Ministry for Primary Industries
Manatū Ahu Matua

2011-2014 Antibiotic Sales Analysis

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Summary

Data from the sales of antimicrobials that have significance to human health, and that are classed as restricted veterinary medicines (RVMs) and agricultural chemicals, are collected by MPI on an annual basis. These data are then used to monitor trends in antibiotic use by class, species and route of administration on a kilogram of active ingredient basis. This period covers from 1 April 2011 to 31 March 31 2014 and is part of the ongoing monitoring programme. Interpretation of use is based on the sales data collected, along with feedback about antimicrobial use from industry and veterinarians in the field.

Compared to the end of the previous 2010/2011[1] reporting period, antimicrobial sales during 2013/14 increased by 13%. This does not include the large spike in the sales of antibiotics that occurred during the 2012/13 season. While disease outbreaks were reported to have occurred during this reporting period, none were considered significant enough to account for this spike. DairyNZ launched its SmartSAMM programme in 2012 which included the key message to protect all cows at dry off with an intramammary treatment. This, coupled with the good returns that the dairy sector received the previous season might have resulted in increased purchasing of animal health-based products including intramammary treatments containing antibiotics the following year.

There has been a 34% increase in aminoglycosides sold compared to the end of the last sales period. This is almost entirely attributable to the 157% increase in antibiotics sold to the horticultural sector during that time. Whilst this is a significant rise in use, total antibiotic sales in New Zealand horticulture only accounted for 0.9% to 1.5% of overall antibiotic sales. The increase in purchasing by the horticultural industry is due to the use of streptomycin and kasugamycin to manage outbreaks of *Pseudomonas syringae* pv. *actinidiae* (Psa) that occurred in kiwifruit during this sales period.

The most significant changes noted with the sales of cephalosporins were seen in products containing cephaphrin benzathine and cephalonium. By far the majority of products containing these actives are sold as intramammary and intrauterine preparations for use in cattle.

There has been a rise by 55% in the sales of 3rd and 4th generation cephalosporins during this reporting period, and most of this rise can be attributed to the purchasing of products containing ceftiofur. The increase in sales containing this active was also noted during the previous reporting period. Given the sales data, the approved indications for use and the withholding periods for the two ceftiofur products with the majority of sales, it seems likely that most ceftiofur was sold for use in the dairy industry. The dairy industry has commented that they are taking an active role in advising more judicious use of this drug.

Sales of fluoroquinolones have increased by 17%. The majority of enrofloxacin based products are used in companion animals and sales have increased by 18% compared to the previous reporting period. Almost all marbofloxacin based products are registered for use in cattle and pigs. Sales of these products have increased by 15% compared to the 2010/11 period.

Sales of trade name products containing macrolides or lincosamides have increased by 26% compared to the end of the previous reporting period. Products for administration via feed and as injectables peaked during the 2012/13 season, with sales registered for administration via feed increasing by 53% compared to the previous season. The poultry industry advised of an outbreak of femoral head necrosis in 2011/12, which may have led to an increase in sales of tylosin based products in anticipation of use the following year.

Products containing tilmicosin are only registered for use in pigs in New Zealand. Net sales have increased from the previous reporting period to the end of the current reporting period by 57%. The increase in use is attributed to outbreaks of pleuropneumonia in some pig herds.

Whilst penicillins are a significant proportion of the antibiotics sold, and are second only to the sales of zinc bacitracin, there has been an 11% reduction in the amounts purchased compared to the previous reporting period.

The sales of tetracyclines increased by 57% when comparing the end of the previous sales period with the end of this sales period. An outbreak of *Theleria orientalis* occurred in New Zealand cattle in 2012/13 and continues to be a disease requiring treatment to the present day. The dairy and beef industries have commented that this disease may in part be responsible for increased use of tetracyclines during this period. Oxytetracycline containing products dominate sales in this class accounting for 69% to 79% of total tetracycline sales. Sales of injectable tetracyclines have increased by 147% during this reporting period.

It is suspected that the numbers of companion animals have not changed significantly during this reporting period. While the mass of antimicrobials sold that are registered for use in these species is small at between 1.3% and 1.8% of total sales, a noticeable proportion of antibiotics considered 'Critically important' to human health are used, including two third generation cephalosporins.

The population of food-producing animals has decreased when considering biomass (taking the weight of an animal into account). This is important when considering the use of antibiotics because the dose administered is dependent on the animals weight, thus an 800kg cattle beast would require significantly more than an 80 kg human), and is due to a fall in beef cattle, pig and sheep numbers. However, when considering absolute numbers of animals, the population has increased. Pig, beef cattle and sheep numbers have all decreased during this reporting period, while the populations of layer and meat producing poultry has increased along with dairy cattle numbers.

The rise in overall antimicrobial use during this period is likely to in part result from the increased populations of poultry and dairy cows in New Zealand. Although systems are in place to manage animal health and encourage the prudent use of antibiotics, the report highlights issues that require a collective focus to identify areas for improvement, especially when it comes to the use of those antimicrobials listed as 'critically important' to human health.

Introduction

Antimicrobial resistance (AMR) is of great global concern as it threatens the ability to prevent and treat infectious disease caused by microbes. While AMR is a natural consequence of antimicrobial use, inappropriate practices hasten its evolution and spread. Resistance is present all around the world in pathogens that are known to cause common diseases.

Antibiotic use in production animals in New Zealand has been estimated to be the third lowest in the world [2]. Although overall veterinary use in New Zealand is very low, there is still room for improvement on ensuring there is only prudent use of antibiotics, and that the most appropriate therapy is used in every case.

The most recent report outlining which antimicrobials are of greatest importance to human health was published by the World Health Organisation (WHO) in 2011[3]. The purpose of that report was to identify an up to date list of 'critically important' antimicrobials, and to ensure their prudent use in both human and veterinary medicine. To be categorised as 'critically important,' two criteria must to be met:

> Criterion 1. Antimicrobial agent which is the sole agent, or one of limited available therapy, to treat human disease.
>
> Criterion 2. Antimicrobial agent used to treat diseases caused by either (1) organisms that may be transmitted to humans from non-human sources or (2) human diseases caused by organisms that may acquire resistant genes from non-human sources.

The report assigned three categories to the antimicrobials named in the report: Antimicrobials **critically important** for human health meet both Criterion 1 and Criterion 2. Those antimicrobials that meet either Criterion 1 or Criterion 2 are categorised as **highly important**, while antimicrobials that meet neither Criterion are ranked as **important**.

The WHO report identifies aminoglycosides, fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides as 'critically important'. It then goes on to prioritise products in the 'critically important' category, giving the fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides the highest priority. One change to the four classes of antibiotics listed as 'critically important', is that all aminoglycosides have now been incorporated into this category, including neomycin and kanamycin, which were previously categorised at highly important. Whilst there are no products containing glycopeptides approved for use in New Zealand registered products, the other four classes of antimicrobials are addressed in this report.

The antimicrobial sales have been 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.

Background

As part of the strategy to manage the risks associated with the development of antibiotic resistance, registrants of Restricted Veterinary Medicines (RVMs) and horticultural products containing antibiotics important to human medicine must provide an annual report of sales by month to MPI as a condition of registration. A preliminary sales data report is presented to industry in order to allow each sector to comment on the significance of the findings relevant to their field. Industry comment is important to the evaluation of the sales data as it provides insight into specific disease challenges that might have occurred over the period, and highlights changes in management practices and the animal population for each species. These sales data, along with industry input, are used to monitor for significant trends that may indicate changes in antibiotic use in the field and thereby provide some insight into the potential for antibiotic resistance.

Last Public Report

The last public report on antibiotic sales was a summary of the data collated from 1 April 2009 to 31 March 2011 (ref: http://www.foodsafety.govt.nz/elibrary/industry/report-antibiotics-sales-2009-2011.pdf).

As per previous reports, this report will not include sales figures for antimicrobials used in animals and not managed as RVMs, such as products containing ionophores, avilamycin, bambermycin and quinoxalines. While there is currently no evidence to suggest that these products could contribute to antibiotic resistance in humans, from 2015, any product containing an antimicrobial will be included to ensure that New Zealand is aligned with international reporting obligations.

Ongoing Reporting of Antimicrobial Sales

This report is focused on antibiotic products used in horticulture, and those that are classed as RVMs and used in animals. As stated in the last sales report, MPI intends to shift the analysis of sales data and reporting to a yearly cycle, and will continue to seek registrant and industry comment concerning the use of antimicrobials to inform the analysis. The resultant report will provide a more reliable indication of actual antibiotic use than sales data alone, and the shift to annual reporting will make the information a more accurate reflection of current trends. The reporting period will also change from financial year to calendar year. This will help align with international reporting and will ensure that the reporting period does not end during the dry cow therapy period.

Internationally, discussions on banning prophylactic antimicrobial use and restricting antimicrobial advertising are being considered and may be adopted globally in the long term. It is recognised on an international level that collecting use information per species adds considerable value in the establishment of trends which can be used to inform resistance strategies. While a move to recording use per species rather than sales is problematic, it will give a clearer picture of which species these products are being used in and why. MPI are considering options for the collection of use data per species while taking international initiatives into account. The associated costs to industry must also be considered in the development of any system to improve data collection.

MPI will also undertake five-yearly reviews to analyse trends over longer periods for those products that can fluctuate from year to year, such as in-feed antibiotics and dry cow therapies.

