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A SURVEY OF ANTIMICROBIAL USAGE IN ANIMALS IN SOUTH AFRICA WITH SPECIFIC REFERENCE TO FOOD ANIMALS

BY

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I, Dr *Hayley Anne Eagar*, do hereby declare that during the course of this study, "A survey of antimicrobial usage in animals in South Africa with specific reference to food animals", except where acknowledgements indicate otherwise and apart from advice from my promoters, this dissertation represents my own original work. Neither the full dissertation nor any part thereof has been, is being, nor will be submitted for another degree at this or any other University.

This dissertation is presented in partial fulfillment of the requirements for the degree of Master of Veterinary Medicine (Pharmacology) in the Department of Paraclinical Sciences, University of Pretoria.

Signed: *Hayley Eagar*

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Summary

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The purpose of this work was to set a benchmark for a monitoring and surveillance programme on the volumes of the eighteen classes of antimicrobials available and consumed by animals for the benefit of animal health in South Africa. In setting up such a programme, risk assessment and possible management and communication strategies of the potential health risks emanating from antimicrobial resistance in bacteria from animals and man were considered and the survey was compared with other overseas surveillance programmes established in Sweden, Denmark, the United Kingdom and Australia.

The aim of the study was to contribute to the establishment of future surveillance programmes that will provide direction for the prudent and rational use of antimicrobials, involving all the relevant stake-holders, in order to preserve the future efficacy of those antimicrobials that are currently available. Such programmes will harmonize with international initiatives and contribute to the provision of databases for policy recommendations in South Africa. There are several benefits to the implementation of such surveys and addressing topical and relevant issues of antimicrobial use in the domain of

animal health and its possible impact on human health. Furthermore, policy decisions to address concerns regarding antimicrobial resistance may be reached in a more informed and judicious manner, with the aim that the efficacy of available antimicrobials may be preserved for use in future generations of humans and animals.

The authorized antimicrobials available in South Africa were firstly reviewed and compared with the volumes of antimicrobials supplied by the veterinary pharmaceutical companies. The majority of antimicrobials were registered under the Stock Remedies Act 36 of 1947. It was found that the class of antimicrobial representing the most registered products was the tetracyclines, followed by the penicillins, the sulphonamides, macrolides, lincosamides and pleuromutilins. This correlated well with the volumes of antimicrobials supplied, as these classes of antimicrobials also represented the top four groups of antimicrobials consumed. Eight of the pool of twenty-five veterinary pharmaceutical companies approached provided more detailed information on the volumes of antimicrobials consumed for the years under review, namely 2002 to 2004. The potency of antimicrobials was also requested, in order to establish trends of increasing or decreasing potency of the active ingredients, versus the volumes of antimicrobials supplied. It was established within the scope of this study, that the majority of consumed antimicrobials was from the classes of macrolides, lincosamides, and pleuromutilins, followed by the tetracycline class, the sulphonamide group and fourthly the penicillins. The potency of the active ingredients supplied by the companies did not change and therefore had no impact on the interpretation of antimicrobials consumed.

These results give cause for concern in terms of the possibility of cross-resistance between antimicrobials used in the domain of animal health, and those used in the human medical field. There is also another concern, namely the exposure of humans to veterinary drug residues in food, causing modifications in the bacterial ecology of the human gut, thereby leading to a possible perturbation in the protective human gut barrier with overgrowth and invasion of pathogenic bacteria. Although much has been written about the possibility of anaphylactic reactions occurring in sensitized human individuals from β-lactams and macrolides administered in food animals, this issue has been reviewed extensively and it has been concluded that allergies from antimicrobial residues in the diet are extremely rare.

The macrolide tylosin was the most extensively sold antimicrobial of all. Tylosin is one of four antimicrobials that was banned by the EU in 1999 because of its structural relatedness

to therapeutic antimicrobials used for the treatment of disease in human medicine. The other three classes mentioned above, the penicillins, tetracyclines and sulphonamides are also relevant because of well-documented evidence of the ability to select for resistance or because of their structural relatedness to human therapeutic antimicrobials and their use in humans. The value of sales of antimicrobials were provided by SAAHA (South Africa Animal Health Association) and also scrutinized within the context of this study in order to obtain meaningful data on the national consumption of antimicrobials. However, as discussed in Chapter 5, the data were not of any value within the context of this study because the sales data were provided in monitory terms only. Volumes of sales of feed were also obtained and companies that mix feed approached to ascertain the percentages of antimicrobial medicated feeds consumed. It was ascertained in this survey that 68,5% of the grand total of antimicrobials surveyed during 2002 to 2004, were administered as in-feed medications. Tylosin was the most extensively used in-feed antimicrobial, followed by oxytetracycline, zinc bacitracin and olaquindox. This result emphasizes the importance of establishing a monitoring programme for the volumes of antimicrobials used, as many growth promoters used in-feed are administered at sub-therapeutic levels over long periods of time that tend to select for antimicrobial resistance. Whereas 17,5% of the total volume of antimicrobials utilized were parenteral antimicrobials, antimicrobials for water medication constituted 12% of the total. “Other” dosage forms such as the topical, aural, ophthalmic, and aerosol antimicrobials and intra-uterine pessaries and tablets constituted 1,5% of the total. Intramammary antimicrobials represented 0,04% of the total.

In Chapters 1, 5 & 6 the surveillance systems for veterinary antimicrobials used by other countries are discussed and compared. It was concluded that a combination of the surveillance systems applied by Australia and the United Kingdom is the best model (with modifications) to apply to the animal health situation in South Africa. Such a surveillance system of the volumes of veterinary antimicrobials consumed should ideally be implemented in conjunction with a veterinary antimicrobial resistance surveillance and monitoring programme to generate meaningful data that will contribute to the rational use of antimicrobials in order to preserve the efficacy of the existing antimicrobials in South Africa. Possible trends of antimicrobial usage in animals may be uncovered over time from implementing a programme for the volumes of antimicrobials used and thereby lead to proactive application of rational policies for the veterinary use of antimicrobials. This

information can also be compared with international data, in order to harmonize as much as possible with global monitoring programmes of veterinary antimicrobial usage.

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List of Abbreviations

AFMA	Animal Feed Manufacturers Association
ACMSF	Advisory Committee for Microbiological Safety in Food
AGPs	Antimicrobial Growth Promoters
AIDS	Acquired Immunodeficiency Syndrome
Anticocc.	Anticoccidials
ATC_{vet}	Anatomical Therapeutic Chemical Veterinary Classification
CR	Colonization Resistance
CNEVA	Centre for National Veterinary and Food Research
CVM	Centre for Veterinary Medicines
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DDD_{animal}	Defined Daily Dose in Animals
DEFRA	Department for Environment, Food and Rural Affairs
ESBLs	Extended-spectrum beta-lactamases
EU	European Union
FAAIR	Facts about Antimicrobials in Animals and the Impact on Resistance
FAO	Food and Agriculture Organization
GDP	Good Distributing Practice
GMP	Good Manufacturing Practice
Growth Pr.	Growth promoters
GWP	Good Wholesaling Practice
HIV	Human Immunodeficiency Virus
Intrauter.	Intrauterine
IVS	Index of Veterinary Specialties
JETACAR	Joint Expert Technical Advisory Committee on Antimicrobial Resistance
Kbp	Kilobase pairs
MCC	Medicines Control Council
MDR	Multiple-Drug Resistant
IMS	Monthly Index of Medical Specialties

MPO	Milk Producers Organization
MRSA	Methicillin-resistant *Staphylococcus aureus*
Na	Sodium
NARMS	National Antimicrobial Resistance Monitoring System
No.	Number
NDA	National Department of Agriculture
NRF	National Research Foundation
OIE	Office International des Épizooties
Oph.	Ophthalmic
OTC	Over-the-counter
SAAHA	South African Animal Health Association
SANVAD	South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs
SAVA	South African Veterinary Association
SAVC	South African Veterinary Council
SIC	Special Import Certificate
STC	Special Treatment Certificate
Spp.	Species
Sulph.	Sulphonamides
STRAMA	Swedish Strategic Programme for the Rational Use of Antibiotics and Surveillance of Resistance
SVARM	Swedish Veterinary Antimicrobial Resistance Monitoring
TB	Tuberculosis (in humans)
TGA	Therapeutic Goods Administration
Tetracycl.	Tetracyclines
UK	United Kingdom
VMD	Veterinary Medicines Directorate
VRE	Vancomycin Resistant Enterococci
WHO	World Health Organization
WCCDSM	WHO Collaborating Centre for Drug Statistics Methodology
WP	Withdrawal period
XDR	Extreme Drug –Resistant
Y	Year
Zn	Zinc

CHAPTER 1

1 GENERAL INTRODUCTION

The increasing prevalence of antimicrobial-resistant bacteria is a public health risk of major global concern. It has been noted that certain, essential, life-saving antimicrobials are becoming less effective and that there are fewer alternatives available for treatment. (JETACAR 1999; Van den Bogaard & Stobberingh 2000; White, Acar, Anthony, Franklin, Gupta, Nicholls, Tamura, Thompson, Threllfall, Vose, van Vuuren & Costarrica 2001). Veterinary requirements for the treatment of established infections with antimicrobials for reasons of animal disease control and welfare are similar to those of human medicine. The use of antimicrobials for treatment, prophylaxis, metaphylaxis and as growth promoters in food-producing animals is essential for a sustainable and economically viable animal industry (Acar & Röstel 2001; SANVAD 2007). However, the use of antimicrobials in animals, particularly in food animals, may lead to selection for resistant strains of bacteria, which in turn may proceed to infect both animals and man (Mellon ,Benbrook, & Benbrook 2001).

The use and overuse of antimicrobials in human medicine is well recognized. However, the association between intensive use of antimicrobials in food animal production and emergence of antimicrobial resistance (including resistance to antimicrobials prescribed in human health for the treatment of human infections) of animal origin is well established. (JETACAR 1999; Van den Bogaard & Stobberingh 2000; Martel, Tardy, Sanders & Boisseau 2001; White *et al.* 2001; Smith & Coast 2002; Stege, Bager, Jacobsen & Thougaard 2003;). In South Africa, a study was undertaken on the establishment and standardization of a veterinary antimicrobial resistance surveillance and monitoring programme (Nel, van Vuuren & Swan 2004; SANVAD 2007). Such information is invaluable, especially if it goes hand in hand with a programme monitoring the volumes of antimicrobials used. This study was therefore an attempt to move in the direction of partially addressing some of the gaps in our knowledge.

The objectives of this survey were as follows:

Primary Objectives:

- To record the number of antimicrobials authorized for use in animals in South Africa according to class, generic type, dosage form, indication and withdrawal periods;
- To determine the total volumes of antimicrobials (kg) manufactured and supplied for animals by the veterinary pharmaceutical industry in South Africa stratified according to the class, generic type, dosage form and indication over the years 2002 through 2004;
- To examine what effect antimicrobial potency has on the interpretation and examination of trends of antimicrobial consumption.

Secondary Objectives:

- To ascertain the total volumes of animal feedstuffs sold during the same period (2002-2004).
- To determine the percentages of this feed medicated with antimicrobials during the same period and to relate the result to the current estimated figure of 60%.
- To determine the total value of sales volumes of antimicrobials over the same time period.

