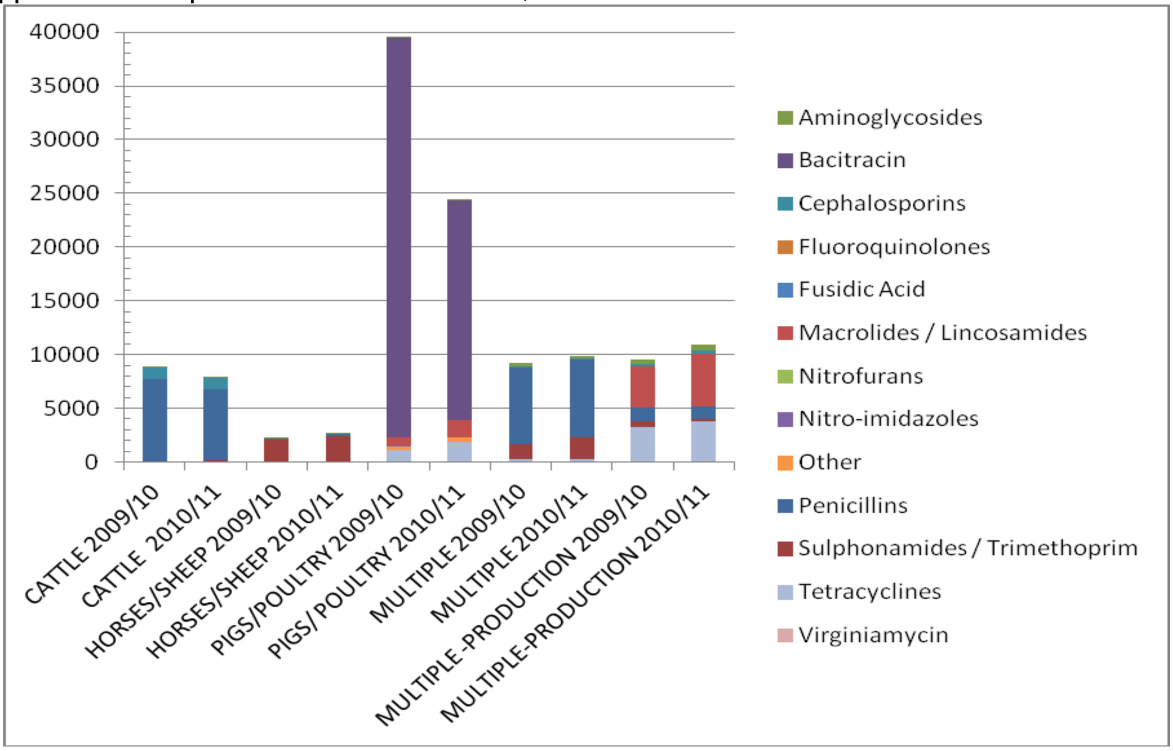
3.4 SALES ANALYSIS BY ANIMAL SPECIES

3.4.1 Use of Antibiotics in Food-Producing Industries

The pig, poultry and dairy industries use the most significant mass of antibiotics in New Zealand, with the majority of those antibiotics being administered to pigs and poultry in feed and/or water. The primary use of antibiotics in the New Zealand dairy industry is by intramammary and injectable antibiotic administration, with the greatest proportion of that use being attributed to intramammary administration of mostly penicillins. As previously noted in other reports, industry regulation of the quality and processing protocols for raw milk mitigate against the potential transfer of resistant bacteria or resistance determinants.

The apparent decrease in the sales of antibiotics in pigs and poultry is partly driven by the decrease in zinc bacitracin sales. As previously identified in the class-specific discussion, a decrease in sales within this group has occurred but the difference is exaggerated due to the over-purchase of zinc bacitracin products in the 2009/10 reporting year. Sales of cattle-only products have most likely been impacted by the reported shift to using injectable products, which are most often approved for multiple production animal species or large and small animal species (multiple). Sales within this group have also been impacted by the de-registration of aminoglycoside-based antibiotics, many of which were intramammary products.