Data Limitations

Sales data as an indicator of antibiotic use and thereby antibiotic resistance is inherently limited due to a number of variables. The amount of antibiotic sold within the evaluated time period might not be used within that same time period and therefore may not be representative of the current use patterns. In addition, sales data do not take into consideration the amount of product that might be lost during administration or transport, non-compliance if owners do not administer a full course, expired stock or stock held for future use. While sales can approximate use over the nominated period, actual use can encompass product sold one or two years prior to and following that nominated period.

Data limitations are more pronounced in antibiotics used in animals than in plants. For example, there is more variability in approved uses of antibiotics in animals, and many products are approved for use in both food producing and companion animal species. In addition, veterinarians have the authorisation to employ discretionary use for products not limited to 'on label' use patterns, target species, dose rates and treatment regimes. Because of the use of products 'off label' (such as when treating minor species), total antibiotic use cannot be accurately predicted by the sales data.

Sales data also do not give any indication of the fluctuations of animal numbers within the New Zealand herd, the health of individual animals, emergent disease trends (plant or animal), or different environmental conditions that occur over time. Increases and decreases of sales can therefore be representative of population changes and/or changes in disease prevalence within that population just as readily as they can be of changes in antibiotic use.

There is no direct monitoring of the sales of human preparations used as veterinary medicines, or the sale and use of compounded veterinary medicines, as their use is at the discretion of the attending veterinarian in specific cases. This is especially important when considering the impact of the sales of antibiotics on the emergence of resistance, as compounded and non-veterinary medicines are often used when available veterinary antibiotics either fail to cure the infection or when the veterinarian determines that multi-modal therapy incorporating non-veterinary medicines is indicated.

Sales data in kilograms does not take into account dose rates. Certain antimicrobial classes might require more or less active ingredient that amounts to one dose of product.

The analysis is based on the weight of antibiotic active ingredient sold, but the sales are reported to MPI in amount of product sold. Product sales are mathematically converted by MPI to active ingredient weights and evaluated based on the sum in kilograms of active ingredient, often from multiple products. MPI is still working with the registrants of antibiotic veterinary medicines to eliminate errors that creep in during the process of that conversion. While there may be some discrepancies in the statistics, MPI believes that any discrepancies that may occur are minor and are unlikely to significantly alter the findings of this report.

A small rise in amount of product sold when the original amount is very small or zero, will result in a large percentage increase. This demonstrates how reliance on presenting materials as percentages can be misleading.

Finally, MPI is aware that a proportion of antibiotics sold in New Zealand, may be used in other countries including the pacific islands. The information passed on from registrants does not take into account how much product sold does not get used on New Zealand based animals.

Glossary

Species and administration definitions remain the same as in the previous report to ensure consistent reporting:

Species or species group are defined as:

- Cattle – dairy and /or beef cattle
- Companion – cat and /or dog
- Horses and sheep – horses and sheep have been identified separately from those classed as 'other'.
- 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 species. This category has been added to gain insight into products used in food producing species.
- Other – this category includes products used in caged birds, pigeons, ornamental fish and plants.
- Plants – products registered for use in plants.

Administration Route

- 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 treatment of animals where other administration methods are not appropriate.
- Water – in dedicated animal water supply for the treatment of animals where other administration methods are not appropriate.
- 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.
- Other – products for ophthalmic, intra-aural, intrauterine or spray –on (plant) use, or products where more than one administration route is possible.

Antibiotic Use in Horticulture

Two products are registered for use in the horticultural industry, both of which belong to the aminoglycoside class of antimicrobials. The detection of *Pseudomonas syringae* pv. *actinidiae* (Psa) was noted for the first time in New Zealand in November 2010. The disease spread rapidly since it was first detected, leading to an increase in the sales of the streptomycin-based product. As would be expected, sales of this product

continued to increase from the 2010/11 season through the reporting period. At the start of the outbreak, there was only one streptomycin-based product registered for use in the horticultural industry; at that time, however, it was only registered for use in tomatoes, pipfruit and stonefruit. The antibiotic was authorised for use on kiwifruit by MPI for the first time during the 2011/12 season. This led to a 122% increase in sales compared to the previous season. Total sales then dropped by 18% in the following season; this was more likely due to a drop in purchasing by the pipfruit and stonefruit sector rather than in the kiwifruit industry, as Psa infections persisted. During the 2013/14 growing season, sales increased by 42% from the previous season and included a new product which was launched specifically for use in kiwifruit. Total antibiotic sales in horticulture, while they have risen significantly compared to the previous report, remain low at 0.9% to 1.5% of overall antibiotic sales. Since this reporting period, management practices to address Psa in the kiwifruit industry have changed, which is likely to result in significant decreases in the use of streptomycin.

Variations in Production Animal Populations

There have been steady declines in the numbers in beef cattle over this reporting period. The total number in New Zealand has declined from 3.95 million in 2010/11 to 3.6 million in 2013/14, down 8.9%. The average New Zealand beef herd size was around 4.4 million between 2000 and 2010 as previously reported.

The national sheep herd in New Zealand has reduced from 31.1 million wintered in 2011 to 29.6 million in 2014 which is a 4.8% drop in total numbers. The average numbers of sheep per year over a ten year period between 2000 and 2009 was previously reported at 34.6 million.

The extensive grazing systems used to rear New Zealand sheep and beef cattle promote good animal health with consequential low use of non-essential veterinary intervention and antibiotic sales for use in these species. One disease challenge to affect beef (and dairy) cattle starting in 2012 was *Theileria orientalis*. This may have increased the use of tetracyclines in the national beef herd although this would not likely have had a significant impact on antibiotic sales concerning this group.

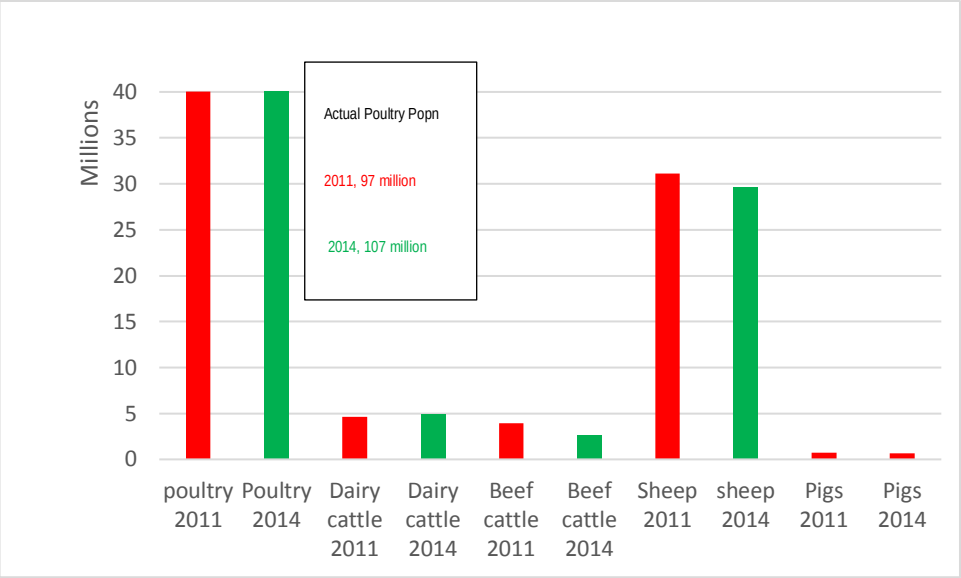
The national dairy cattle herd has increased from 4.6 million in 2011/12 to 4.9 million in 2013/14, up 8.7%. Whilst the total number of dairy cows has increased, the number of herds has remained reasonably constant. Dairy herd sizes continue to increase from an average of 386 cows per herd in 2010/11 to an average of 413 per herd in 2013/14, large numbers of animals coming together in close proximity, leads to an increased risk of disease and cross contamination. This in turn results in a greater need for clinical treatments including antimicrobials. The dairy industry reports that clinical mastitis cases have remained similar or may have improved somewhat due to greater use of dry cow therapy. While *Theileria orientalis* has affected the dairy industry over the reporting period, potentially leading at least initially to an increased use of tetracyclines, no other disease processes have been reported that could have increased antimicrobial use during this reporting period.

The national pig herd has declined from 719,678 slaughtered at commercial premises in the year ending September 2012 to 672,108 slaughtered at commercial premises in the year ending September 2014. While no new disease challenges were reported, outbreaks of pleuropneumonia has occurred in a small number of herds.

The NZ poultry industry has continued to grow throughout this period. There has been an 11% increase in chickens bred for meat from 93 million (2011) to 103 million (2014). The number of free range chickens bred for meat has also increased by 67% from 9 million to 15 million. Numbers of layers have risen by 10% from 3.2 million caged birds and 300,000 free range birds in 2011 to 3.4 million caged layers and 450,000 free-ranged layers in 2014. An outbreak of femoral head necrosis may have led to increased use of macrolides during the 2011/12 season.

The population of horses in New Zealand has not been established. The New Zealand Equine Veterinary Association (NZEVA) has commented however that the numbers are likely to be declining with regard to breeding. The foal crop of Thoroughbreds and Standardbreds is diminishing, with a drop in over 20% of Standardbred mares bred, and a drop of over 10% in Thoroughbred mares bred from 10 years ago. A survey of the number of horses considered pets in New Zealand was undertaken by The New Zealand Companion Animal Council in 2011 and stood at 87, 000 at that time [4].