It is a well-established fact that the use of antimicrobials in the field of animal health impacts on the development of resistance in the human medical field. However data on the supply and consumption of volumes of antimicrobials utilized in animal health are very scanty in South Africa (SANVAD 2007). By the collection of such data, policy decisions to address concerns regarding antimicrobial resistance may be reached in a more informed and judicious manner, such that the efficacy of antimicrobials may be preserved for use for future generations of humans and animals (WHO 2000; Mellon *et al.* 2001; Mitema, Kikuvi, Wegener & Stohr 2001; Nicholls, Acar, Anthony, Franklin, Gupta, Tamura, Thompson, Threlfall, Vose, van Vuuren, White, Wegener & Costarrica 2001; Nel *et al.* 2004; SANVAD 2007).

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

Antimicrobials are used extensively in animal health in South Africa for the treatment, prophylaxis and metaphylaxis of diseases as well as for growth promotion in food producing animals (SANVAD 2007). The availability of effective and safe antimicrobials is essential for animal health in both livestock and companion animals, and for sustainable and economically viable animal production (Acar & Röstel 2001). However, the use of antimicrobials in animals, particularly in food animals, may lead to selection for resistant strains of bacteria, which in turn may proceed to infect both animals and man (Witte 2000; White *et al.* 2001; Stege *et al.* 2003;). The circumstances favouring the development of antimicrobial resistance are manifold, but the most important factor is the widespread use of antimicrobials that induces selective pressure for the development of resistant genes (Van den Bogaard & Stobberingh 2000; Witte 2000; White *et al.* 2001). The use of antimicrobial drugs by the medical health profession and in the agricultural and veterinary domains is responsible for these developments due to the over-prescription and imprudent use of antimicrobials. (White *et al.* 2001; Stege *et al.* 2003;).

The phenomenon of resistance to antimicrobial drugs which represents a global public health risk is also of concern in South Africa, and similar to other developing countries, is higher than in industrialized countries (SANVAD 2007). In South Africa, a study was undertaken to establish and standardize a veterinary antimicrobial resistance surveillance and monitoring programme (Nel *et al.* 2004). Such a programme should ideally go hand in hand with one monitoring the volumes of antimicrobials used in food animals. Hence, the study undertaken for the purpose of this dissertation was a further step in establishing a future sustainable surveillance programme for obtaining data on the use of antimicrobials in food animals in South Africa to support a veterinary drug policy in which prudent antimicrobial use shall play an essential role.

2.2 Definition of antimicrobial resistance

Antimicrobial resistance is defined as the capability of bacteria to survive exposure to a defined concentration of an antimicrobial substance, be it therapeutically, prophylactically,

as a growth promoter or as a disinfectant (Acar & Röstel 2001).

2.3 Types and mechanisms of antimicrobial resistance

Bacteria may have either intrinsic tolerance or acquired resistance to an antimicrobial. Intrinsic tolerance may be defined as the natural tolerance that the majority of a bacterial genus have against an antimicrobial. For example, this may be seen in Gram-negative bacteria such as members of the family Enterobacteriaceae that are inherently tolerant of penicillin G; whereas Gram-positive bacteria are tolerant of polymixin B, because these microbes lack the cellular mechanisms required for the action of these particular antimicrobials. This intrinsic or natural form of tolerance is not an important concern in antimicrobial resistance (Schwarz & Chaslus-Dancla 2001). Acquired resistance is the situation whereby a genetic change in the bacterial genome occurs, which can be a consequence of (Schwarz & Chaslus-Dancla 2001; Hogan & Kolter 2002; Guardabassi & Courvalin 2006; Boerlin & White 2007):

- Mutation in the DNA of the bacterium ie endogenous resistance (an important but uncommon mechanism). Endogenous resistance plays an essential role in bacteria that are not known to acquire foreign DNA under natural conditions, such as the *Mycobacterium* spp. For all bacteria, it represents the main mode of acquiring resistance when high –level resistance by mobile genetic elements is not available.

- The horizontal transfer of events of mobile genetic elements carrying one or more resistance genes ie exogenous resistance (the most common and important mechanism of acquiring antimicrobial resistance). Among them, plasmids, transposons and integrons/ gene cassettes play a major role. Plasmids are extrachromosomal elements which have been detected in virtually all bacterial genera of medical or veterinary importance and also in bacteria which constitute the physiological flora of the skin and the various mucosal surfaces in humans and animals. Plasmids have their own replication systems. Plasmids may form co-integrates with other plasmids, may integrate or be integrated, either in part or *in toto*, into the chromosomal DNA or can act as vectors for transposons and integrons/ gene cassettes. In contrast to plasmids, transposons do not possess replication systems and therefore must integrate for their stable maintenance into replication-proficient vector molecules such as chromosomal DNA or plasmids in cells. Gene cassettes

represent small mobile elements of less than 2 kilobase pairs (kbp) and to date, have only been detected in gram-negative bacteria. They commonly consist of only a specific recombination site and a single gene which is in most known cases an antimicrobial resistance gene. Gene cassettes usually differ from plasmids by the lack of replication systems, and from transposon systems by the lack of transposition systems. They are usually present at specific sites within an integron. Integrons most often represent intact or defective transposons.

- Resistance can also result from a combination of mutational and gene transfer events, such as in the case of mutations that expand the spectrum of beta-lactamases or confer on them resistance to beta-lactamase inhibitors.

There are five biochemical mechanisms whereby resistant bacteria will express interference with the mechanisms of action of the antimicrobials (Cebula & LeClere 1998; White 1998; Acar & Röstel 2001; Schwarz & Chaslus-Dancla 2001; Hogan & Kolter 2002; Summers 2002; Guardabassi & Courvalin 2006; Boerlin & White 2007;):

- Enzymatic inactivation, for example bacterial β-lactamases acting on the β-lactam bond of β-lactams such as the penicillins and cephalosporins.

- Prevention of the antimicrobial from reaching its target site, for example efflux pumps actively extruding the antimicrobial such as the tetracyclines.

- Modification of the antimicrobial target site, for example modification of DNA-gyrase resulting in the development of resistance to fluoroquinolones.

- Metabolic bypass, for example in resistance to sulphonamides.

- Reduced drug uptake as a result of permeability/ impermeability of the bacterial cell wall or membrane, for example in resistance of gram-positive bacteria to beta-lactams and resistance to fluoroquinolones in gram-negative bacteria.

- Other minor biomedical mechanisms of resistance include target protection and drug trapping. Resistance by protection of the drug target has been reported for tetracyclines and more recently also for fluoroquinolones. This entails specific

ribosomal proteins binding to the ribosome in proximity to the binding site of the and dislodging the tetracyclines from the binding site. Bacteria may trap a drug by increasing the production of the drug target or another molecule with affinity for the drug. In both cases, the consequence is a reduction of the free drug at the target site (titration). Drug trapping has for example been implicated in low level glycopeptide resistance in staphylococci.

2.4 Routes of transfer of antimicrobial-resistant bacteria from animals to man

Animal bacteria, including resistant strains and/or their resistance determinants may spread to humans by direct contact, through the food chain and by environmental contamination; the two former routes being of major importance. Typical zoonotic pathogens include *Salmonella* spp., *Campylobacter* spp. and shiga-toxin producing *E. coli* strains. However, many other bacteria are known to spread from animals to humans including other *E. coli* strains, *Yersinia enterocolitica* and enterococci (Van den Bogaard & Stobberingh 2000; White *et al.* 2001).

2.5 Concerns in regard to the development of antimicrobial resistance

There may be several facets of disquiet arising from issues of antimicrobial resistance:

- The emergence and spread of of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing. MRSA infections have been isolated from farm animals and commercial meats (Chan, Wakeman, Angelone & Mermel 2008). Studies from the Netherlands suggest that animals may be a source of major human MRSA colonization in this country. MRSA has been isolated from 2.5% of pork and beef samples in a study in The Netherlands. This demonstrates that MRSA has entered the food chain. As the amounts of MRSA detected were very low, the pathogen is not likely to cause disease, especially if meat is properly prepared before consumption. However, contamination of food products may be a potential threat for the acquisition of MRSA by those who handle the food (van Loo, Diederen, Savelkoul, Woudenberg, Roosendal, van Belkum, Lemmens-den Toom, Verhulst, van Keulen & Kluytmans 2007). Also, a large hospital outbreak with MRSA due to contamination of food products has been described at a university hospital in Rotterdam in the Netherlands. (Kluytmans, van Leeuwen W., Goessens, Hollis, Messer, Herwaldt, Bruining, Heck, Rost, & van Leeuwen N. 1995). Although this outbreak was as a result of

transmission from a colonized food handler, the potential exists for transmission to humans directly from contaminated meats. Several other studies have also demonstrated serious disease caused by food-borne illness due to MRSA contamination or colonization of the GI tract (Jones, Kellum, Porter, Bell & Schaffner 2002).

- Gram-negative bacteria such as *Escherichia coli* strains expressing extended-spectrum beta-lactamases (ESBLs) or plasmidic C beta-lactamases in food animals have emerged globally and this has limited the treatment strategies available for bacterial infections. In a Spanish study from 2003, the prevalence of resistant ESBL-expressing *Escherichia coli* was 2.8% in isolates tested from sick animals (Briñas, Moreno, Teshager, Sáenz, Concepción, Domínguez & Torres 2005). In a study of 34 resistant ESBL-expressing *Salmonella* from the Netherlands during 2001 to 2002 from poultry, poultry products and patients, a high prevalence of ESBLs was found amongst the test isolates of animal origin (Hasman, Mevius, Veldman, Olesen & Aarestrup 2005). The first resistant ESBL-expressing *E. coli* was identified in a sample of meat as part of the antimicrobial resistance surveillance programme of food animals in Denmark. This resistant ESBL-expressing *E. coli* was isolated from sliced beef imported from Germany. This type of result highlights the spread of such resistant ESBLs and other food-borne bacteria expressing resistant genes from meat sold at retail, and is expected to increase since global trade is likely to increase in the future (Jensen, Hasman, Agersø, Emborg & Aarestrup 2006).

- Vancomycin resistant enterococci (VRE) are a cause for concern in the medical field. Vancomycin is a glycopeptide antibiotic that is used to control multi-resistant *Staphylococcus aureus*. It has been suggested that the use of avoparcin (a glycopeptide antimicrobial used in poultry and pigs for growth promotion) has selected for the emergence of one type of VRE resistance in man. In countries where avoparcin was used as an antimicrobial growth promoter, VRE was not only found in food animals fed with avoparcin, but also in the faecal flora of healthy humans and pet animals (Van den Bogaard & Stobberingh 2000; Witte 2000; Wegener 2003;).

- The emergence of fluoroquinolone resistant strains in zoonotic *Salmonella* and of *Campylobacter* bacteria have been reported in Denmark, the United States and the

United Kingdom. Fluoroquinolones are an important group of antibiotics used in human medicine and resistance to this group leaves few treatment options as multiple cross-resistance to other antibiotics is now commonplace. Fluoroquinolones are approved for therapeutic medication in animal health in many countries, including South Africa, and it is suspected that such use contributes to the emergence of resistant bacteria in humans (White *et al.* 2001; McEwen & Fedorka-Cray 2002).