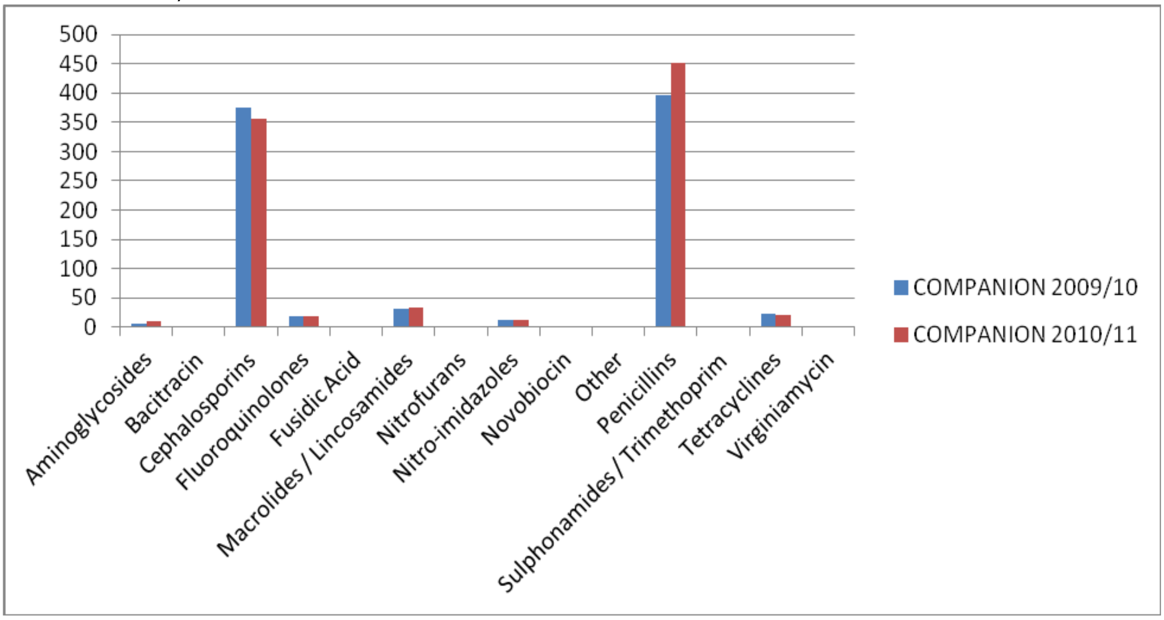
Figure 2: Antibiotic sales (in kilograms of active ingredient) for use in production animals by approved label species and antibiotic class, 2009/10 and 2010/11



3.4.2 Use of Antibiotics in Companion Animal Species

Because the most significant mass of antibiotics is used in food-producing species, the sales data analysis and resistance monitoring programmes have tended to focus on products sold for use in those species. However, a recent New Zealand based epidemiological study into the veterinary authorisation practices of companion animal veterinarians has revealed a large percentage of critically important antibiotics being authorised frequently in companion animal medicine, often without bacterial culture and sensitivity testing dictated by the principles of prudent use. At the same time, another New Zealand based investigation revealed the emergence of multidrug resistant strains of Extended Spectrum β–lactamases (ESBLs) and co-resistant strains of Enterobacteriaceae in companion animal medicine. Given the close relationship people have with their pets and the potentially significant route of exposure to resistant bacteria or resistance determinants, the common use of antibiotics critically important to human medicine in companion animal medicine, and the emergence of multidrug antibiotic resistance in these species, the prudent use of antibiotics in companion animals is imperative to the prevention of antibiotic resistance.

Figure 3: Antibiotic sales (in kilograms of active ingredient) for use in companion animals by antibiotic class, 2009/10 and 2010/11



The vast majority of companion-only antibiotics are pencillins (41%) and cephalosporins (35%). According to the sales data, the most commonly used active ingredients in these classes are the penicillin amoxycillin, which is a JETACAR Category C drug and determined to be of low concern to human medicine by the EAGAR, and the first generation cephalosporin cephalexin.