Figure 1. Production animal numbers

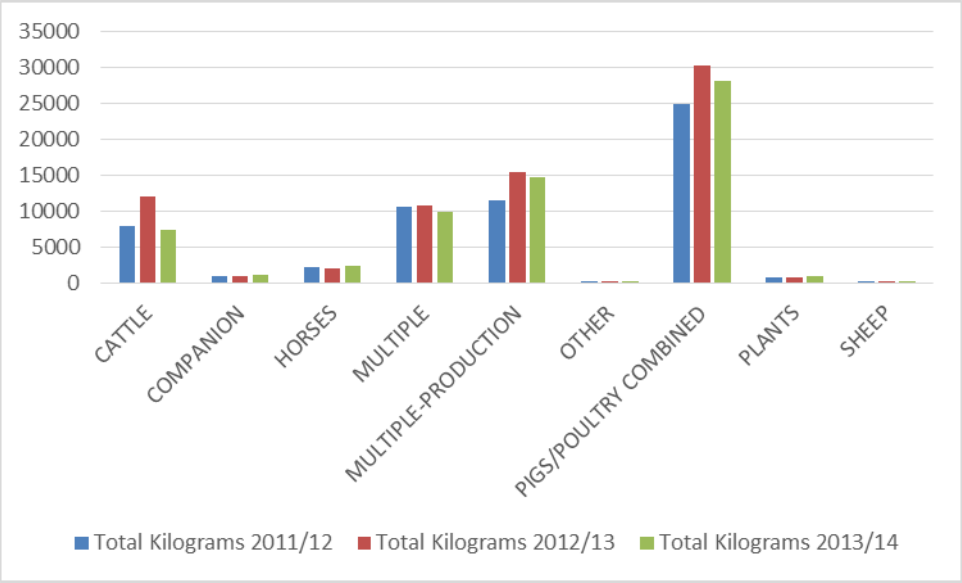


Use of Antimicrobials in Food-Producing Animals

The pig, poultry and dairy cattle industries continue to use the greatest mass of antimicrobials in New Zealand agriculture. There will be several reasons for this including the more intensive farming practices compared to sheep and beef cattle farming, and a higher biomass as in the case of cattle.

The majority of antimicrobials used in pigs and poultry are given via feed since this is the most appropriate administration route in these species; while a small amount is administered in water. Sales of products registered for use in these species have increased by 13% during this period, which is likely to be mostly attributable to the 11% increase in the poultry population. Zinc bacitracin is used prophylactically in the poultry industry to prevent necrotic enteritis and the severe animal welfare implications including death of whole flocks that would result if it were not used in this manner. Dry cow therapy (DCT) and lactating cow intramammary preparations continue to be the most frequently used antimicrobials within the dairy industry, with penicillin based products being the most common active ingredient administered in these products. Use of injectable antimicrobials is also very common in dairy cattle and likely to account for the majority of products sold that are registered for use in 'multiple production' animals. Antimicrobial use in sheep, beef cattle and deer appears to be very low in New Zealand when compared to other species.

Figure 2. Total Antibiotic sales by species (in kilograms)



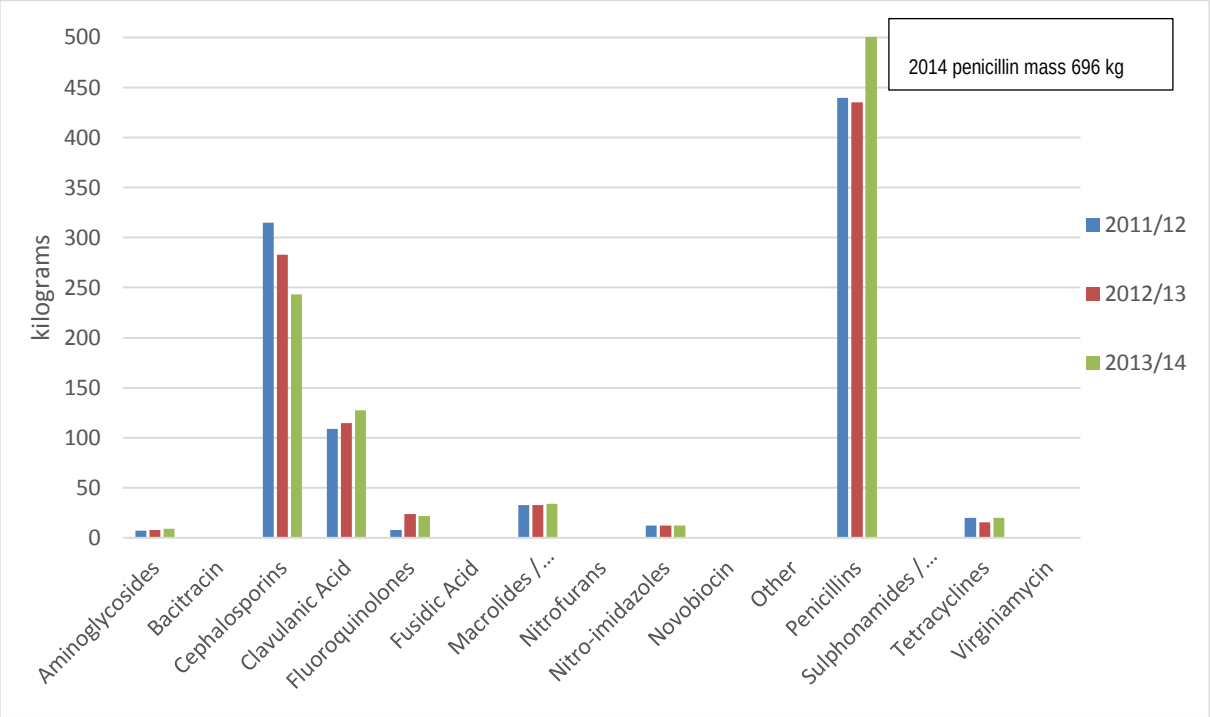
Use of Antibiotics in Companion Animal Species

The size of the New Zealand companion animal population is estimated at 1.4 million cats and 700,000 dogs. The total amount of antimicrobials sold for companion animal use was very small at between 1.3% and 1.8%, during the three reporting years.

The companion animal space has two third generation cephalosporins registered for use which equates to 9% of all third generation cephalosporin sold during this period. Fluoroquinolones sold for use in companion animal's account for 1% to 2% of all sales in this class of antibiotic over the three year time period. Macrolides sold for small animal use have comprised of 3% of all macrolides sold. While these numbers appear small, use of these 'Critically important' antimicrobials is considered significant given the close physical relationship humans have with their pets and the potential for resistance to pass from one species to another. It is imperative that prudent use of 'Critically important' antimicrobials is employed in every case in order to prevent the development of antimicrobial resistance.

This report does not include the amount of antimicrobials registered for use in humans that are administered to animals off–label, or those antimicrobial preparations that are compounded for veterinary use. It is generally agreed that the majority of these medications are prescribed for use in small animals due to the lack of availability of alternative or effective treatments.

Figure 3. Antibiotic sales in companion animals by class



Sales Analysis by Administration Route

By far the majority of antibiotics sold were registered to be administered via food in the pig and poultry industry, accounting for just above 50% of all antimicrobials sold during the period. This is an 18% increase compared to the end of the previous reporting period. As in preceding reports, the majority of in-feed antimicrobial sales consist of zinc bacitracin, which is used to manage necrotic enteritis caused by *Clostridium perfringens* in the poultry industry. Sales of antimicrobials for administration via food peaked during the 2012/13 season before dropping to levels that were slightly higher than at the end of the previous reporting period.

Other classes of antimicrobials to be administered in food include tetracyclines, macrolides and lincosamides, and aminoglycosides. In-feed aminoglycosides are registered for use in pigs only, and have reduced steadily by 83% since the 2010/11 season. It is a very minor component of in-feed antimicrobials. The in-feed tetracyclines sold are mainly for use in the pig and poultry industry, although a significant amount sold is registered for use in multiple species. Sales have increased by 21% since the 2010/11 season, but have remained stable apart from a peak in the 2012/13 season. Macrolide and lincosamide in-feed sales have steadily increased to 24% since 2011/12. These products are used in the pig, poultry and cattle industry.