- Multi-resistant *Salmonella* typhimurium DT 104 has become a problem. A distinctive feature associated with most DT104 isolates is a multiple antimicrobial resistance phenotype to ampicillin, chloramphenicol/ florfenicol, streptomycin, sulphonamides and tetracyclines. This *Salmonella* strain produces more severe symptoms leading to a greater percentage of mortalities. Such resistance has become commonplace overseas, leaving fewer treatment options (Van den Bogaard & Stobberingh 2000; Witte 2000; White *et al* 2001). A very specific concern arising from resistance to this *Salmonella* strain is that HIV-infected individuals have been shown to be at greater risk for non-typhoidal *Salmonella* infection than the general population. A study undertaken at Chris Hani Baragwanath hospital, in South Africa in 2000 revealed an increasing rate of invasive *Salmonella* infection in HIV/AIDS patients, increasing antimicrobial resistance and the presence of a multi-resistant *Salmonella* typhimurium DT 104 (Crewe-Brown, Karstaet, Keddy, Khoosal, Sooka & Kruger 2003).

- The first *L. monocytogenes* resistant strains were reported in 1988. Since then, *Listeria* spp. isolated from food, the environment and sporadic cases of human listeriosis have been shown to be resistant to one or several antimicrobials (White *et al.* 2001).

- Wide-spread appearance of multi-resistant versus mono-resistant strains is of great concern. In a study carried out in France from 1986 to 1995, the incidence of antimicrobial–resistant strains in avian and farm-animal *Salmonella* spp. was collated by the National Veterinary and Food Research Centre (CNEVA). For the first six years most strains were resistant to only one antibiotic. Thereafter, multi-resistant strains predominated (JETACAR 1999).

- Another cause for disquiet is the volumes of antimicrobials used as feed additives in the animal health industry. It is estimated that 60% of all antibiotics used in the

industry in South Africa are for this purpose. In the USA, it has been estimated that 70% of the 8,1-11,2 x $10^{6.0}$ kg of antimicrobials that are consumed annually in animal health are used for non-therapeutic purposes (Mellon *et al.* 2001). The quantities of antimicrobials have recently been estimated for each animal production group in the USA in a 2001 publication entitled "Hogging it" published by the Union of Concerned Scientists. Extrapolations were made of the mean doses, numbers of animals in production and slaughtered for meat annually, percentages of animals to which antimicrobials were administered and durations of treatment, albeit that such extrapolations rely heavily on assumptions and expert opinions (Mellon *et al.* 2001). In Australia, 0,7 x $10^{6.0}$ kg of antimicrobials are imported annually (JETACAR 1999). Of these quantities 67% are for animal use and 33% for human use. Of the animal health portion no less than 57% is destined for non-therapeutic purposes and included as feed additives. Approximately 50% of all the antimicrobial agents used annually in the EU are given to the animals (van den Bogaard & Stobberingh 2000). These antimicrobials are not only used for prevention and treatment but may also be added continuously to animal feeds to promote growth and increase feed efficacy. In France, in 1999, the total consumption of antimicrobials in the animal health sector was 1,4 x $10^{6.0}$ kg of which 93,2% was intended for use in food animals (JETACAR 1999; Nicholls *et al.* 2001). The antimicrobials which are administered in feeds are delivered at a dose concentration that will inhibit most but not all of a bacterial population. Accordingly, these bacteria are under selective pressure to become more resistant (Wegener 2003).

2.6 Consequences of antimicrobial resistance

The consequences of antimicrobial-resistant bacterial infections are manifold and far-reaching. Of great note is the economic and health impact. In the medical field, many times more expensive antibiotics have to be utilized and multiple courses of antibiotics must be administered. There is also the increased duration of hospital stay, increased morbidity and mortality and the effective antimicrobial agents may be more toxic, expensive and more difficult to administer, as well as an increased use of hospital resources (Barza 2002; FAAIR 2002; Smith & Coast 2002). In assessing the economic and health impact of antimicrobial resistance holistically, rapid and accurate diagnosis and susceptibility of the causative bacterial organism must also be taken into consideration. It has been noted in South Africa, as an example, that management of tuberculosis (TB) is complicated by the emergence of

drug-resistant strains of *Mycobacterium tuberculosis* and this poses a threat to the success of TB control programmes. In the long-term, costs incurred as a result of antimicrobial resistance may have a significant impact on the economy of the country, let alone the welfare of the human and animal populations! To date, no investigation or projection of possible costs of antimicrobial resistance has been carried out in South Africa.

2.7 International initiatives

Antimicrobial resistance is a global concern, requiring harmonized global initiatives. Various international initiatives have been undertaken to address this issue (Acar & Röstel 2001):

- In the UK it was recommended by the Swann Committee Report (1969) that in legislation, antibiotics must be clearly designated as either "in feed" (i.e. growth promoters) or "therapeutic", and that growth-promoting antibiotics should, by definition, have no therapeutic use in humans or animals. This regulation, however, did not include a provision to withdraw approvals of antimicrobial growth promoters (AGPs) should members of the same class at a later time come into use for humans.

- From 1986, Sweden was the first of the Scandinavian countries to take the initiative to ban all antimicrobial growth promoters (AGPs). Interestingly enough, this has not had a detrimental effect on livestock production (Van den Bogaard & Stobberingh 2000; WHO 2003). For instance, in the production of slaughter pigs, specialized beef, and turkeys, no negative clinical effects were reported as a consequence of the ban. In broiler chicken production, expected problems with necrotic enteritis were prevented by a continuous use of antimicrobials, largely to the same extent during the first 2 years after the ban. Following the implementation of results from experimental activities during that period, the general usage of antimicrobials could be stopped and expected problems with outbreaks of necrotic enteritis were prevented. In piglet production, significant clinical problems emerged that created a demand for antibiotic-medicated feed at therapeutic dosages. During the subsequent 4-year period, the use of antimicrobials increased, involving up to 75% of the pigs. Thereafter, the use of antimicrobials decreased because of improved management, and could be halved in 1993 followed by a gradual further decrease supported by the addition of zinc oxide to the feed. In 1998, compared to 1994, the total use of zinc decreased by 90%. In 1998/1999, only 5% of weaning piglet producing herds used antimicrobial medicated

feed and 17% used zinc. The AGP ban has shown that under good production conditions it is possible to reach good and competitive production results for the rearing of poultry, calves, and pigs without the continuous use of AGPs. As a result of the ban and a focus on disease prevention and correct use of antimicrobials, the total use of antimicrobial drugs to animals in Sweden decreased by approximately 55% during the last 13-year period, and a relatively low prevalence of antimicrobial resistance has been maintained (Wierup 2001). Banning the use of AGPs in Danish swine also concurred with the results from Sweden (Middlebo 2003; Wegener 2003).

- In 1997, the World Health Organisation (WHO) met in Berlin to discuss the medical impact of the use of antimicrobials in food animals (WHO 1997).

- In Geneva, in June 1998, a discussion was held on the use of quinolones in food animals and the potential impact on human health (WHO 1998).

- In Prague, in 1998, the Office International des Épizooties (OIE) discussed the role of international trade in animals, animal products and feed in the spread of transferable antibiotic resistance and also possible methods for the control of the spread of resistance or resistance factors (OIE 1998).

- As a result of the documentation on the use of antimicrobials for growth promotion in food animals leading to the creation of a major food animal reservoir of bacteria resistant to AGPs and also to medically important last resort antimicrobials, such as vancomycin for example, the European Union then imposed a ban on all AGPs that belonged to classes also used in human medicine (Wegener 2003). Avoparcin was banned in 1997. The EU then also invoked the “Precautionary Principle” in 1998, which propounds that even if there is not enough scientific evidence on the frequency of the risk of a hazard, but nevertheless the hazard is still seen as a possible risk, then this “Precautionary Principle” may be invoked. On this basis, the use of tylosin, spiramycin, virginiamycin and bacitracin were banned as feed additives in EU countries in 1998 (Witte 2000). Finally, with effect from 1 January 2006, the last four AGPs used in the EU, monensin sodium, salinomycin, flavophospholipol and avilamycin were banned. In this regard Regulation 1831/2003/EC on additives for use in animal nutrition, replaced Directive 70/524/EEC on in-feed additives (Sanders 2005) which includes three important criteria to authorize use in-feed:

- Approval may only be granted if the concentration at which the antimicrobial is administered does not adversely affect human or animal health or the environment;
- There are no serious reasons to restrict the use to human or veterinary medical uses;
- The permitted concentrations have no therapeutic or prophylactic effects.

- The OIE established an *ad hoc* expert committee on resistance to antimicrobial drugs in 1999. (SANVAD 2007). The terms of reference of the Committee were to develop guidance documents for member countries of the OIE relating to:
  - Guideline for the harmonisation of national antimicrobial resistance monitoring and surveillance programmes;
  - Guideline for controlling the volumes of antimicrobial agents used in animal production;
  - Guideline for the responsible and prudent use of antimicrobial agents in veterinary medicine;
  - Guideline for the methodology for bacterial antimicrobial susceptibility testing;
  - Guideline for the risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals.
- In 2000, the WHO met in Geneva to discuss the global significance of antimicrobial resistance in food animals (WHO 2000).
- In Australia, United States and Canada, feed additives are available as over the counter (OTC) medicaments, as is the case in South Africa, with the large majority of authorized products. Australia has adopted a conservative approach (JETACAR 1999) and does not allow the use of in-feed antimicrobials (low dose and long-term) unless:
  - There is demonstrable efficacy in livestock production;
  - The drugs are never or rarely used as therapeutic, systemic medicines in humans and animals or are not considered critical medicines for human health;

  - The drugs are not likely to impair the efficacy of any other antimicrobials for human or animal infections, through the development of resistant bacterial strains.

- In the United States, the Centre for Veterinary Medicine (CVM), Food and Drug Administration is responsible for regulation of veterinary antimicrobials. The CVM proposed to categorize new antimicrobial drugs based on their importance in human medical therapy. Category I drugs (or members of a class of drugs) are essential for treatment of life-threatening diseases of humans, or are important for treatment of foodborne diseases of humans, or are members of a unique class of drugs used in humans (e.g., fluoroquinolones, glycopeptides). Category II drugs are important for treatment of human diseases that are potentially serious, but for which suitable alternatives exist (e.g., ampicillin, erythromycin). Category III drugs have little or no use in human medicine, or are not the drug of first choice for human infections (e.g., ionophores). Extralabel use of an approved animal or human drug in animal feed is not permitted (Viola & DeVincent 2006).

- In Copenhagen, in 2007, the World Health Organization held an expert workshop to meet the following objectives as part of the initiative to address antimicrobial resistance concerns (WHO 2007):

  - To update the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and comments from the review recently undertaken by the WHO expert committee for the Selection and Use of Critical Medicines.

  - To develop criteria for prioritization of antimicrobials within the updated category of critically important agents for human medicine.

  - To apply these criteria to prioritize the critically important antimicrobials for developing risk-management strategies in order to preserve their effectiveness in human medicine.

  - To provide recommendations to FAO, OIE and WHO, as well as the Codex Alimentarius Commission, on current and future activities regarding non-human use of antimicrobials.

- The OIE International Committee unanimously adopted the List of Antimicrobials of Veterinary Importance at its 75th General Session in May 2007. This was in response to a recommendation made by the FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance to develop a list of the critically important antimicrobials in veterinary medicine. The OIE addressed this task through its *ad hoc* Group on antimicrobial resistance. The Group decided to address all antimicrobials used in food-producing animals to provide a comprehensive list, divided into critically important, highly important and important antimicrobials. The following criteria were selected to determine the degree of importance for classes of veterinary antimicrobials (OIE 2007):

    - Criterion 1. Response rate to the questionnaire regarding Veterinary Critically Important Antimicrobials:
    - This criterion was met when a majority of the respondents (more than 50%) identified the importance of the antimicrobial class in their response to the questionnaire that was circulated.
    - Criterion 2. Treatment of serious animal disease and availability of alternative antimicrobials:
    - This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.