While these active ingredients are not considered critical to human medicine, resistance to these antibiotics and cross-resistance to other β-lactams, cephalosporins or other antibiotic classes can still develop if prudent use is not observed. In addition, resistance to antibiotics of low concern can also lead to the increased use of more critical antibiotics, and an increased potential risk of resistance to those critical antibiotics and classes if a bacterial culture is not performed.

It is difficult to determine the total mass and identity of the antibiotics used in companion animal medicine due to the large number of injectable products that are approved for use in both small and large animal species. It is important to note, however, that when considering all antibiotic veterinary medicines approved for use in companion animals including those multi-species products, and the use of veterinary and human antibiotics off-label, most if not all of the antibiotic classes are likely to be represented in companion animal medicine.

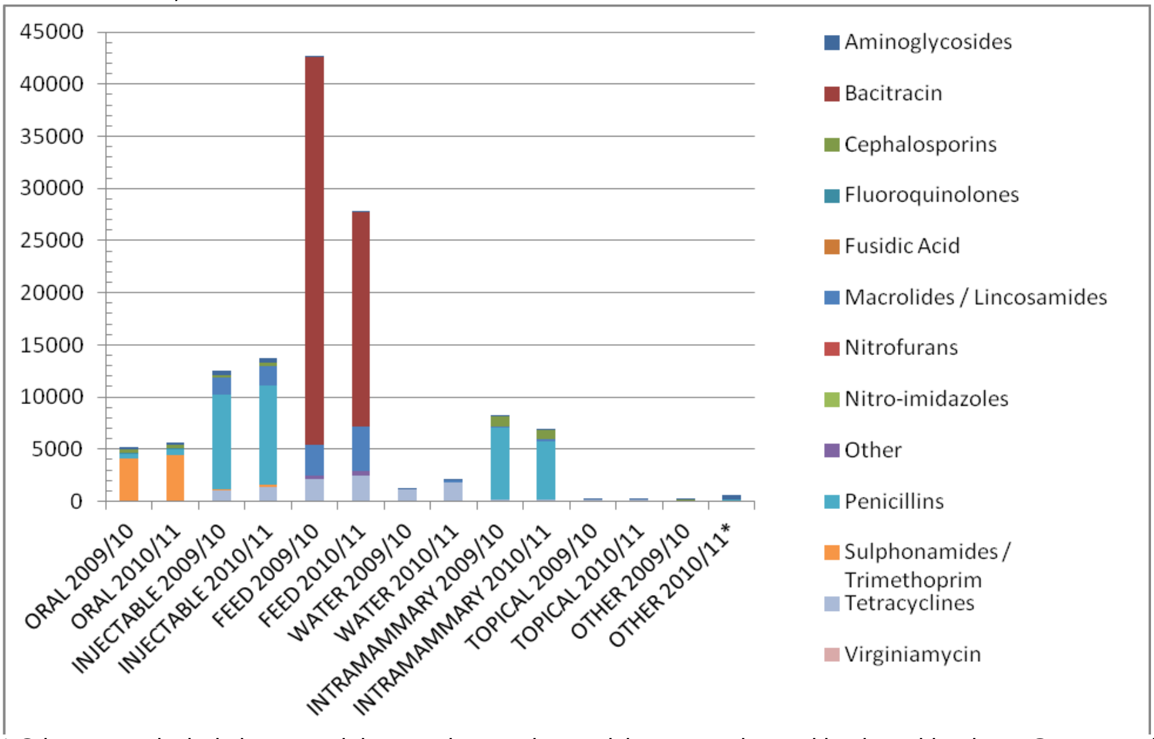
3.5 SALES ANALYSIS BY ADMINISTRATION ROUTE

The most common form of antibiotic use in food-producing animals is the administration of in- feed antibiotics, mainly zinc bacitracin based products in pigs and poultry. It was noted earlier in this report that the decrease in the zinc bacitracin sales evident in the 2009/10 and 2010/11 data has been exaggerated by purchasing practices in industry, but that there is an overall decrease in the sales of this active.