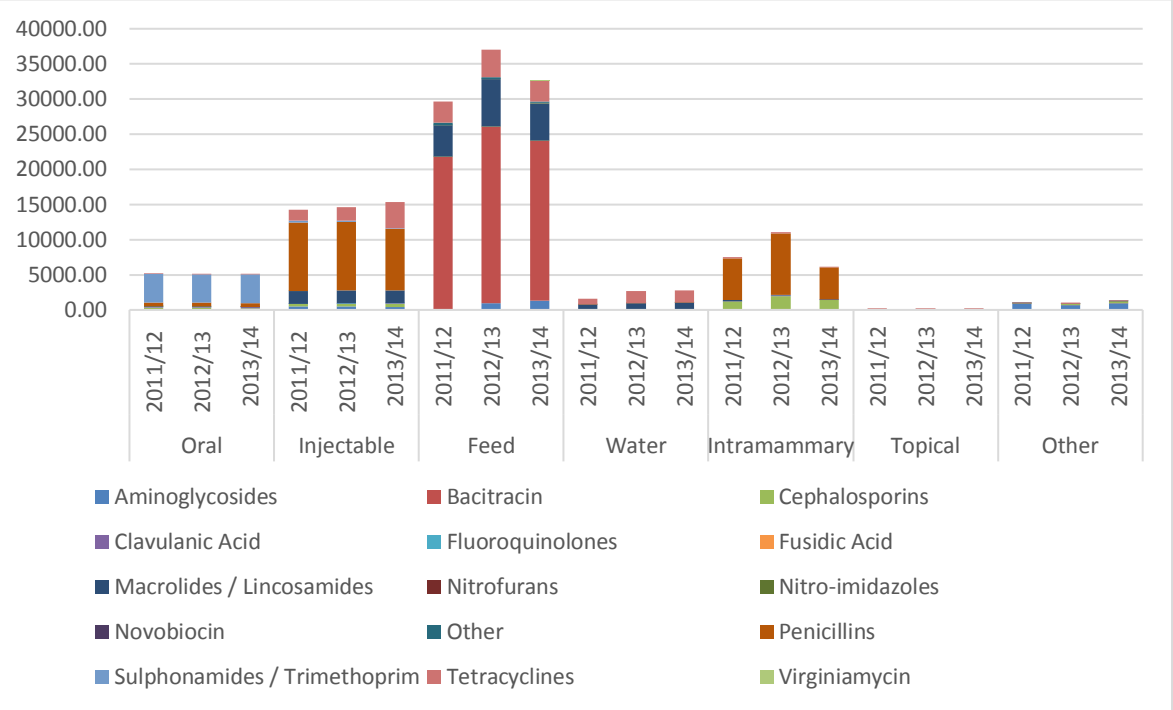
The next largest mass of antimicrobial sold are injectables, which accounted for 20% to 24% of all antimicrobials sold. Compared to the end of the previous reporting period, injectables have increased in sales by 12%, an increase which is likely in-part due to the ease of administration. The majority of these products are registered for use in 'multiple' and 'multiple production' species. This includes a 28% increase in the sales of 3rd and 4th generation cephalosporins injectables of which the majority are registered for use in multiple species. Feedback from veterinarians, suggest that 3rd generation cephalosporin injectables may be favoured during periods of high milk return as they have a nil WHP which prevents milk from having to be discarded.

The third largest mass of antimicrobials sold was for intramammary administration and accounted for 10% to 15% of all antimicrobials sold. During this reporting period there has been quite some variation in the amounts purchased from year to year and reflects the likely farm returns with the 2012/13 year having the most intramammary products sold. Further discussion can be found in the 'Dry Cow Therapies' section of this report.

The only antimicrobial products evaluated by administration route that have decreased in mass sold compared to the previous period were those products administered orally. As these products are primarily registered for use in horses and companion animals, this decline may be due in part to a decline in equine numbers, but it may also reflect a change in preference in favour of injectable products in these species.

While antimicrobials administered via water, topical application, or 'other' administration routes all increased, they are a relatively small proportion of all antimicrobials sold. The largest increase at 133% (compared to the end of the previous reporting period) was in the 'other' category and is accounted for by the use of kasugamycin and streptomycin in kiwifruit since the Psa outbreak.

Figure 4. Antimicrobial sales by route of administration



Dry cow therapies

Dry cow therapy (DCT) products will from now on be discussed as its own category given the importance of these formulations to the dairy industry and the extent of their use. Dry cow therapy products are used to treat existing infections that were not cured during lactation and to treat any new infections that occur during the dry period. There were 6011 kilograms of dry cow products sold in 2011/12, increasing 61% to 9641 kg in 2012/13 before decreasing 49% to 4922 kg in 2013/14. Sales of this type of product are known to fluctuate year to year based on clinical need, on-farm practices, the environment, and farm finances. Use of these products are also seasonal, leading to fluctuations that can be unrelated to use. During 2011/12, DCT products accounted for 10% of all antimicrobial sales. This was an extremely profitable season with record milk production and high milk prices. Some of these financial gains may have been spent the following season, and could account for the rise in DCT products sold in 2012/13, an increase to 13% of overall sales. DCT product sales then

decreased to 7% of total antimicrobials sold during 2013/14 period, no doubt in part due to widespread drought the previous season resulting in a shorter milking period, reduced returns, and reduced milk solid prices. It is also possible that veterinarians overstocked in the 2012/13 season due to good sales, which would have led to reduced purchasing the following season, and thus decreased sales reporting.

DCT product sales are comprised of two classes of antibiotics: cephalosporin-based products and penicillin-based products. Penicillin-based preparations made up the majority of DCT product sales and comprised of 74% to 81% of all sales in this category. Cloxacillin-based products comprised of between 56% and 62% of the total sales within this category for all three reporting years. It must be pointed out that cloxacillin-based products require approximately double the weight of active per syringe compared to ampicillin or cephalosporin based dry cow therapies, which will result in more kg of active sold, and is not reflective of the number of cows treated. Cloxacillin is listed as "Highly important" by the WHO as its use in the veterinary field could result in transmission of *S. aureus* including MRSA to humans, thus, its use should be carefully considered and justified.

The two cephalosporin-based antibiotics used in DCT products contain cephapirin benzathine and cephalonium. Both of these actives are first generation cephalosporins which are considered by the WHO to be "Highly important" antimicrobials as their use in animals could result in *Enterbacteriaceae* including *E. coli* transmission to humans. Sales of the cephalosporin-based dry cow therapies comprised of 19% to 26% of all sales in this category. Compared to overall antimicrobial sales for this period, cephalosporin-based DCT products made up 2% to 3% during the three reporting years.

DairyNZ SmartSAMM (Smart Approach to Minimising Mastitis) programme was launched in 2012, which encourages the use of intramammary treatments at dry off (to improve udder health) whether it be a teat sealant, an antimicrobial, or a combination of both. Industry has commented that this has likely lead to an increase in the number of cows receiving DCT treatments. DairyNZ has remarked on an increase from 77% of cows receiving some form of DCT treatment in 2008 to approximately 85% of cows receiving treatment in 2013/14. Unfortunately, no data exists to determine what proportions of antibiotic-containing treatments have been used compared to teat sealants alone. Industry has stated that a 20-25% drop in somatic cell counts has occurred since 2008. This will have resulted in a drop in clinical mastitis cases, and thus a drop in lactating cow antibiotic use. However, not enough information is available to determine how much DCT product use would reduce the use of other antibiotics.

Sales Trends 2011 – 2014

Overall, net antibiotic sales increased in mass by 13% from the previous reporting period, with a sales increase of 20% from 59,350 kilograms in 2011/12 to 71,718 kilograms in 2012/13, then a decrease of 12% to 64,444 kilograms in 2013/14. This trend was not absolute, with increases and decreases in certain classes of antibiotics considered important to human health occurring in all three years. Industry comment was sought regarding the overall increases in sales, especially with respect to the significant increase reported during the 2012/13 sales period. While two disease outbreaks occurred during this reporting period, one in poultry and one in kiwifruit, neither alone could have contributed to the 2012/13 increase. The previous year is known to have been a very good season for the dairy industry and it is speculated that this would have rolled on to increased veterinary spending during the 2012/13 period.

Table 1 Total Antibiotic Sales by Class (in kilograms active ingredient)

Antibiotic Class	2010/11	2011/12	Difference 2010/11-2011/12	2012/13	Difference 2011/12-2012/13	2013/14	Difference 2012/13-2013/14
Zinc Bacitracin	20,476	21,714	↑ 6%	25,175	↑ 16%	22,726	↓ 10%
Macrolides/Lincosamide	6524	7018	↑ 8%	9601	↑ 37%	8150	↓ 15%
Penicillin	15,683	16,203	↑ 3%	18,997	↑ 17%	14,032	↓ 26%
Clavulanic Acid	193	152	↓ 21%	161	↓ 6%	158	↓ 2%
Cephalosporin	1707	1960	↑ 15 %	2766	↑ 41%	2325	↓ 16%
Tetracycline	6019	5757	↓ 4%	8010	↑ 39%	9435	↑ 18%
Sulphonamide/Trimethoprim	4696	4440	↓ 5%	4314	↓ 3%	4309	↓ 0.1%
Aminoglycoside	1235	1553	↑ 26%	1384	↓ 11%	1651	↑ 19%
Fluoroquinolone	40	29	↓ 28%	51	↑ 80%	47	↓ 9%
Novobiocin	Nil	Nil		Nil		Nil	
Nitro-imidazole	57	57.1	↑ 0.2%	56	↓ 3%	51	↓ 9%
Nitrofuran	0.89	0.85	↓ 4%	0.89	↑ 5%	0.57	↓ 40%
Virginiamycin	11	Nil	↓ 100%	Nil		11	↑ 11%
Fusidic Acid	0.85	0.09	↓ 89%	0.54	↑ 500%	0.61	↑ 13%
Other	399	373	↓ 7%	270	↑ 28%	202	↑ 25%
Total	57042	59,350		71,718		64,444	

Table 2. Net Change in Sales by Class

Antibiotic Class	**Net Change between 2010 and 2014**
Zinc Bacitracin	↑ 11%
Macrolides/Lincosamide	↑ 25%
Penicillin	↓ 11%
Clavulanic Acid	↓18%
Cephalosporin	↑ 36%
Tetracycline	↑ 57%
Sulphonamide/Trimethoprim	↑ 8%
Aminoglycoside	↑34%
Fluoroquinolone	↑ 18%
Novobiocin	
Nitro-imidazole	↓ 11%
Nitrofuran	↓ 36%
Virginiamycin	0
Fusidic Acid	↓28%
Other	↑ 49%

Although sales are not necessarily directly indicative of product use, the increase in the sales of certain classes may represent an increased risk in the incidence of resistance to antibiotics of importance within those classes. A review of the most recently registered antibiotic trade name products (Appendix 1) between April 2011 and March 2014 reflected the potential increased use of these classes, with 14 of the 18 most recently registered products containing antibiotics that are 'critically important' according to the WHOs "Critically Important Antimicrobials for Human Health" report. However, 11 of the 14 above mentioned registrations contained active ingredients that were already available on the market, thus the new registrations represented products generic to those already available. In terms of sales, it would likely represent a shift in purchasing from one product to another, rather than increased use. The remaining three products included a new active

ingredient for use in horticulture as a response to the Psa outbreak in kiwifruit, a new active for use in bovine respiratory disease and a generic type tylosin based product combined with a non-steroidal anti-inflammatory.