- On the basis of these criteria, the following categories were established:

    - Veterinary Critically Important Antimicrobials: **are those that meet criteria 1 AND 2.**
    - Veterinary Highly Important Antimicrobials: **are those that meet criteria 1 OR 2.**
    - Veterinary Important Antimicrobials: are those that meet NEITHER criteria 1 OR 2.

2.8 Local initiatives

In South Africa, certain initiatives have been undertaken to address some of these concerns

(Nel *et al.* 2004; SANVAD 2007). In October 2003, an Antimicrobial Resistance Congress was held in Durban to discuss research undertaken in both the medical and veterinary fields and to determine national policy on antimicrobial resistance. This was a collaboration between the medical and veterinary professions. Another initiative undertaken was the creation of The South African National Veterinary Surveillance and Monitoring Programme (SANVAD) for Resistance to Antimicrobial Drugs. This association was started as a result of an appeal made by the OIE to member countries to undertake efforts to establish national programmes for the management of antimicrobial resistance (SANVAD 2007). To this end, international standards for the detection and quantification of antimicrobial resistance in animal bacteria were established by the OIE in May 2002 and South Africa took cognizance of these standards. In order to develop and standardize a practical surveillance and monitoring programme in South Africa, a network of participating laboratories was set up and training was provided to laboratory technologists to make use of the new methodologies published in 2003 in the OIE International Standards on Antimicrobial Resistance. A pilot study was undertaken and completed in 2001 in South Africa to determine whether a surveillance programme could be managed with the aid of reagents prepared in-house (Nel *et al.* 2004). As a result of this research, a final decision was taken to perform antimicrobial surveillance in South Africa with standardized, commercially-produced microdilution panels, due to logistical considerations.

2.9 Surveillance systems for veterinary antimicrobial consumption

There are surveillance systems dealing with volumes of veterinary antimicrobials consumed in various countries such as Sweden and Denmark. These surveillance systems were established in response to an invitational conference hosted by the EU in 1998 in Copenhagen called The Microbial Threat. It was recommended (as one of The Copenhagen Recommendations) that member countries collect data on the supply and consumption of antimicrobial agents as part of a European surveillance system on antimicrobial resistance:

- SVARM (Swedish Veterinary Antimicrobial Resistance Monitoring) is a surveillance system for the volumes of veterinary antimicrobials (both food and companion animals) consumed in Sweden and was established in 1995. This system is part of a holistic approach to limit development of antimicrobial resistance by means of surveillance of antimicrobial resistance and use, control and preventive measures, education, research and training through an agency called the Swedish Strategic

Programme for the Rational Use of Antibiotics and Surveillance of Resistance (STRAMA) and is funded by the Swedish government. Antimicrobials for use in animals in Sweden are only available on veterinary prescription and all pharmaceuticals are dispensed by pharmacies. Since 2003, these statistics are based on sales figures provided by the National Corporation of Swedish Pharmacies (Apoteket AB) and represent the total amount of antimicrobials authorized for veterinary use sold from wholesalers to pharmacies calculated to kg active substance. These statistics are tabulated in the annual report into the different classes or substance groups (using ATC_{vet} classification) of antimicrobials and statistics are available from 1980 onwards. The annual reports include figures for both food and companion animals. The different substances are not equal in their biological activity per weight unit and therefore, each substance group should be evaluated separately. Nevertheless, the total figures indicate trends of usage. Furthermore, these statistics include antimicrobials marketed with a special license, sales for products for use in individual animals (mostly companion animals but also some food animals), as well as annual sales of antimicrobials authorized for group (food animals) treatment and ionophoric anticoccidials sold, also expressed as kg active substance. Also included are the annual sales of antimicrobials mostly or exclusively intended for treatment of pigs through feed and water. Yearly volumes of antimicrobials (kg active substance) prescribed for use in farmed fish as well as yearly amounts of antimicrobials prescribed for in–feed medication per fish species are also set out in a tabular form. It is assumed that the amount sold is also the amount used during the observation period. Extra-label use of human drugs is not included within these statistics – such drugs are primarily prescribed in small animal medicine and their use is decreasing as the number of available veterinary antimicrobials is increasing. Trends of antimicrobial resistance are also discussed in zoonotic *Salmonella* species as well as selected *Campylobacter* species (SVARM 2003, SVARM 2007). A parallel report, on the utilization of antimicrobials by humans as well as trends of antimicrobial resistance in bacteria from humans is included in the same document (SWEDRES 2007).

- VETSTAT - The Danish Ministry of Food, Agriculture and Fisheries funds a monitoring system based on drug usage information collected at the herd level, known as VETSTAT. VETSTAT is constructed as a relational database. A relational

database is a database that groups data using common attributes found in the data set. The resulting "clumps" of organized data are much easier to understand (DANMAP 2004). Since 1996, trends on the use of antimicrobials in food animals in Denmark have been published in the annual reports provided by the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). VETSTAT data originate from three sources: pharmacies, veterinarians and feed mills. All administration of drugs for use in animal production is reported on a monthly basis. The data input for VETSTAT is very detailed and includes farm identification, animal species, age group, date of administration, antimicrobial identification, volumes of antimicrobials, disease category and the identification of the prescriber. Each food animal species is allocated a species code number and then the species is subdivided into the different age groups and codes allocated for each of these age-groups. The age-groups can be further subdivided into body systems for example, respiratory system, gastro-intestinal system. As an example, pharmacies provided 95% of the total weight of antimicrobial compounds used in Denmark in 2001. More than 80% of the antimicrobial compounds reported by pharmacies were sold on prescription to end-users (owners) and included information on animal species, age-group and body systems. More than 90% of the total volume of antimicrobials sold on prescription was used for pigs (Stege *et al.* 2003). Human antimicrobial consumption data are also compared with veterinary consumption and trends and incidence of antimicrobial resistance in bacterial strains in the field of animal health as well as in the domain of human health are discussed and compared (DANMAP 2004).

- In Australia, trends in the level and type of antimicrobial use can be assessed from import records. These records may include information on the indications for which the imported antimicrobials will be used. Importers of antimicrobials (merchants, pharmaceutical companies and private individuals) must hold a permit issued by the Therapeutic Goods Administration (TGA) to import antimicrobials. Since 1992, all importers have had to declare the indication of the antimicrobial that they are importing, whether it is intended for human therapeutic use, veterinary therapeutic use, as a growth promoter, research in the laboratory or for another special purpose. The commonwealth Department of Health and Aged Care, through the TGA is responsible for collecting and reporting these end-use data. The TGA issues permits,

collects and maintains this information in an electronic system in a tabulated format. The information is expressed as kg of active ingredient but does not accurately reflect the difference in potencies between agents. These data have been subject to only limited scrutiny but results show that approximately two thirds of all antimicrobials imported are intended for veterinary use and only one third is intended for human use. Veterinary consumption data are only available from the pharmaceutical companies and are not systematically collected by species (JETACAR 1999).

- The Veterinary Medicines Directorate (VMD), an Executive Agency of the Department for Environment, Food and Rural Affairs (DEFRA), is responsible for the authorization of veterinary medicines in the UK (United Kingdom). For the past ten years, in response to recommendations made by the Advisory Committee on the Microbiological Safety of Food (ACMSF), statistics have been collected and collated and figures have been published on UK sales volumes of active antimicrobial ingredients used in products authorized as veterinary medicines, growth promoters or coccidiostats. The report has been extended over time to include anti-protozoal and antifungal products. These reports are based on sales data provided voluntarily by the veterinary pharmaceutical companies marketing these products in the UK from 1998-2004. Data for 2005 and later were collected as a statutory requirement in accordance with the provisions of EC Directive 2001/82 (as amended), following entry into force of the Veterinary Medicine Regulations 2005. Since 2006 this report includes products imported by veterinarians under Special Import Certificate (SIC) or Special Treatment Certificate (STC) arrangements. The volumes are expressed in tonnes of active ingredient and include information for food animals and non-food animal usage as well as being broken into sales for each food animal species (VMD 2008).

- In the United States, surveillance of antimicrobial resistance in food-borne bacteria is undertaken by the National Antimicrobial Resistance Monitoring System (NARMS) for enteric bacteria. However, the United States still lacks a system for collecting antimicrobial consumption data (Nunnery, Angulo & Tollefson 2006). There are several obstacles to obtaining correct estimates of the antimicrobial usage in US agriculture. Many drugs that are used in food-producing animals require no prescription and are sold straight from manufacturers to distributors, without going

through a pharmacy. Also, when the sponsors of approved animal drugs in the United States submit their annual reports on the sales of each drug they are not required to specify whether the substance is meant for domestic use or export or what the actual conditions for use are. The US Food and Drug Administration is proposing changes in this recording system to enable a more accurate estimate of the antimicrobial usage in food animals (WHO 2002).

The ideal surveillance system used for collection of antimicrobial consumption data should be clear and transparent to facilitate trend analysis and make comparisons possible within the country itself as well as internationally between countries. For this purpose data on animal populations and production should be provided, for example numbers of animals slaughtered per year or animal census figures as well as data on the volumes of milk yielded on an annual basis. In each country, the competent regulatory authority should collect data on the total usage of antimicrobials in food animals. The methods of how to collect or obtain this usage will depend upon the national situation because different countries might have different distribution and registration processes.

This can be done by collecting data from one or more of the following sources:

- Importers and exporters as well as production data from manufacturers;
- Data on intended and actual usage from manufacturers, distributors including feed mills, pharmacies and veterinary prescription records;
- Veterinarians, farmers, animal producers.

The following details should preferably be collected and reported in priority order:

- Usage in the various animal species and may include animal production classes;
- Routes of administration such as oral, including in-feed or in-water, parenteral (injection), intramammary, intrauterine, and topical;
- Therapeutic, prophylactic and growth promotion use.

Such a surveillance system should also ideally include antimicrobials imported under

"special license." In addition, it could also be of added value to further subdivide the consumption of antimicrobials into regional or local usage. If it is difficult to collect detailed data for an entire country, the data could be collected in a representative area by a statistically robust sampling scheme. The figures should be expressed in kg active ingredient and the development of a system that better takes into account the potency of the drugs and differences in the dosages, such as the DDD (defined daily doses) system in human medicine, is needed. At a minimum, countries should collect data on the overall use of each antimicrobial agent and report these data in kilograms of active ingredient on an annual basis. Standardized national and international terminology and methodology of reporting is essential so that it is clear which antimicrobials are used. A system is required to identify and classify antimicrobials similar to the Anatomical Therapeutic Chemical (ATC), which is used for human antimicrobials. One such system being developed is ATC-vet. The system chosen should be adapted to the needs of the monitoring programmes and be compatible with other relevant international systems. These statistics should be available both electronically as well as in a printed form and preferably should be posted onto an appropriate website. Within each country, confidentiality agreements and laws should be reviewed and obstacles to reporting usage data resolved. However, where it is necessary to protect confidentiality in certain countries, data may be aggregated into compound classes prior to publication by the national government (WHO 2002). Countries should also keep a register of all the available antimicrobials for specific animal species and specific diseases as this will help to identify possible illegal usage (WHO 2004). The consumption data should be compared with the resistance data to decrease further trends of antimicrobial resistance and such a comparison should be undertaken timeously and made available to all interested parties (WHO 2002).