Sales of other classes of in-feed antibiotics, namely the macrolides/lincosamides and the tetracyclines, have risen in this period. It was noted in the last review that the pig industry reported an increase in the use of tetracyclines use to meet prescribed therapeutic levels for diseases managed by in-feed formulations. This previous increase may also account for some of the increase in the sales of in-feed formulations in this reporting period, due to the variability in monitoring this type of product. This is supported by the relatively small increase in sales for this group, and reports from the industry of no increase (poultry) or a decrease (pigs) in tetracycline use.

It is difficult to interpret the sales of in-feed products within a given reporting period because of the fluctuations inherent to the purchase and use of these types of products, i.e. buying product in bulk for eventual use. Sales of these products are therefore best analysed over a longer period to minimise the impact of year to year sales fluctuations. The next five-year analysis will be performed on data from 2009 to 2014, inclusive.

Figure 4: Antibiotic sales (in kilograms of active ingredient) by administration route and antibiotic class, 2009/10 and 2010/11

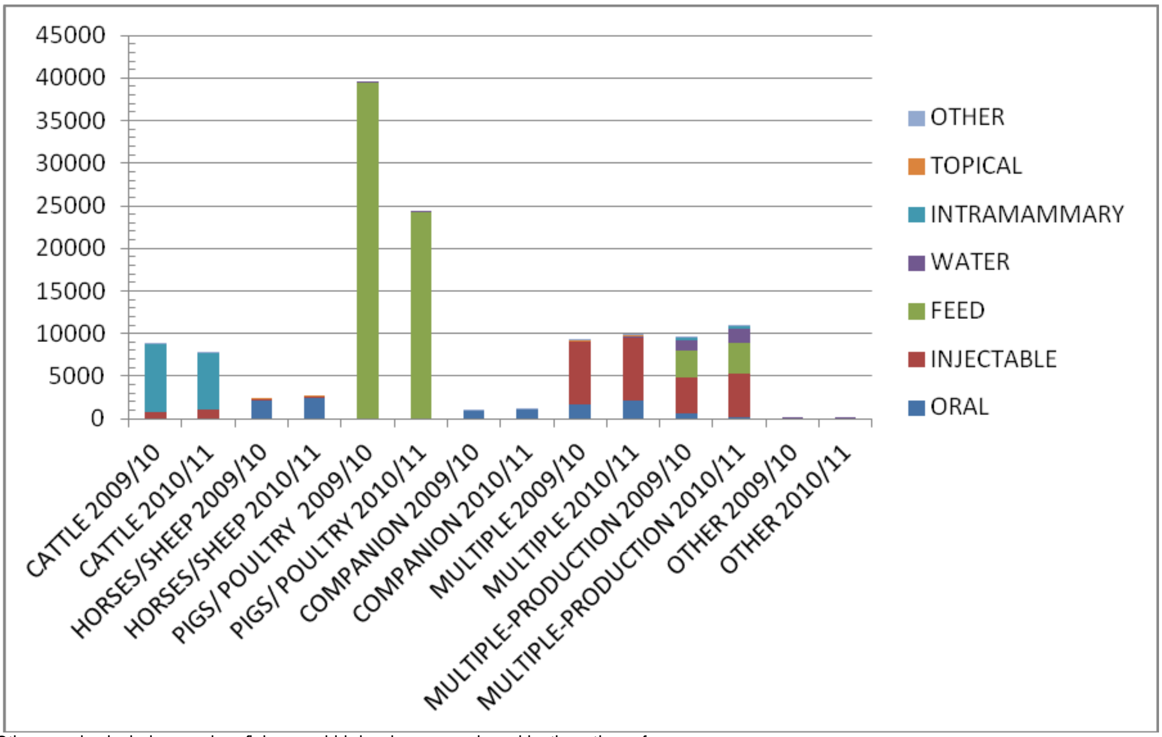


* Other routes include intra-aural, intrauterine, ocular, and those uses in combination with others. Streptomycin (aminoglycoside) is currently approved for spray-on administration to plants.