During this sales period, 21 trade name products were deregistered Appendix 2). Eight of these products contained active ingredients in the WHOs list as critically important to human health. It is presumed that the majority were cancelled due to lack of purchasing or other market drivers and thus would not have had an impact on sales.

Variations to registered antimicrobial containing products which have been approved during this reporting period, and could have had an effect on use, are outlined in appendix 3. All products are registered for use in cattle +/- other species. The majority of variations approved were to extend the treatment period. While this change will result in increased sales, it is unclear whether it could have an effect on antimicrobial resistance as while a longer treatment period could ensure all the microbes causing the disease are killed, longer exposure periods might also give the microbe more time to adapt. The second most common approved variation was to reduce withholding periods. While this change may affect which products are sold, it would be unlikely to contribute antimicrobial resistance in the affected products.

Aminoglycosides

All aminoglycosides are now classified as 'critically important' by the WHO because there are certain medical conditions where this class of antimicrobial is the sole treatment, and because cross-resistance occurs across this class. Although classified as critically important, this class of drugs is not on the 'highest priority' list because there are not a high number of people affected by the infections they treat and because aminoglycosides are not widely used in human medicine which would favour selection for resistance.

Initially, sales of aminoglycoside-based products increased in 2011/12 by 26% above the previous year. Sales then decreased by 11% over the 2012/13 period before increasing by 19% in 2013/14. This equates to a net 34% increase in aminoglycoside sales since the 2010/11 season.

The total sales of antibiotics for use in plants changed significantly within this reporting period, with an increase of 122% during 2011/12, which then decreased by 18% in 2012/13, before increasing 42% by in 2013/14. Comparing the end of the previous reporting period to the end of this reporting period, this equates to a net 157% increase in horticultural sales. The increase is due to the use of streptomycin and the new horticultural antibiotic kasugamycin, both approved for the treatment of *Pseudomonas syringae* pv. *actinidiae* (Psa), to manage outbreaks that occurred in kiwifruit during this time. Unlike streptomycin, kasugamycin is approved solely for use in kiwifruit. Sales of kasugamycin made up 11% of the horticultural aminoglycoside sales during the 2013/14 period. Increased use of aminoglycosides during this period can be directly attributable to sales in the horticultural industry, with a 4% decline in sales to the animal sector. While aminoglycosides are considered critical to human health, kasugamycin is not used in human or animal medicine. However, its sales are included in this report because expert opinion cannot put the risk of using this antimicrobial in plants and its potential to contribute to antimicrobial resistance at zero.

The majority of aminoglycosides sold included streptomycin and dihydrostreptomycin. This is a direct result of the large increase in streptomycin sold for horticultural use as already mentioned. While use of neomycin increased by 30% during the reporting period, most of the increase occurred in 2013/14 and was a result of sales of an oral neomycin-based antibiotic registered for use in multiple species. This increase parallels a reduction in sales of orally administered spectinomycin-based product, also registered for use in multiple species. Gentamycin sales have steadily dropped over the reporting period by 24%, while all other aminoglycoside sales have remained stable. As noted in the previous report, sales of aminoglycosides between 2004 and 2009 averaged 1,540 kilograms per year. Average sales throughout this period are similar with 1553 kg sold 2011/12, 1384 kg sold in 2012/13 and 1651 kg sold during 2013/14.

Cephalosporins

Third and fourth generation cephalosporins are classed as 'critically important' to human health in the WHO report since they meet both Criterion 1 and 2. These drugs include some of the limited therapies available for the treatment of acute meningitis caused by *Salmonella*, multi drug resistant *E. coli,* and pyrexia in neutropaenic patients. Use of 3rd and 4th generation cephalosporins is known to select for cephalosporin-resistant *Salmonella* and *E. coli* in animals.

There has been an overall net increase in cephalosporin sales by 36% since the previous reporting period. Sales of these products increased 15% during the 2011/12 season, then increased a further 41% in 2012/13, before decreasing 16% in 2013/14. The sales of antibiotics within this class have historically oscillated due to their inclusion in intramammary preparations, whose sales are known to fluctuate year to year.

The most significant changes were evident in two first generation cephalosporins: cephapirin benzathine and cephalonium. Most cephapirin containing products are sold as intrauterine preparations, with a small percentage contained within in dry cow therapies. Cephapirin benzathine sales increased 26% from the previous sales period during 2011/12, 30% during the 2012/13 season, and then another 80% in 2013/14. All cephalonium containing products are sold as intramammary preparations for use in cattle. Cephalonium sales increased 21% in 2011/12 above that previously reported, then increased another 71% in 2012/13 before decreasing by 31% in 2013/14. The other registered first generation cephalosporin, cephalexin, is predominately used in companion animal medicine. Use of this active ingredient has reduced during the reporting period by 43%.

The only registered second generation cephalosporin is used as an intramammary preparation in lactating cows. Its use since the last reporting period has declined, however, sales did increase during the 2012/13 period as is the case with most of the antimicrobial treatments registered for use in the dairy industry.

Sales of 3rd and 4th generation cephalosporins have increased substantially by 55% since the previous reporting period, and most of this rise is attributed to the active ceftiofur. Sales of most of the 3rd and 4th generation cephalosporins increased slightly during 2011/12 from the previous report, and again in 2012/2013 before decreasing during 2013/14. Ceftiofur sales, however, have continued to rise throughout, increasing 35% from the previous report in 2011/12, then by another 4% in 2012/13, before a further increase of 11% during 2013/14. This continual rise in ceftiofur sales was also noted in the last antimicrobial sales report. Most ceftiofur-based products are approved for use in multiple production animal species, making it difficult to identify increased sales for any particular sector. However, industry has stated that the majority of sales of this active were for use in cattle. Approved indications for use, along with withholding periods give further support that the majority of these products are used in the dairy cattle industry. The dairy industry has commented that they have been taking an active role in advising more judicious use of this drug since the continuously increasing sales have been identified.

The reported increase in sales of the third generation cephalosporin cefpodoxime by 87% is slightly misleading, as sales within the three year reporting period actually decreased by 8%. While it was registered for use in early 2010, it likely only came onto the market part way through the 2010/11 season, which would have resulted in fewer sales during that period when compared to the other periods. The only other third generation cephalosporin, cefovecin, has declined when comparing the end of the last reporting period with the end of this reporting period. This is a result of an increase in sales during the 2010/11 period followed by a steady decline which the registrant stated is expected post-launch.

Table 3. Cephalosporins by Generation

Family	Active Ingredient	Percent Change (Between 2011 & 2014)	Primary Use and Route(s)
FIRST GENERATION	Cephapirin	↑ 188%	Cattle: Intramammary and intrauterine
	Cephalexin	↓ 43%	Companion animal oral; multiple species injectable; lactating cow intramammary
	Cephalonium	↑ 28%	Dry cow intramammary
SECOND GENERATION	Cefuroxime	↓ 29%	Lactating cow intramammary
THIRD GENERATION	Cefovecin	↓ 10 %	Companion animal injectable
	Ceftiofur	↑ 56%	Production animal injectable
	Cefpodoxime	↓ 8%	Companion animal oral
FOURTH GENERATION	Cefquinome	↑ 21%	Production animal injectable; lactating cow intramammary

Although the use of fourth generation cephalosporins has increased by 24% compared to the previous reporting period, the amounts purchased are very small with less than 3kg sold annually between 2011 and 2014. A small rise in amounts sold, of less than half a kg, resulted in a large percentage increase. This demonstrates how reliance on presenting materials as percentages can be misleading when referring to very small amounts.

Fluoroquinolones

Fluoroquinolones are listed as 'critically important' by the WHO because they are included in a limited number of drugs available for use in the therapy for human *Campylobacter*, *Salmonella*, and MDR (Multidrug Resistant) *Shigella* infections. Use of this class is known to select for fluoroquinolone–resistant *Salmonella* and *E. coli* in animals.

Fluoroquinolone sales first decreased 28% from the previous reporting period to 2011/12 before increasing 80% in 2012/13 and again decreasing 9% during 2013/14. The result is an overall net increase of 18% in

sales of this class since the end of the last reporting period. The increase in sales of these actives is across the board and not attributable to one specific trade name product or one particular species.

There are two fluoroquinolone active ingredients registered for use in veterinary products: enrofloxacin and marbofloxacin. The majority of enrofloxacin-based products are registered for use in companion animals, while almost all of the marbofloxacin based products are registered for use in production animals (pigs and cattle). No new fluoroquinolone products have been registered recently, however, three products were registered during the middle of the last reporting period; two in the companion animal space and one for use in cattle. Purchase of these three products has been low since registration and would not have significantly attributed to the 17% increase in fluoroquinolone sales during the 2011 to 2014 period.