The desired outcome of such surveillance systems is to ultimately preserve the efficacy of the existing antimicrobials for future use by predicting possible directions in the development of antimicrobial resistance derived from the data generated by such systems. Data on the volumes of antimicrobials supplied and used in animal husbandry in South Africa are very scanty (SANVAD 2007). The establishment of such a monitoring programme in combination with a veterinary antimicrobial resistance surveillance and monitoring programme is very briefly mentioned by Nel *et al.* 2004. Such information would be a key element in attempting to resolve several issues of antimicrobial resistance in South Africa; namely:

- To set a benchmark for a monitoring and surveillance programme on the volumes of antimicrobials supplied and consumed by animals in South Africa;

- To undertake risk analysis of the potential health risks from antimicrobial resistance in animals and man. During the JETACAR (Joint Expert Technical Advisory Committee on Antimicrobial Resistance) deliberations in Australia in 1999, there was sufficient evidence obtained from a review of the literature that there is qualitative evidence that antimicrobials fed to animals lead to resistant bacteria and that these bacteria or their resistant genes may be passed on to man, principally via the food chain. However there is less information on the frequencies of any such transmissions. The OIE/ FAO have proposed a risk assessment model for surveillance of antimicrobial consumption. Risk analysis is defined in the OIE code as the process of hazard identification, risk assessment, risk management and risk communication. It encompasses assessing and managing the risk together with all the appropriate communication between risk assessors, stakeholders and risk managers.

2.10 Conclusion

The general perception is that antimicrobial use leads to selective pressure for the development of antimicrobial resistance, both in the domains of human and animal health. When considering this development of cross-resistance, the following observations may be made. Most classes of antimicrobial drugs used in animals have their equivalent in the human health field. This fact is of great concern both in South Africa as well as internationally because of the potential to compromise therapy in the medical field for people suffering from multi-drug resistant bacterial infections, where there are few drug choices left to treat such patients. The global health phenomenon of resistance to antimicrobials is also a serious problem in South Africa and has been confirmed by the results of the first annual report of the national veterinary surveillance and monitoring programme (SANVAD 2007).

There are also specific concerns regarding antimicrobial resistance in South Africa, in that legislation is very fragmented with regards to control of residues of veterinary medicines and the monitoring of veterinary residues in foods of animal origin in South Africa is export driven, so there is not enough emphasis on establishing food safety for the local consumer (Act 36 of 1947 2005; Act 101 of 1965 2005). There is also no formal surveillance system of

the volumes of antimicrobials consumed by food animals in South Africa and also no formal surveillance and monitoring programme on antimicrobial resistance testing of zoonotic or indicator bacteria from animals and foods of animal origin. There is therefore no documented evidence on patterns of use of antimicrobials in the different farm animal species and there is no integrated approach to recognizing trends of antimicrobial resistance (Nel *et al.* 2004). There is therefore a lack of information in South Africa about the volumes and patterns of antimicrobial usage in food animals that this study will in part address. By the collection of such data, policy decisions to address concerns regarding antimicrobial resistance may be reached in a more informed and judicious manner (Mellon *et al.* 2001; Mitema *et al.* 2001; Nicholls *et al.* 2001; WHO 2001; Nel *et al.* 2004; SANVAD 2007)

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CHAPTER 3

3. MATERIALS AND METHODS

3.1 Introduction

The volumes of antimicrobials consumed were sourced from veterinary pharmaceutical companies only. It was originally intended to also source this information from the importation data of the South African Revenue Service (SARS 2004) but such data were found to be invalid for several reasons. These included the fact that both veterinary and human antimicrobial figures were added together within the SARS statistics and there was no system in place to differentiate these antimicrobials. Also substances such as anthelmintics were included within the tariff headings for antimicrobials in order to reduce import duties! Due to the sensitive nature of the information requested, as perceived by the companies, only eight companies participated in the survey which influenced the discussion and the conclusions within the context of these data.

3.2 Study design

The type of study entailed here was a survey, collation and comparison of the volumes of the antimicrobials sourced from direct sources that were supplied and administered during the years 2002-04 to animals in South Africa, expressed as kg of active ingredient.

3.3 Sites of collection

3.3.1 Range of Antimicrobials authorized for veterinary use in South Africa

Information was obtained from applications made under the two Acts which control the availability of all antimicrobials in South Africa:

- The Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act 36 of 1947, administered by the National Department of Agriculture

- The Medicines and Related Substances Control Act 101 of 1965 as amended by Act 90 of 1997, administered by the National Department of Health.

The last quarterly Index of Veterinary Specialties (IVS) of 2004 and the MIMS IVS Desk

Reference (IDR) 2003/ 2004 was also consulted.

3.3.2 Volumes of Antimicrobials used during 2002 to 2004 as sourced from Veterinary Pharmaceutical Companies

Information on the volumes of antimicrobials manufactured and supplied for animals by the veterinary pharmaceutical industry in South Africa were sourced from the veterinary pharmaceutical companies. There were 25 veterinary pharmaceutical companies manufacturing, importing or distributing antimicrobials in South Africa, at the time of collection of the data. Data were obtained from eight of these veterinary pharmaceutical companies. Six of the eight companies were able to provide data for each of the three years. Two of the eight companies were able to provide data as a total for all three years under review.

3.3.3 Volumes of antimicrobials included in feed

In scrutinizing the volumes of antimicrobials included in the feed, the following statistics were included to obtain a more accurate calculation and interpretation of this parameter:

- Sales of animal feed during 2002 – 2004;
- Livestock census figures for 2002 – 2004;
- Postulated percentages of antimicrobial-medicated feed.

The national feed sales for 2002-2004 were sourced from the Animal Feed Manufacturers Association (AFMA).The Directorate: Animal Health of the National Department of Agriculture was consulted for the census of animals in South Africa separated into the various livestock categories. The estimated percentages of feeds medicated with antimicrobials during the period were obtained from one feed mix manufacturing company. The volume of in-feed antimicrobials sold was calculated from the figures provided by the 8 pharmaceutical companies.

3.3.4 Value of sales of Antimicrobials

This information was obtained from The South African Animal Health Association (SAHAA).

3.4 Data Collection/Observations

3.4.1 Availability of antimicrobials authorized for food animal use in South Africa

The Act which controls the antimicrobials was also indicated in this information, as it controls the channels of availability of the antimicrobial.

Act 101 of 1965 medicines requires a veterinary prescription, whereas Act 36 of 1947 remedies are over the counter (OTC) medications. The proposed data observations were tabulated in Addendum I. These observations included:

- Class of antimicrobial
- Trade name of antimicrobial
- Active pharmaceutical ingredient (API)
- Dosage form and strength
- Indication (i.e. species of food animals and whether for treatment, prophylaxis or growth promotion)
- Act under which the antimicrobial is administered
- Withdrawal period

3.4.2 Volumes of antimicrobials used during 2002 to 2004 as sourced at the Veterinary Pharmaceutical Company Level

The collection of these data entailed the following details as also set out in Addendum I:

- Class of antimicrobial
- Active pharmaceutical ingredient (API)
- Kg active ingredient
- Dosage form

- Indication (ie specie of food animals and whether for treatment, prophylaxis or growth promotion)

Dosage forms in this survey included: parenteral injection, tablets, enteral solutions, water solubles for mixing into the drinking water, premixes, intramammary preparations, intrauterine preparations and topical preparations.

3.4.3 Volumes of antimicrobials included in feed from 2002-2004

The quantities of animal feed sold were collected in tonnes (kg x 10^3) for each year (1 April to 31 March of each year) as also contained in Addendum I for each of the following species:

- Dairy cows
- Slaughter cattle, sheep and goats
- Pigs
- Layers
- Broilers
- Broiler breeders
- Ostriches
- Aquaculture (freshwater fish)
- Other

The percentages of medicated feed sold for each year[1] were then postulated. This postulated information was expressed as a percentage of the quantities of feeds as set out in Addendum I for the following species:

- Dairy cows
- Slaughter cattle and sheep
- Pigs
- Layers
- Broilers
- Broiler breeders

3.4.4 Value of Sales of antimicrobials[2]

The volumes of sales of antimicrobials reflected in South African Rands were collected for the years 2002-04 according to the classes of antimicrobials. This information was supplied in a very specific format by SAAHA, as seen below and did not correlate exactly with the other proposed formats of the various classes of antimicrobials set out in Addendum I.

Injectable Antimicrobials:
Tetracyclines (long-acting)
Tetracyclines (short-acting)
Sulphonamides
Sulphonamides/ potentiated sulphonamides
All penicillins& streptomycins
All others

[1]**There was a study deviation in 3.4.3 – The percentages of medicated feed sold for each year. Please refer to Addendum III.**

[2]**There was a study deviation in 3.4.4 – Values of sales of Antimicrobials. Please refer to Addendum III.**

(Soluble Powders/ Tablets & Liquids):

Tetracyclines

Sulphonamides & potentiated sulphonamides

Nitrofurans

Other oral/ soluble powders – poultry

All others

Antimicrobial Feed Additives (AFAs):

Tetracyclines

Tylosin

Nitrofurans

Growth promoters, including ionophores

Anticoccidials, excluding ionophores

All others

Intramammaries:

Lactating cow

Dry cow

Antimicrobials:

Intrauterine

Topical

Eye/ ear

Capsules/ tablets/ drops

Other

3.5 Data analysis

Volumes of antimicrobials were calculated in kilograms of active ingredient for each particular antimicrobial class. The collected data were entered into MS Excel 2000 programmes and Microsoft Word documents. The data sourced from the various sites of collection were depicted as bar graphs and tabulated. Descriptive calculations of the volumes of antimicrobials were done, e.g. determination of means, standard deviations and minimum and maximum values. These were set out in Addendum IV. An attempt was made to estimate the volume of illegal importation of antimicrobials, applications for trial samples and importation of analytical samples of antimicrobials. A correction factor was obtained from information supplied by the South African Animal Health Association on the illegal importation of antimicrobials which was estimated at 5%.

3.6 Potency of antimicrobials versus volumes of antimicrobials

The effect of potency of the antimicrobials in the interpretation and examination of trends of antimicrobial consumption was also given consideration. The relative potency of antimicrobials can be compared through a unit called the Defined Daily Dose in Animals (DDDanimal) (Grave, Greko, Nilsson, Odenvik, Mørk & Rønning 2000; Jensen, Jacobsen & Bager 2004). The definition of this unit is the assumed average dose per day for a drug used for its main indication in each adult animal species. Only veterinary medicines which were classified according to the Anatomical Therapeutic Chemical veterinary classification (ATCvet) were evaluated (WHO Collaborating Centre for Drug Statistics Methodology 2006). The use of the ATCvet/ DDDanimal system allows for standardization of drug groups. This is a stable unit of measurement to enable comparisons of drug use between countries and regions and allows examination of trends in drug use over time and in different settings. This system serves as a tool for presenting drug utilization statistics. In the raw data, some of the companies specified the potency of the raw active antimicrobials. In these raw data, the specified potency of the raw actives remained consistently the same. In human medicine, the number of DDD annually consumed was calculated according to the following formula (Capellà 1993):

Amounts of drug sold in one year (mg) x 1 000 inhabitants

= DDD/ 1000 inhabitants/ day

DDD(mg) x 365 days x no. of inhabitants/ 1000

The following formula may be used to calculate the annual $DDD_{food\ specie\ animal}$ consumed (Grave *et al.* 2000):

Amounts of antimicrobial sold in one year (mg) x 1 000 food animals at risk

= DDD_{animal}/ 1 000 food animals at risk/ day

= DDD_{animal}(mg) x 365 days x no. of animals at risk.