Sales of injectable products, oral products, and in-water products have increased during the reporting period. As discussed in the antibiotic class analyses, the increases in oral and injectable products in production animals are likely due in part to the de-registration of a number of intramammary aminoglycosides. Increases in injectable products have been reported by industry also to be due to a shift to administration methods that are quicker and easier to administer due to larger herd sizes and staff with less training and time to administer treatments.

The majority of the sales of orally administered antibiotics were sulphonamides/trimethoprim in both reporting years, accounting for 76% of all oral products. Amoxycillin was the next highest selling oral antibiotic, which accounted for 10% of the total sales in 2010/11. The majority of the injectable products were penicillins, comprising 73% and 70% of the 2009/10 and 2010/11 reporting years, respectively. Other notable injectable products in the 2010/11 reporting year were tylosin (14%) and oxytetracycline (10%), all mainly used in the production animal industries.

Figure 5: Antibiotic sales (in kilograms of active ingredient) by approved label species and administration route 2009/10 and 2010/11



* Other species include aquarium fish, caged birds, pigeons, and combinations thereof.
Other routes include intra-aural, intrauterine, ocular, and those uses in combination with others. Streptomycin is currently approved for spray-on administration to plants.

Products grouped as "other," especially companion animal intra-aural products, have also increased within the reporting period. Although the increase is small (4%), the feedback received from practicing veterinarians and the New Zealand epidemiological study identified a potential issue with the marketing of intra-aural products, particularly those that are aminoglycoside based.

Companion animal veterinarians reported that intra-aural products, like some other products, are being marketed based primarily on convenience. The recent New Zealand based epidemiological study identified that intra-aural medications are often authorised with no testing to determine the most appropriate antibiotic treatment, specific guidelines or request for re-examination. The study also indicated that systemic fluoroquinolones (35% of cases) are the most often used secondary treatment when intra-aural treatment fails to respond, with or without bacterial culture and sensitivity.

The promotion of intra-aural products on the basis of convenience, rather than on the basis that a particular product is the most appropriate therapeutic choice, could therefore result in an increased risk of the development of antibiotic resistance if systemic therapy is used without culture and sensitivity to determine why the primary treatment failed. The risk is heightened when aminoglycoside and/or fluoroquinolone therapy is chosen systemic therapy, especially if these drugs are chosen without culture and sensitivity testing.

4 Antibiotic Use in Horticulture

During the 2009 to 2011 reporting period, there was only one antibiotic product registered for horticultural use in New Zealand. The product, containing streptomycin as the active ingredient, is registered for use in tomatoes for bacterial disease, in pipfruit for fireblight, and in stonefruit for blast and bacterial spot. The sales figures for both 2009/10 and 2010/11 were lower than reported for any year since 2006/07. The drop in sales observed in 2008/09 following the reassessment of aminoglycoside use in horticulture continued in 2009/10 with a further decrease of 16.9%. This trend may be at least partially related to the tighter controls imposed in mid 2008 (mentioned above) as a result of the reassessment, after which off- label use was prohibited unless formal permission was obtained from MPI.

While there was an increase in sales of 14.6% from 2009/10 to 2010/11, this variation is similar to fluctuations observed in earlier years which at the time were predicted as being correlated to natural variation in disease incidence and climatic factors. It is also noted that in 2010/11 MPI permitted the use of streptomycin off-label in a high value seed line, and that in the absence of this use the increase would have only been 1.1% higher than the previous year. Sales volumes are expected to increase in the 2011-2013 reporting period due primarily to use in kiwifruit for control of *Pseudomonas syringae* pv. *actinidiae* (Psa).

5 Conclusion

While many antibiotics are still being used appropriately and effectively, there are some classes of antibiotics and or particular active ingredients for which there may be some issues related to their use. Because of this, the controls in place on the sale and use of some antibiotics need to be reviewed to determine whether they are still sufficient to manage the risk of antibiotic resistance.