Registered use of fluoroquinolones is split approximately 50/50 between companion animals and production animals. There was a large reduction in the sales of fluoroquinolones for use in companion animals during 2011/12. It is unclear why this occurred but it may have been due to unavailability of certain products rather than a reduction in use. Comparing the end of the previous reporting period to the end of this reporting period, enrofloxacin sales registered for use in companion animals have increased by 18%. Suggestion has been made by companion animal veterinarians that the increased sales of the active enrofloxacin could in part be due to intensified advertising of these products. It is also noted that the NZ pet rabbit population has increased substantially since 2011 from 88,000 individuals to 116, 000 individuals. Since enrofloxacin is usually the first line antibiotic used in this species, the increased sales of this drug could be attributable at least in part, to the increased population of this species.

Use in production animals has increased by 15% since the previous period. Use of these products in both companion and production animals has historically been limited to the management of disease in individual animals by oral or injectable administration. Reports from industry indicate that there is minimal use of fluoroquinolones in the pork industry and that it is not the first choice of antibiotic used in dairy medicine. However, it is noted that heavier use of this class of antibiotics inI the dairy industry may be seen over time due to different pathogens more commonly causing disease. No fluoroquinolones are used in the poultry industry.

Macrolides and Lincosamides

The WHO classifies macrolides as ‘critically important’ to human health because, along with fitting Criterion 2, this class of antimicrobials in one of a limited number to drugs able to treat *Legionella*, *Campylobacter*, MDR *Salmonella* and MDR *Shigella* infections. Macrolides are known to select for macrolide-resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. Lincosamides, although a distinctly different compound structurally, shares a similar mode of action and spectrum of activity to macrolides and bacteria will generally develop resistance to both macrolide and lincosamide antibiotics. For this reason, these two antimicrobial classes, along with streptogramins which also share similarities leading to cross-resistance, are often grouped together. For the purposes of this report, macrolides and lincosamides are considered as one group; the only New Zealand-registered veterinary medicine in the streptogramins class, virginiamycin, is discussed later in this report.

Sales of macrolides and lincosamides have increased 25% since the end of the previous reporting period. Purchasing trended upwards through the first two years, with the 2011/12 total sales representing an increase of 7.8% above that reported previously, followed by a 37% increase in the 2012/13 period. Sales then decreased by 15% during 2013/14.

As stated in previous years, tylosin, an active ingredient used predominantly in the pig and poultry industries, continues to be the primary macrolide utilised in veterinary medicines. Tylosin has accounted for 83% or more of macrolide and lincosamide sales over all three reporting years. Of the tylosin based products, between 64% and 75% were sold for administration in feed and registered for use in pigs to treat ileitis, poultry to treat respiratory disease as well as necrotic enteritis, and in beef cattle to treat liver abscess. Up to 27% of products sold were injectables registered for use in cattle, pigs, sheep and goats. Sales of tylosin-based products for use in-feed and as injectables peaked during the 2012/13 season, with sales for use in-feed increasing by

53% above the previous season. The poultry industry has advised of a disease outbreak of femoral head necrosis in 2011/12, which would account for the increase of sales in that year. This does not, however account for the increase in sales the following season.

During this period, six new products containing tylosin have been registered. All of the new products were registered as generic products, and would therefore not be expected to increase sales as no new use patterns would have been approved. The products were registered with claims to treat respiratory infections, mastitis, metritis, foot rot and infectious arthritis. Only two of these products have come onto the market, one of which is registered for use in cattle only, while the other is registered for use in multiple production animals. Sales of these new products accounted for 3.5% of overall macrolide sales for the year 2013/14, so were only a small proportion of the sales in this class of antimicrobials.

Products containing the active ingredient tilmicosin are registered for use in pigs and multiple production species, however, only those registered for use in pigs have been sold during this reporting period. While there are products registered for administration by other routes, only product to be administered within feed has been sold during this reporting period. Net sales have increased from the previous reporting period compared to the end of the current period by 57%. This is despite a reduction in the national swine herd by 7.8%. Initially sales dropped by 80% compared to the 2010/11 season, then increased by 233% during 2012/13, before increasing a further 135% in 2013/14. These wide fluctuations in sales are common to in-feed products because they are generally sold in bulk which leads to sales over-reporting or under-reporting depending on how much product has been carried over at the point of data collection. The pig industry has reported that increased use of tilmicosin is the result of several outbreaks of pleuropneumonia (APP) in a small number of herds over this time. Alternative management strategies have been developed to address this disease so the use of tilmicosin is expected to drop in future sales reports.

There is one macrolide, spiramycin, and one lincosamide, clindamycin, registered for use in companion animals. The sale of both these actives was stable during the reporting period and hence the increase in sales of this class cannot be attributed to use in companion animals.

Olandeomycin, which is used in intramammary preparations and registered for use in cattle only, decreased in sales by 10% during the reporting period. Sales of lincomycin containing products, registered for use in cattle as an intramammary preparation and in pigs and poultry for use in feed, also declined to almost half of that sold at the end of the previous reporting period.

In terms of use per species, products registered for use in ‘multiple production’ animals accounted for over 75% of sales throughout the period. Of this, over 70% was registered for use in feed and is likely to be attributable to use in pigs and poultry rather than cattle. The remainder was an injectable product where the majority would have been likely been used in pigs and cattle, although it is also registered for use in sheep and goats. Products registered for use in poultry or pigs, or both species, account for the majority of the rest of macrolides and lincomycins, while products registered for use in companion animals and cattle only were minimal and ranged from between 0.4% to 3.6% of the total class sold.

Comparing sales use by route of administration, the majority of product sold was for administration in feed. Amounts purchased differed considerably from year to year with 46% of the total class being sold in 2011/12 to 96% sold in 2012/13, then 65% sold in 2013/14. This is likely because in feed products are often stock-piled and not necessarily used in the year they were bought.

Virginiamycin

Virginiamycin is a streptogramin and this class of drug is listed by WHO as a “highly important” antimicrobial because it is used to treat *Enterococcus* species and MRSA from non-human sources. Because virginiamycin is only used in animals and in very small amounts, it is unlikely to be of concern with regard to its use being associated with antimicrobial resistance.

There are two products registered for therapeutic use within this class: one for use in horses and the other in poultry. Previously, sales of the horse product have been consistently low, and no sales have been reported for the poultry product. Over this reporting period, there were nil sales of virginiamycin-containing products in 2011/12 and 2012/13, before a return to previous sales levels in 2013/14. This is likely due to a product ownership change and the reintroduction of the horse preparation onto the market. As per previous years, there were no sales of the poultry product.

Nitrofurans

This class of antimicrobials includes two active ingredients: nitrofurazone and furazolidone. Both products are poorly absorbed systemically and thus tend to be administered topically or orally. The majority of sales within this class are for use as a topical preparation on horses, while the remainder is for use in aquarium fish. Sales continue to be very small (between 0.57 and 0.89 kilograms). Purchases decreased by 4% in 2011/12, then increased by 5% in 2012/13, before decreasing by 40% in 2013/14 which was due to a reduction in the sales of one nitrofurazone product. While this class of antimicrobial has broad-spectrum activity, it is not very potent compared to other antimicrobials. Resistance is rare and slow to emerge. A product previously registered for use in pigeons has been discontinued.

Nitro-imidazoles

There are two active ingredients in this class of antimicrobial. One is dimetridazole used in pigs and poultry while the other is metronidazole used in companion animals only. Both actives have anaerobic and anti-parasitic activity. They are absorbed almost completely when administered orally and resistance is rarely described. Sales of products in this class continue to be relatively stable (between 51 and 57 kilograms), decreasing 3% in 2012/13 and a further 9% in 2013/14. Overall, there has been an 11% drop in sales since the end of the previous reporting period.

Novobiocin

There were nil sales of products containing active ingredients from the novobiocin class during the reporting period. Only one product is registered for use and is formulated as an intramammary preparation.

Other

This category contains antimicrobials that cannot be attributed to other classes and include carbadox, tiamulin, florfenicol, polymyxin, ronidazole and fusidic acid. Sales within this category decreased 28% between 2011/12 and 2012/13, then a further 25% between 2012/13 and a further 25% in 2013/14. Overall, the drop in sales from the end of the previous reporting period and 2013/14 is 49%.

Carbadox, approved for use in pigs, is the dominant active in this class. Decreases in carbadox sales have accounted for most of the category's reduction. Carbadox is a preferential treatment used in young pigs and has an important role in the control of spirochaetal diarrhoea during the weaner phase, and ileitis caused by *Lawsonnia intracellularis* in the grower phase.

Products containing the active tiamulin are registered for use in pigs and poultry and are used in-feed for the treatment of respiratory disease. Sales of products containing this active declined during the reporting period until almost none was sold during 2013/14.

One florfenicol-containing product registered for use as an injectable in cattle and swine has been cancelled. Another florfenicol product remains registered but has never been sold. Florfenicol is not used in human medicine globally, but it is categorised as a 'highly important antimicrobial' by the WHO. This is because its use in animals could result in transmission resistant bacteria from the *Enterobacteriaceae* family on to humans.