These defined daily dosages for the antimicrobials may be calculated for each of the years under review, using the available data from this study.

However, within the context of this specific study, clarification needed to be sought on the calculation of the defined daily dosage per species of food animal in South Africa.

The volumes of antimicrobials sold per year obviously differed but it was debatable as to the value of calculating the volumes of antimicrobials sold per year, per 1000 animals, as opposed to calculating the defined daily dosage in South Africa as follows:

Defined daily dosage per food animal species for antimicrobial type =

Volumes of antimicrobial sold for the year/ number of species of food animal x average mass (kg) x dosage of antimicrobial (mg/kg). Please refer to Addendum V, for the temporary Defined Daily Dosages.

CHAPTER 4

4. RESULTS

4.1 Introduction

Results of the volumes of antimicrobials consumed were presented as tables and bar graphs depicting the use of the various antimicrobials for each of the three years surveyed. Increasing or decreasing trends were noted. The other results, such as the availability of registered antimicrobials in accordance with Act 101 of 1965 and Act 36 of 1947, the quantities of feed sold, percentage of medicated feed and volumes of antimicrobials sold were also tabulated and depicted as bar graphs. A description of the patterns of use of antimicrobial consumption at each animal species was not possible as information at this level was not supplied by the pharmaceutical companies. Trends were noted.

4.2 Availability of authorized antimicrobials for food animal use in South Africa

The number of products for each class of antimicrobial authorized for sale in South Africa were depicted in Table 4.2.1 and Figure 4.2.1 and details provided in Addendum II. Table 4.2.2 depicted all antimicrobial growth promoters registered in South Africa in terms of Act 36 of 1947. There was a total of 234 registered antimicrobials available for food animals. The majority of registered antimicrobials (72%) were Act 36 of 1947 stock remedies as opposed to the antimicrobials registered in terms of Act 101 of 1965 (28%).

A comparison between the numbers of registrations available in the various classes of antimicrobials available in South Africa was shown in Figure 4.2.1.

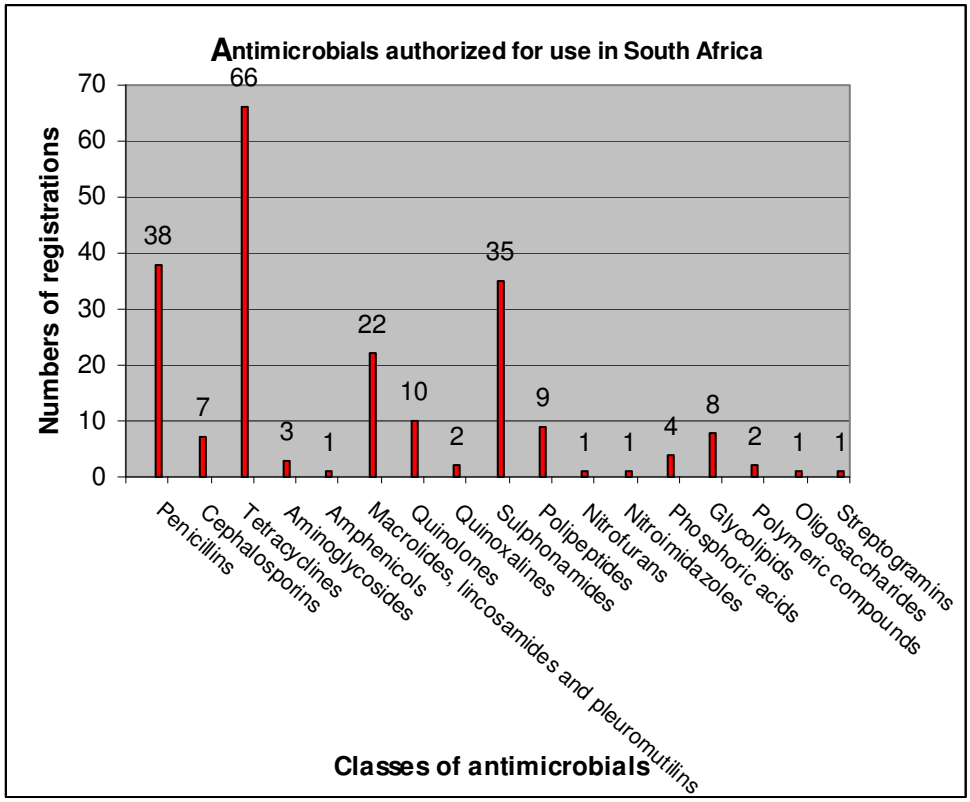

Figure 4.2.1: Comparison of numbers of registrations within the various classes of antimicrobials authorized in South Africa.

Table 4.2.1: Summary of authorized veterinary antimicrobials for use in food animals in South Africa.

Class and type of antimicrobial	Authorized products	Dosage forms								
		Inj.[2]	Tab.[2]	Oral sol.[2]	Pre.[2]	Po.[2]	Intra-mam.[2]	Intra-uter.[2]	Ae[2]	Oph.[2] /aural
Penicillins	Stock remedy	(12)[1]				1 & (1)[1]	16 & (8)[1]			
Cephalosporins		(2)[1]					(5)[1]			
Tetracyclines		24 & (3)[1]	1		11 & (2)[1]	14	(1)[1]	5	**3**	**2**
Aminoglycosides		(2)[1]				(1)[1]				
Macrolides, lincosamides and pleuromutilins		(5)[1]		(1)[1]	7 & (4)[1]	7 & (2)[1]				
Amphenicols		(1)[1]								
Quinolones		(5)[1]		(1)[1]		(1)[1]				
Quinoxalines					2					
Sulphonamides and potentiated sulphonamides, including combinations		10 & (4)[1]	1	7	1	8 & (1)[1]		1		**2**
Polipeptides		(1)[1]			6	1 & (1)[1]				
Nitroimidazoles					1					
Nitrofurans					2					
Ionophores					20					
Streptogramins					1					
Glycolipids					8					
Oligosaccharides					1					
Phosphonic acids					2	2				
Polymeric compounds				2						

[1]All figures in brackets were veterinary medicines (Act 101/ 1965)

[2]Abbreviations: Inj. = Injectables; Tab. = Tablets; Oral sol. = Oral solutions; Pre. = Premix; Po. = Powder; Intramam. = Intramammaries ; Intra-uter. = Intra-uterine; Ae. = Aerosols; Oph. = Ophthalmics.

The percentages of the various dosage forms of antimicrobials registered in South Africa was shown in Figure 4.2.2.

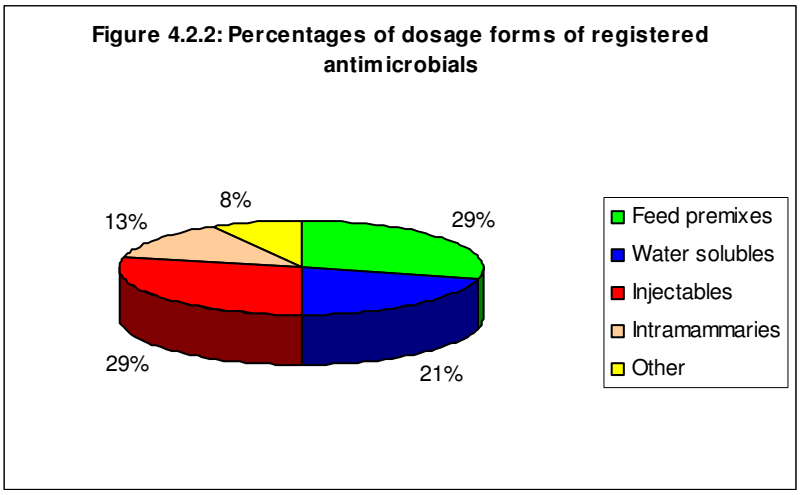

Figure 4.2.2: Percentages of dosage forms of antimicrobials that are registered in South Africa.

The tabulated summary of the number of growth promoters registered in South Africa were set out in Table 4.2.2.

Table 4.2.2: Number of in-feed (premixes) antimicrobial products authorized for growth promotion in food animals in South Africa.

Antimicrobial		Stock remedies	Total
Class	**Type**	**No.**	
Tetracyclines	Chlortetracycline oxytetracycline	11	13[1]
Macrolides, lincosamides and pleuromutilins	tylosin; kitasamycin; josamycin tiamulin tilmicosin.		12[1]
Quinoxalines	carbadox; olaquindox.	2	2
Polipeptides	Bacitracin Zn[2]	7	7
Nitrofurans	nitrovin	2	2
Ionophores	monensin; salinomycin; lasalocid.	18	18
Streptogramins	virginiamycin	1	1
Glycolipids	flavophospholipol	9	9
Oligosaccharides	avilamycin	1	1
Phosphonic acids	fosfomycin	2	2
Polymeric compounds	Poly 2-propenal 2-propenoic acid	2	2
	TOTAL	**62**	**69[2]**

[1]There were five antimicrobial growth promotants registered under Act 101/ 1965 – josamycin, tilmicosin, two tiamulins and a tylosin-sulpha combination.

[2]One of the registered bacitracins was a water soluble dosage form.

4.2.1 Comparison between numbers of registered antimicrobials versus the volumes sold during 2002 to 2004

There was a good correlation between the total volumes of antimicrobials consumed and the available registered antimicrobials. The largest number of available registered antimicrobials were the tetracyclines (66), followed by the penicillins (38), the sulphonamides (35) and then the macrolides, lincosamides and pleuromutilins (26). The top four groups of antimicrobials sold in decreasing order were:

- macrolides, lincosamides and pleuromutilins;
- tetracyclines;
- sulphonamides;
- penicillins.

4.3 Volumes of antimicrobials consumed per annum from 2002-2004.

The increasing and decreasing trends of the classes of antimicrobials sold were observed and compared as percentages over the three years under discussion and then tabulated in Table 4.3.1. Penicillin sales increased by 3,8% in 2003 and by 21% in 2004, in comparison to 2002. Cephalosporin sales decreased by 39% in 2003 and 2004 compared to 2002. Tetracycline sales increased by 23% in 2003 and 22% in 2004 respectively, compared to the consumption in 2002. Aminoglycoside sales were very low in 2002, almost negligible. However, in comparing 2003 with 2004, consumption increased by 10,7%. Macrolide, lincosamide and pleuromutilin sales increased by 8% in 2003 and remained much the same in 2004, from 2002. No data were obtained for the use of amphenicols. Quinolone sales remained at identical values in both 2002 and 2003 but almost doubled in 2004. Quinoxaline sales decreased by 12% in 2003 as compared to 2002 but then increased to just above the same level compared to 2002, in 2004. Sulphonamide sales more than doubled in 2003 (as compared with 2002) and thereafter in 2004, remained at the same high levels. Polipeptide sales decreased very slightly in 2003 but increased sharply by 56% in 2004, in comparison to 2002-03. There was no sale of nitroimidazoles recorded by the participating companies from 2002 to 2004. In 2002, only 6 kg of nitrofurans was recorded as sold and thereafter no more. Ionophore sales decreased by 62% in 2003 but almost trebled in 2004, in comparison to 2002. Glycolipid antimicrobial sales increased by 13% in 2003 and 17% in 2004. The

various antimicrobial classes were discussed and changing trends of sales noted.