The new approach to the sales data analysis has proven invaluable to the interpretation of these data. Many of the trends noted, such as the off-label use of marbofloxacin in horses and the large increases and decreases often attributable to the variability in monitoring in- feed antibiotic sales, would not have been elucidated if it were not for the input of the industry. Additionally, consultation with industry and practicing companion animal and production animal veterinarians, have raised issues that would not have otherwise been revealed by data analysis alone, such as the "convenience marketing" of antibiotics of importance to human health. MPI will continue to consult with industry and veterinarians to ensure that future sales and use analyses will continue to be a comprehensive and informative resource.

Appendix:
Antibiotic Active Ingredients Used in Agricultural Compounds

All active ingredients listed below were included in formulations registered but not necessarily marketed in New Zealand during the 2009 to 2011 reporting period. Antibiotic classes are in bold.

Classes with multiple veterinary active Ingredients				
Macrolides and Lincosamides	Clindamycin Erythromycin Lincomycin	Oleandomycin Pirlimycin Spiramycin	Tiamulin Tilmicosin Tylosin	
Penicillins	Amoxycillin Ampicillin Cloxacillin Dicloxacillin	Nafcillin Penethamate hydriodide	Penicillin G potassium Penicillin G procaine Penicillin G benzathine	
Cephalosporins	**First Generation** Cephapirin Cephalexin Cephalonium	**Second Generation** Cefuroxime	**Third Generation** Ceftiofur Cefpodoxime	**Fourth Generation** Cefquinome
Tetracyclines	Chlortetracycline Doxycycline		Oxytetracycline Tetracycline	
Sulphonamides	Sulfadiazine Sulphadimethoxine Sulphaguanidine Sulphamerazine Sulphamethazine	Sulphamethoxazol Sulphamethoxypyridazine Sulphanilamide Sulphamethoxypyridazine Sulphanilamide	Sulphapyridine Sulphaquinoxaline Sulphathiazole Sulphasoxazole Trimethoprim	
Aminoglycosides	Apramycin Dihydrostreptomycin Framycetin Gentamicin		Kanamycin Neomycin Spectinomycin Streptomycin	
Fluoroquinolones	Difloxacin Hydrochloride Enrofloxacin		Marbofloxacin Orbifloxacin	
Nitro-imidazoles	Dimetridazole Metronidazole		Ronidazole	
Nitrofurans	Furazolidone		Nitrofurazone	
Other	Bambermycin Carbadox		Florfenicol Polymyxin B	

Classes with a single veterinary active ingredient	
Zinc Bacitracin	Zinc bacitracin, like actinomycin, colistin and polymyxin B, is a polypeptide antibiotic. Although polymyxin B is used in New Zealand registered veterinary medicines (monitored in the "other" category), zinc bacitracin sales are monitored as their own category due to the large mass of active sold in New Zealand and the active ingredient's potential impact on resistance. The other polypeptide antibiotics are not used in veterinary medicine.
Novobiocin	Novobiocin is an aminocoumarin antibiotic that is produced by *Streptomyces niveus*. Other bacteria in this genus also produce lincosamides, aminoglycosides, and tetracyclines for both human and veterinary use. There is currently only one registered trade name antibiotic product containing novobiocin, with no reported sales within the reporting period.
Virginiamycin	Virginiamycin belongs to the streptogramin class of antibiotics, used to treat vancomycin-resistant *Staphylococcus aureus* infections in humans. It is the only streptogramin used in veterinary medicine in New Zealand.
Fusidic Acid	Fusidic acid belongs to its own class of antibiotics, the fusidanes. Fusidanes are naturally occuring and are active against most Gram positive bacteria including Methicillin-resistant *Staphylococcus aureus* (MRSA).

6 Acknowledgement

The antibiotic sales data analysis was completed with input from industry representatives and practicing veterinarians on the use of antibiotics in New Zealand's production and companion animals. MPI would like to thank the following groups for contributing to the content of this report:

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- Horticulture NZ
- National Mastitis Advisory Committee (NMAC) New Zealand Feed Manufacturers
- New Zealand Veterinary Association (NZVA) and NZVA member veterinarians
- NZ Pork
- Pipfruit NZ
- Poultry Industry Association New Zealand (PIANZ) Registrants of antibiotic trade name products in New Zealand

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