Polymyxin B is registered for use as topical, aural and ocular preparations in horses and companion animals. Sales increased by 30% between the end of the previous reporting period and 2013/14. Sales were then constant until another increase during the 2013/14 period when a new product was released for use in

companion animals for topical and intra-aural use. Despite the increase in sales of products containing polymyxin, the sales of this active is only 0.002% of overall sales during the 2013/14 period. Polymyxin has been newly classified as a 'critically important' antimicrobial to human health by the WHO because of dramatic increases in multi-resistant Gram negative infections in humans for which agents including colistin (a polymyxin) are now one of the only effective treatments.

Penicillins

Penicillins were a significant proportion of all antibiotic sales during the reporting period, comprising 27% of the overall total in 2011/12, 27% in 2012/13, and 22% in 2013/14. Sales of penicillins were second only to sales of zinc bacitracin. The purchasing of these products reduced by 11% between the end of the previous reporting period and 2013/14, with sales within the reporting period increasing by 17% during 2012/13, then decreasing by 26% in 2013/14.

Nearly half of the purchases in this class are attributed to products approved for use in cattle, and consisted of 40% of total 2011/12 penicillin sales, 50% of total 2012/13 penicillin sales, and 40% of total penicillin sales in 2013/14. Within this category, most of the sales were attributable to DCT products and comprised of 65% to 81% of the penicillins sold that were registered for use in cattle. The majority of these were cloxacillin or cloxacillin combination products. The other main sales within this class were treatments approved for use in 'multiple' species. Within this category, sales were consistent throughout the period, and comprised of between 42% and 53% of total penicillins sold. As with previous sales reports, a significant portion of injectable penicillin, mainly penicillin G based products, of which approximately 8900 kg was sold during the 2013/14 period (63% of totals penicillins sold), are presumed to be for use in the dairy industry.

The WHO categorises amoxicillin, ampicillin and the penicillin G as 'critically important' to human health. This is because these actives are one of a few antibiotics which work against human diseases including syphilis and infections caused by *Listeria*, *Enterococcus* species and MDR *Pseudomonas*, and because certain of these diseases can be passed on from non-human species including *Pseudomonas* and *E. coli*.

During this reporting period, total purchases of amoxicillin-based products averaged 5% of penicillins sold, approximately half of which was sold to the companion animal sector. An average of 7% of products containing amoxicillin were purchased as intramammary preparations for use in cattle. No sales of injectable amoxicillin specifically registered for use in cattle has been reported since 2011/12; however, the rest of the amoxicillin-based products were injectable formulations registered for use in 'multiple' and 'multiple-production' species which were likely to have been sold for use in the dairy sector. No amoxicillin-based products are registered for use in pigs or poultry. The purchasing of amoxicillin-containing products has remained largely unchanged throughout this period and compared to the previous reporting period.

Penicillin G based products include those containing procaine, potassium and benzathine. The procaine component has a local anaesthetic effect and is used in both intramuscular and intramammary preparations. The benzathine component gives long lasting activity when administered intramuscularly, allowing for a one-off injection in many cases. By far the majority of this group of penicillins are injectable with less than 10% being intra-mammary treatments. Penicillin G accounted for 55% of all penicillin purchased in 2011/12, 48% in 2012/13 and 63% in 2013/14. Most of the products sold are registered for use in 'multiple' species and as injectables containing the local anaesthetic procaine. Sales of penicillin G specifically registered for use in cattle accounted for 10% of sales during 1011/12, 8% in 2012/13 and 12% in 2013/14. A small proportion of long-acting penicillin based products containing benzathine and are registered for use in sheep only. These accounts for approximately 0.5% of penicillin sales throughout the period.

Cloxacillin is ranked by the WHO as 'highly important' for human health in some regions. It has received this regional ranking because it is one of a limited number of treatments effective against *S. aureus* infections in these regions, and because that organism may result in transmission of MRSA infections from animals to humans. Cloxacillin is registered for use as an intramammary in cattle and as an ocular medication for use in 'multiple' species. Cloxacillin sales accounted for 24% of all penicillins sold during the 2011/12 season, of which 97% of the products were DCT products. During 2012/13, cloxacillin accounted for 32% of penicillin

sales of which 96% were DCT, and 21% of penicillin sales during 2013/14 of which 91% were sold as DCT. Approximately 5% of cloxacillin is sold as an intramammary for use during lactation, while a small proportion is sold for use in 'multiple' species as an ocular preparation. Cloxacillin sales increased 52% between 2011/12 and 2012/13 before dropping by 50% between 2012/13 and 2013/14. Comparing the end of the previous sales period to 2013/14, purchases dropped by 11%.

All ampicillin based products registered in the reporting period were intra-mammary DCT preparations for use in cattle only. Like cloxacillin, sales of products containing ampicillin almost doubled from the previous year during 2012/13 before halving again the following year; this is because all of the DCT products containing ampicillin are cloxacillin/ampicillin combination products, so these two actives trend together. On average sales of products containing ampicillin accounted for 8% of all penicillins sold.

Table 4. Penicillins by Active Ingredient

Active Ingredient	Percent change (Between 2011 & 2014)	Primary Use and route
Amoxicillin	↑ 24%	Companion animal oral, Multiple injectable, cattle intramammary
Ampicillin	↓ 33%	Cattle intramammary
Cloxacillin	↓ 11%	Cattle intramammary
Penethamate Hydriodide	↓ 82%	Multiple production injectable
Penicillin G Benzathine	↓ 28%	Multiple Injectable
Penicillin G Procaine	↓0.6%	Multiple injectable, cattle intramammary

Sulphonamides

In line with previous years, sulphonamide-based product sales have been very stable with annual purchasing between 4,300 and 4,500 kilograms, compared to an average of 4,995 kg annually during 2004 to 2009. Very small decreases in sales were observed over this period (3% in 2012/13 and 0.1% in 2013/14). 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. Unlike the previous report, sales of injectables have reduced to approximately half of what was sold at the beginning of this period.

Overall sales within this class are small and sit at an average of 7% of total antimicrobial sold. The WHO categorise sulphonamides as "Highly important" as they meet Criterion 2 where they are used to treat infections in animals such as *Enterobacteriaceae* including *E. coli* that could be passed to humans. The sales of sulphonamides remains relatively low and constant.

Tetracyclines

During this reporting period, the WHO have re-categorised tetracyclines as 'Highly important' down from 'Critically important' in regions where *Brucella* infections do not occur in food-producing animals which includes New Zealand.

As with the previous report, overall sales of tetracycline-based products climbed during this survey period. Purchases increased 39% during 2012/13 then a further 18% in 2013/14. Compared to the end of the last report period, tetracycline sales have risen by 57%. The injectable administration route has increased most notably (180%), with the in-water route also increasing (121%). Oral, in-feed and topical routes of administration have all remained similar over this time.

Oxytetracycline-containing products continued to dominate sales in this class with a 29% increase during 2012/13 and a further 34% increase in 2013/14. Over this reporting period, sales of oxytetracyclines comprised of 69% to 79% of total tetracycline sales; similar to the previous reporting period. Most are sales are attributable to use of injectables which have increased by 147% and are all registered for use in 'multiple production' species. Products registered for in-water use have increased by 121% and are approved for 'multiple production' species. Intramammary products containing Oxytetracycline have decreased by 12% during this reporting period. Topical products sold increased by 12% during this period and are registered for use in 'multiple' species.

Chlortetracyclines are only registered for use in pigs and poultry, and all products sold during this period were for use in-feed. Overall, sales increased by 7% compared to the end of the previous report. During 2011/12, purchases decreased by 22% compared to the previous year, then increased by 70% in 2012/13. Over the 2013/14 season, sales reduced by 19%. Fluctuations in the purchase of this active are likely due to the products being for administration in food feed as they are known have variability between seasons due to pre-ordering. The poultry industry has estimated that approximately 100kg of tetracyclines (equivalent to approximately 1% of tetracyclines sold) was used in chickens during 2014, which indicates that the majority of the chlortetracycline sold in the reporting period was used in the pork industry.

Doxycycline sales have been stable during this period, accounting for approximately 3% of tetracycline sold. By far, the majority of doxycycline–based products are used in companion animals with a small proportion being used in pigeons and other caged birds (~3%), and cattle (~6%).

An outbreak of *Theleria orientalis* occurred in New Zealand cattle in 2012-13 and continues to be a disease requiring treatment to the present day. The dairy industry has suggested that this likely led to an increase in tetracycline sales during the 2012/13 period, when tetracyclines were used for treatment prior to the introduction of buparvaquone. While sales did increase during that time, sales continued to climb during later years also. While some veterinarians continued to use tetracyclines to treat *Theleria*, the increase is not likely to be solely resultant from the emergence of this disease. The pig industry uses tetracyclines for their treatment in pleuropneumonia on some farms, as well as being used intermittently for endometritis in breeding sows. Tetracyclines are also used in the pork industry for *Mycoplasma hyorhinus* in weaner's and *Mycoplasma hyosynoviae* in growers.

The previous report stated concern among veterinarians and industry representatives that increasing sales of injectable oxytetracyclines is likely in part due to convenience rather than determination of best treatment choice, particularly with long-acting injectable oxytetracyclines for use in dairy cattle. The trend of increased injectable use by 147% with this class supports the concern that it is the result of convenience, and suggests a review of the use patterns approved for these products, as well as a review of how they are actually being used in industry, is required.