4.3.1 A comparison of the volumes of classes of antimicrobials sold for food animals

There was a significant increase in the sales of penicillins and ionophores over the three year period. There was a marked increase in the use of tetracyclines in 2003. The mean antimicrobial sales for the three year period, from the data collected from eight companies was 1 538 443 kg active ingredient. This was distributed as follows:

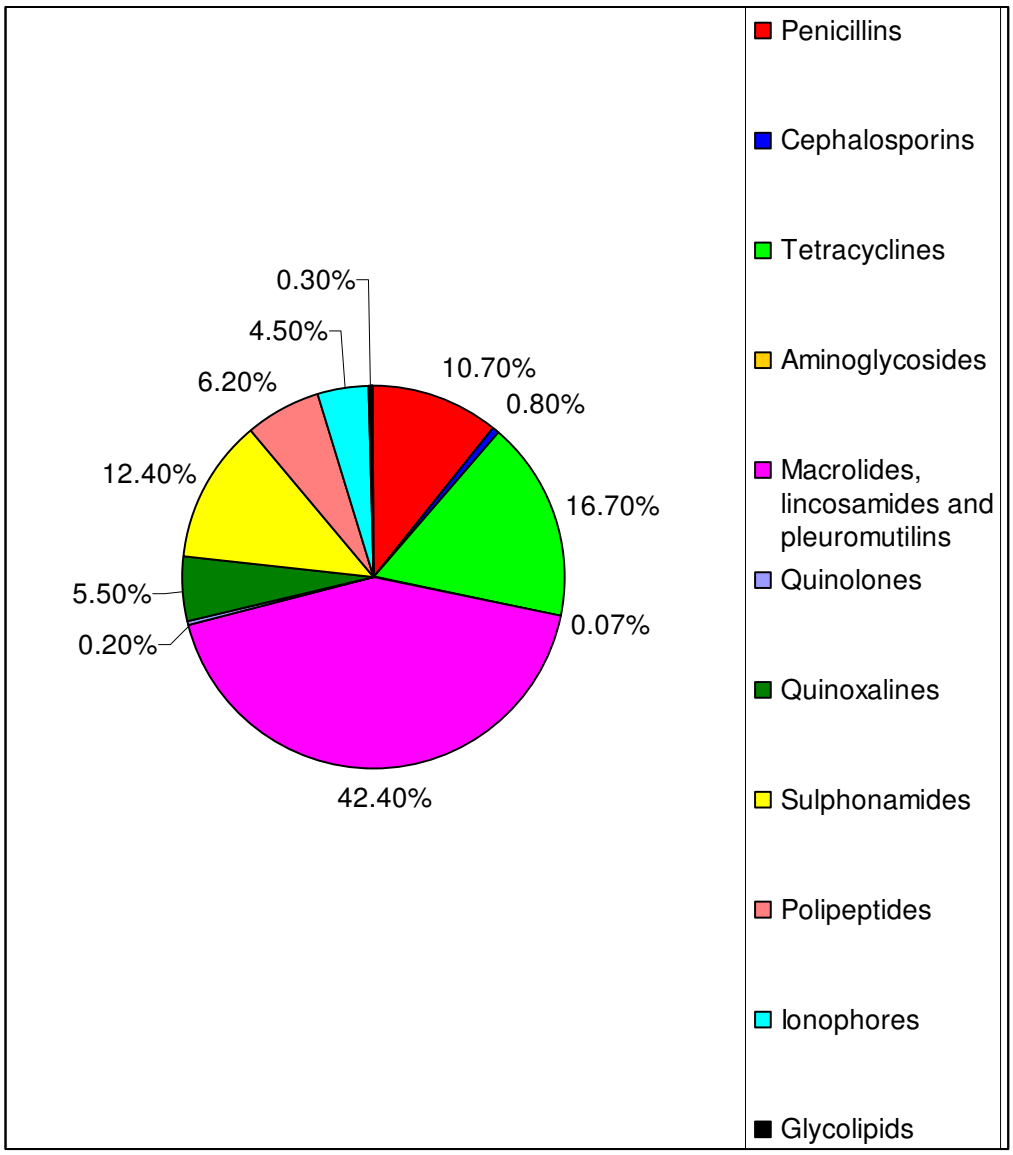

Figure 4.3.1: Percentages of volume (kg) for sales of antimicrobials for the period 2002 – 2004.

In terms of total volumes of sales (kg), the macrolides, lincosamides and pleuromutilins represented 42,4% of the antimicrobials sold. Tylosin was specifically the most extensively sold antimicrobial. This class had the fourth largest number of active registrations, at the time of collection of these data (Act 101 of 1965 2005; Act 36 of 1947 2005; Swan editor IVS 2004). The group with the second largest sales was the tetracyclines. Oxytetracycline had the largest sales in this group. There were 11 registered in-feed tetracyclines and 14 water soluble powders. These were all readily available as stock remedies under Act 36 of 1947. Sulphonamides had the third largest sales at 12,4% and penicillins the fourth largest sales at 10,7%. The volumes of cephalosporins and quinolones sold were relatively low at 0,80% and 0,20% respectively. The volumes of antimicrobials for each year according to each class of antimicrobial were indicated in Table 4.3.1.

Table 4.3.1: Volumes (kg) of antimicrobials used during 2002-2004[1] as sourced from veterinary pharmaceutical companies.

Class of antimicrobial	Volume (kg)			Total (kg)over 3 y
	2002	2003	2004	
Penicillins	49 465	55 677	59 688	165 171[1]
Cephalosporins	5 470	3 321	3 316	12 107
Tetracyclines	58 342	71 842	58 974	257 755[1]
Aminoglycosides	3	242	268	1 048[1]
Macrolides, lincosamides and pleuromutilins	204 325	221 275	223 412	651 690[1]
Quinolones	582	582	1 082	3 094[1]
Quinoxalines	30 043	26 468	30 448	86 959
Sulphonamides	35 041	72 277	75 098	190 676[1]
Polipeptides	27 011	26 985	42 191	96 187
Ionophores	14 736	5 582	43 674	69 820[1]
Glycolipids	370	425	432	3 936[1]
TOTAL	**425 388**	**484 676**	**538 583**	**1 538 443[1]**

[1]Two of the eight veterinary pharmaceutical companies that provided data were only able to access their data for the whole three year period and not for each year individually.

4.3.2 A comparison between the dosage forms of antimicrobials sold for food animals

4.3.2.1 In-feed antimicrobials sold

A total of 1 054 177 kg of the antimicrobials were sold as in-feed medications for the three years under review, adding up to 68,5% of the grand total. This figure was calculated from the eight pharmaceutical companies which provided comprehensive data. It was not unreasonable to consider that this percentage approximated that for the industry as a whole because it was close to the popular estimate made by both industry and academia that 60% of the feed sold for food animals, was medicated feed.

The results of the in-feed antimicrobials were tabulated in Table 4.3.2:

Table 4.3.2: Volumes of in-feed antimicrobials (kg) sourced from veterinary pharmaceutical companies 2002-2004.

Antimicrobial		**Volumes sold**		**No. of registered products (for specific actives mentioned)**	
Class	**Type**	**Kg**	**Percentage of total**	**No. of registered stock remedies**	**No. of registered veterinary medicines**
Tetracyclines	chlortetracycline; oxytetracycline.	34 525 112 985	3,3% 10,7%	3 7	1 2
Quinoxalines	olaquindox.	86 959	8,2%	1	0
Macrolides, lincosamides and pleuromutilins	tylosin phosphate; tylosin tartrate; tiamulin.	642 710 2 424 4 631	61,0% 0,2% 0,4%	5 1 0	1 0 2
Polipeptides	Bacitracin Zn	96 187	9,1%	6	0
Ionophores	Monensin sodium	69 820	6,7%	8	
Glycolipids	Flavophospholipol	3 936	0,4%	8	0
TOTAL		**1 054 177**	**100%**	**39**	**6**
				45	

In summary, the percentages of volumes of in-feed antimicrobials used were depicted in Figure 4.3.2:

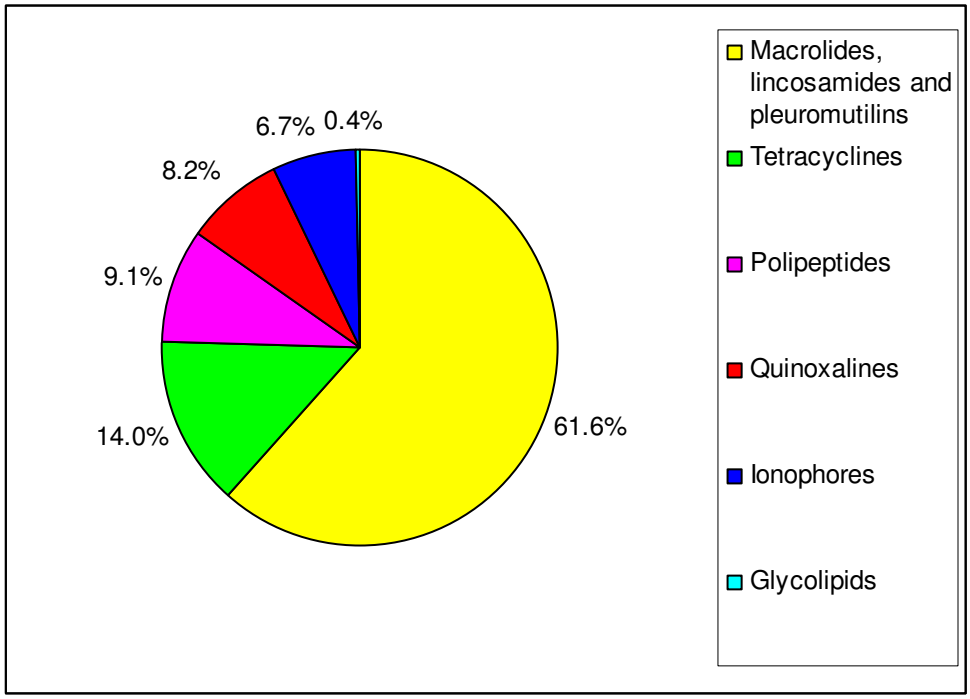

Figure 4.3.2: Percentages of volume (kg) of in-feed antimicrobials sold during 2002 – 2004.

4.3.2.2 Antimicrobials used for water medication

A total of 190 400 kg of antimicrobials or 12% of the total antimicrobials sold from 2002-04, were indicated for administration through the drinking water. The results were tabulated in Table 4.3.3.

Table 4.3.3: Volumes of antimicrobials (kg) sold for water medication sourced from veterinary pharmaceutical companies 2002-2004.