Zinc Bacitracin

Zinc Bacitracin is registered for use in the pork and poultry industry to prevent Necrotic Enteritis caused by *Clostridium perfringens*. The antibiotic is categorized as 'important' to human health which means it fits neither

criterion 1 or 2. Sales of zinc bacitracin were once again a large part of all antibiotic sales, comprising 37% of the overall total in 2011/12, 35% in 2012/13 and 35% in 2013/14, and 70% (2011/12), 63% (2012/13) and 64% of all antimicrobials sold for use in feed or water.

While sales of this active ingredient represent a smaller percentage of overall antibiotic used when compared to the last report (53%), the total sales fluctuated during the reporting period. Purchasing increased by 6% in 2011/12 over the previous reporting period, then increased by 16% in 2012/13, before decreasing by 10% in 2013/14. Purchases when compared to the end of the previous reporting period increased by 11%.

It was noted in the last report that zinc bacitracin was predominately used in poultry, with industry estimating use in pigs at less than 5% of sales. It is expected that this is still the case.

The size of the national poultry flock has increased by approximately 11% which matches the increase in bacitracin sales over that time. The national poultry flock has increased from 93 million meat producing birds in 2011 to 103 million meat-producing birds in 2014. Of these, around 9 million birds were free range in 2011 compared to approximately 15 million in 2014. This is an increase in free range farms from 10% in 2011 to around 15% in 2014, and is a space where zinc bacitracin is not used. Average zinc bacitracin sales since 2004 have been 22,176kg per year, whereas the average over this reporting period is 23,204kg, a 5% increase. This increase aligns with the 6% increase in the size of the national flock that uses bacitracin i.e. meat-producing chickens that are not free range. Thus, it can be concluded that the use of zinc bacitracin when compared to the national poultry flock has not increased during this reporting period.

Conclusion

Antibiotic use in production animals in New Zealand has been estimated to be the third lowest in the world [2]. Despite this, the information outlined in this report suggests that the prudent use of antimicrobials still requires attention when choosing the most appropriate therapy for the patient or patients in question. This is of concern when it comes to those antimicrobials which are critically important to human health, and therefore should be considered the last line of defence in animal infections.

There are four classes of antibiotic of 'critical' importance to human medicine, and all of these classes have increased significantly in sales between the end of the previous reporting period and the end of this reporting period: Macrolide sales have increased by 25%, fluoroquinolones by 18%, and aminoglycosides by 34%. In addition to that, the third generation cephalosporin ceftiofur has increased in sales by 55%.

The content of this report will contribute to the direction of MPI's antimicrobial resistance (AMR) work programme which includes a review of the classification system and controls on antibiotic products.

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New Zealand Feed Manufacturers

New Zealand Veterinary Association (NZVA) and NZVA member veterinarians

NZ Pork

Pipfruit NZ

Poultry Industry of New Zealand (PIANZ)

Registrants of antibiotic trade name products in New Zealand

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Appendix 1: Recently Registered Antibiotic Products 2011-2014

Date registered	Registration number	Application type[1]	Product name	Registrant	Active ingredient(s)	Class
18/03/2014	A011026	B2	Norocef RTU	Norbrook NZ Ltd	Cetiofur	Cephalosporins
30/01/2014	A010848	B2	Kelacef	Phoenix Pharm	Cetiofur	Cephalosporins
10/01/2014	A010984	B2	Neove 200 Tylosin Injection	Neove Pharma Australia Pty Ltd	Tylosin	Macrolides/Lincosamides
23/10/2013	P008603	A1	Kasumin	Etec	Kasugamycin	Aminoglycosides
17/10/2013	A010814	A1	Draxxin Injectable Antibiotic Solution	Zoetis NZ Ltd	Tulathromycin	Macrolide/Lincosamide
21/03/2013	A010884	A2	PenClox 1200 High Potency Milking Cow	Virbac New Zealand Ltd	Penicillin + Cloxacillin	Penicillins
17/12/2012	A010555	B2	Genta 100	Phoenix Pharm	Gentamicin	Aminoglycosides
4/12/2012	A010742	B2	BaciMax 150 Granular	Agrihealth NZ Limited	Zinc Bacitracin	Bacitracin
18/11/2012	A010714	B2	Tylosin 300 Injection	Bayer NZ Ltd	Tylosin	Macrolides/Lincosamides
15/08/2012	A010672	B2	TMPS Powder	Caledonian Holdings Ltd	Trimethroprim +Sulphamethazine	Sulphonamides/Trimethoprim
20/07/2012	A010807	B2	TyloVet Injection	Agrihealth NZ Limited	Tylosin	Macrolides/Lincosamides
10/07/2012	A010772	A2	Tylofen	Bayer NZ Ltd	Tylosin	Macrolides/Lincosamides
17/11/2011	A010667	A2	Furan-2	Brooklands Aquarium Ltd	Nitrofurazone + Furazolidone	Nitrofurans
4/11/2011	A010727	B1	Romagel VS	Merial NZ Ltd	Cephalomium	Cephalosporins
3/10/2011	A010691	B2	Eficur	Hipra NZ Ltd	Ceftiofur	Cephalosporins
8/08/2011	A010697	B1	Cefaject	Bayer NZ Ltd	Ceftiofur	Cephalosporins
8/08/2011	A010685	B2	Pharmasin 10% Granular Premix	Agrihealth NZ Limited	Tylosin	Macrolides/Lincosamides
11/04/2011	A010637	B2	Tylomix 250	Bayer NZ Ltd	Tylosin	Macrolides/Lincosamides

[1] Application Type: A1 – New active ingredient, A2 – New risk profile, B1 – Identical to another trade name product, B2 – Similar to another trade name product.

Appendix 2: Recently deregistered Antibiotic Products 2011-2014

Year deregistered	Registration number	Product Name	Registrant	Active Ingredient(s)	Class
2014	A009813	Oxymac Aerosol	Bayer New Zealand	Oxytetracycline	Tetracycline
2014	A009135	Bovicillin	Bayer New Zealand	Penicillin G Procaine	Penicillin
2014	A004188	Nitrofurazone Ointment	Bayer New Zealand	Nitrofurazone	Nitrofuran
2014	A003626	Trimazol	Bayer New Zealand	Sulphisoxazole	Sulphonamide
2013	A010054	Lactoclav NP	Bayer New Zealand	Amoxycillin/Clavulonic acid	Penicillin
2013	A010025	Lactoclav GT	Bayer New Zealand	Amoxycillin/Clavulonic acid	Penicillin
2013	A009304	Nubatrin	Image Holdings Ltd	Zinc Bacitracin	Bacitracin
2013	A009040	Bomox LA	Bayer New Zealand	Amoxicillin	Penicillin
2013	A008207	Marbocyl Bolus	Ethical Agents	Marbofloxacin	Flouroquinolone
2013	A007149	Doxycycline 5% Soluble Powder	Phoenix Pharm Distributors Ltd	Doxycycline	Tetracycline
2013	A004721	Techmulin-S Feed Premix	MainFeeds	Tiamulin & Sulfadimidine	Tiamulin & Sulphonamide
2013	A004642	Hydocortiderm	Ethical Agents	Neomycin	Aminoglycoside
2013	A004147	Alphamycin	MainFeeds	Oxytetracycline	Tetracycline
2013	A004146	Furamycin	MainFeeds	Furazolidone	Nitrofuran
2013	A001544	Aureomycin Antibiotic Powder	Zoetis New Zealand Limited	Chlortetracycline	Tetracycline
2013	A001076	Negasunt	Bayer New Zealand	Sulphanilamide	Sulphonamide
2012	A010051	Opticillin Eye Ointment	Ethical Agents	Cloxacillin	Penicillin
2012	A007819	Nuflor	Schering Plough Animal Health Ltd	Florfenicol	Florfenicol
2012	A007538	Furan-2	Brooklands Aquarium	Furazolidone	Nitrofuran
2012	A006846	Tecamox LA	Virbac New Zealand	Amoxicillin	Penicillin
2012	A001811	Neobiotic-P Pump	Zoetis New Zealand	Neomycin	Aminoglycoside

Appendix 3: Approved Significant Variations to Registered Antibiotic Products 2011-2014

Year of change	Change	Registration Number	Product Name	Registrant	Active Ingredient	Class
2014	Dose/rate	A005945	Clavulox LC	Zoetis	Amoxicillin/clavulonic acid	Penicillin
2013	WHP	A010884	PenClox 1200 High Potency Milking Cow	Virbac	Penicillin G, Cloxacillin	Penicillin
2013	WHP	A009887	Maxalac L C, Intramammary Antibiotic	Jurox	Cefuroxime	Cephalosporin
2013	WHP	A003664	Orbenin LA	Zoetis	Cloxacillin	Penicillin
2013	Dose/rate	A009887	Maxalac L C, Intramammary Antibiotic	Jurox	Cefuroxime	Cephalosporin
2013	Dose/rate	A003664	Orbenin LA	Zoetis	Cloxacillin	Penicillin
2012	WHP	A010772	Tylofen	Bayer	Tylosin	Macrolide
2011	WHP	A010279	Nitroclox LA	Virbac	Cloxacillin	Penicillin
2011	WHP	A009423	Penethaject	Bayer	Penethamate	
2011	disease	A010150	Excede LA Sterile Suspension	Zoetis	Ceftiofur	Cephalosporin
2011	disease	A007812	Vetrimoxin LA	Ceva	Amoxicillin	Penicillin