Antimicrobial		**Volumes sold**		**No. of registered products (for specific actives mentioned)**	
Class	**Type**	**Kg**	**Percentage of total**	**No. of registered stock remedies**	**No. of registered veterinary medicines**
Penicillins	amoxicillin.	3 460	1,8%	1	1
Tetracyclines	oxytetracycline	859	0,5%	9	0
Macrolides	tylosin tartrate; kitasamycin tartrate; spiramycin.	773 50 1 102	0,4% 0,03% 0,6%	5 1 1	0 0 0
Quinolones	enrofloxacin; norfloxacin.	305 2 222	0,2% 1,1%	0 0	1 2
Sulphonamides		181 629	95,4%	15	1
TOTAL		**190 400**	**100%**	**32**	**5**
				37	

In summary, the percentages of volumes of antimicrobials used for water medication were depicted in Figure 4.3.3:

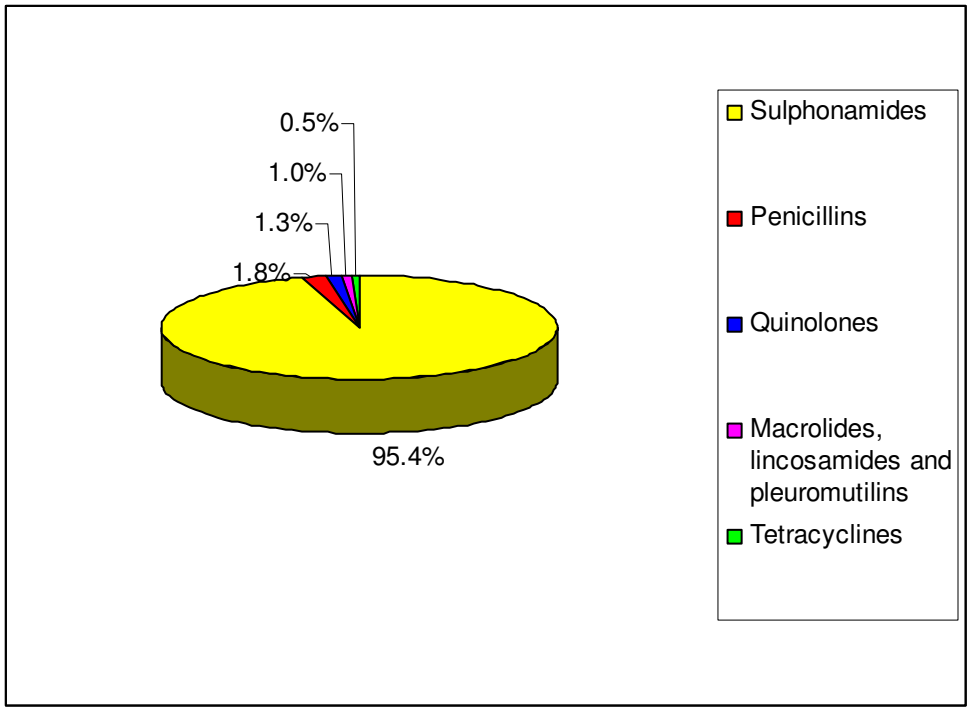

Figure 4.3.3: Percentages of volume (kg) antimicrobials sold for water medication during 2002 – 2004.

4.3.2.3 Parenteral antimicrobials sold

In all, 269 794 kg of antimicrobials were administered parenterally. This constituted 17,5% of the total dosage forms of antimicrobials utilized.

These results were tabulated in Table 4.3.4.

Table 4.3.4: Volumes of parenteral antimicrobials sourced from veterinary pharmaceutical companies.

Antimicrobial		Volumes sold		No. of registered products (for specific actives mentioned)	
Class	**Type**	**Kg**	**Percentage of total**	**No. of registered stock remedies**	**No. of registered veterinary medicines**
Penicillins	procaine penicillin; benethamine penicillin; benzathine penicillin; ampicillin;	161 363	60,0%	0	12
Aminoglycosides	dihydrostreptomycin	401	0,1%		
Cephalosporins	ceftiofur; cefquinome.	12 105 2	4,5% 0,0007%	0 0	1 1
Tetracyclines	oxytetracycline	86 820	32%	22	3
Quinolones	enrofloxacin;	567	0,2%	0	2
Sulphonamides	sulphadimethoxine; sulphamethazine; sulphadiazine; sulphadimidine Na.	165 565 362 7 444	0,06% 0,2% 0,1% 2,8%	2 2 2 2	0 0 0 0
TOTAL		**269 794**	**100%**	**30**	**19**
				49	

The percentages of volumes of injectable antimicrobials were depicted in Figure 4.3.4:

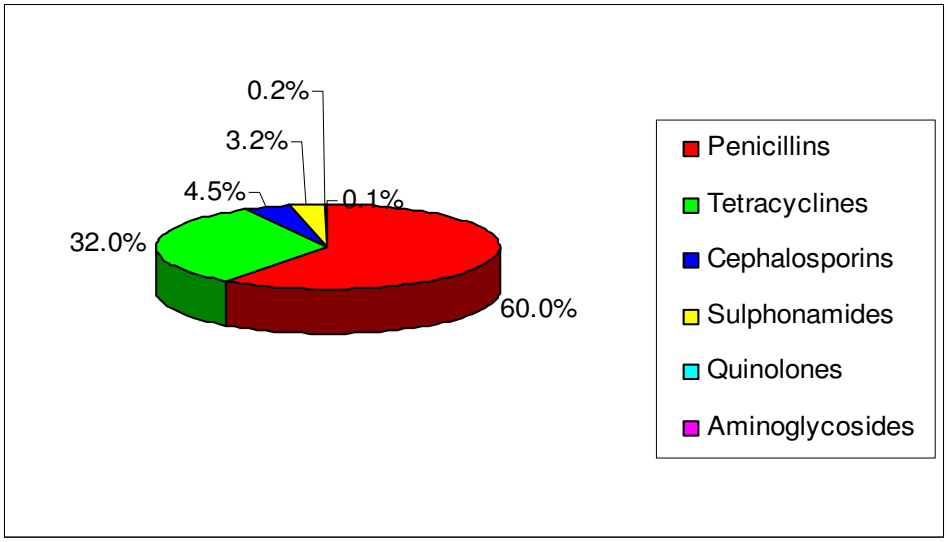

Figure 4.3.4: Percentages of volume (kg) of parenteral antimicrobials sold during 2002 – 2004.

4.3.2.4 Intramammary preparations sold

Intramammary preparations were calculated at 575 kg of antimicrobials used, only constituting 0,04% of the total amount of antimicrobials consumed. Of these intramammaries, the greatest majority (97%) were penicillins or penicillin-dihydrostreptomycin combinations. Apart from the above, ampicillin, nafcillin and cloxacillin were recorded. It was noted that 24 of the penicillins or penicillin-combinations registered were intramammary preparations. The other 3% of the intramammaries comprised tetracyclines and cephalosporins. There were five cephalosporin intramammaries and one tetracycline intramammary preparation registered under Act 101 of 1965 (Swan editor IVS 2004; Act 101 of 1965 2005).

4.3.2.5 Other dosage forms sold

Other dosage forms of antimicrobials available in South Africa included topical ointments, ophthalmic and aural preparations, intra-uterine pessaries and tablets. Some of these formulations were available for use in minor species such as pigeons. In total, 23 497 kg of these dosage forms were administered. This comprised 1,5% of the total volume of antimicrobials sold. These other dosage forms were tabulated in Table 4.3.4:

Table 4.3.5: Other dosage forms of antimicrobials available in South Africa

Antimicrobial		Dosage form	No. of registered products (for specific actives mentioned)	
Class	**Type**		**No. of registered stock remedies**	**No. of registered veterinary medicines**
Tetracyclines	oxytetracycline tetracycline	Aerosol Intra-uterine pessaries Ophthalmic/ aural	3 6 2	0 0 0
Sulphonamides	Suphafurazole Sulphapyridine and sulphadimidine	Intra-uterine pessaries Tablet	1 1	0 0

The comparative percentages of the various dosage forms of antimicrobials consumed in animal health were indicated in Figure 4.3.5.

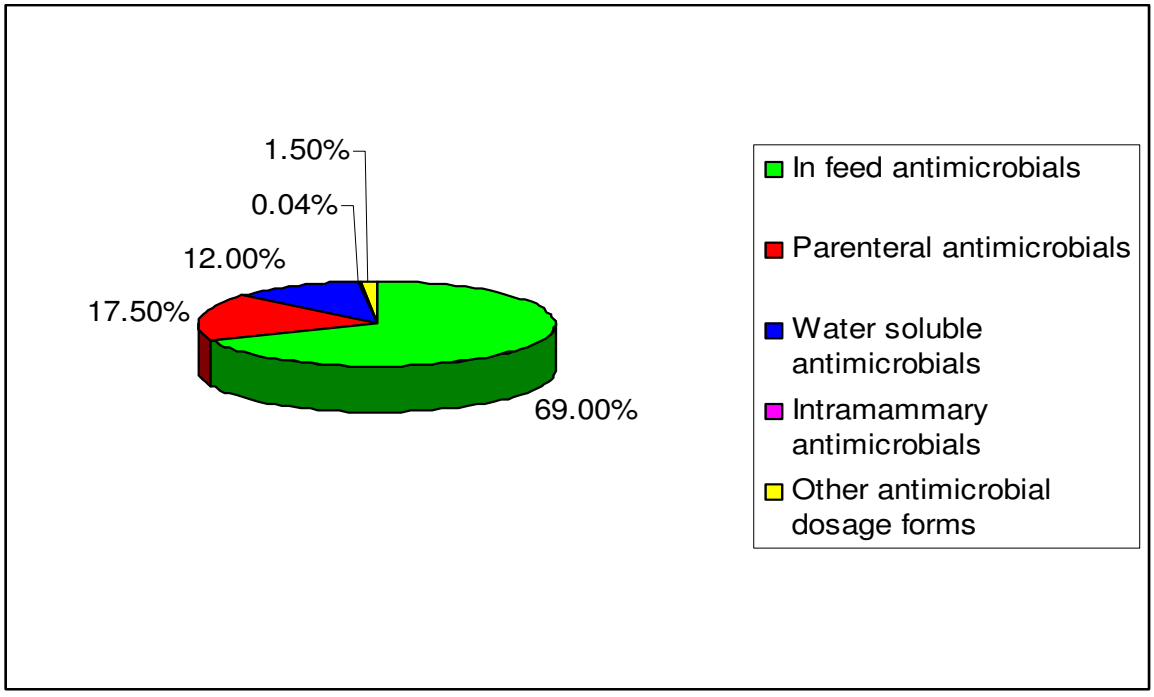

Figure 4.3.5: Percentage of dosage forms of antimicrobials sold

4.4 Percentage of medicated feed consumed during 2002-2004:

As mentioned earlier in Chapter 3, for Materials and Methods, the following statistics were

included to obtain a more accurate interpretation of the volumes of antimicrobials included in the feed:

- Sales of animal feed during 2002 – 2004;
- Livestock census figures for 2002 – 2004;
- Postulated percentages of antimicrobial-medicated feed.

The sales of animal feed were provided in metric tonnes (kg x 1000) for each year (1 April to 31 March) in Table 4.4.1 according to the various production animal classes.

Table 4.4.1: Volume of feed (tonnes) sold from 2002 to 2004

Type of feed	**Year of sale of feed (measured in metric tonnes)**		
	2002/03	**2003/04**	**2004/05**
Dairy	596 011	679 068	657 207
Beef and Sheep	247 469	317 180	401 561
Ruminants – other (mostly goats)	1 100	1 073	764
Pigs	222 984	174 736	185 209
Layers	699 984	680 616	684 798
Broilers	1 925 023	1 946 658	2 003 263
Broiler breeders	296 024	284 214	288 897
Ostriches	38 352	32 367	25 296
Other mixtures	16 941	18 617	11 801
Aquaculture freshwater	1 854	1 711	3 254
TOTALS	**4 045 742**	**4 136 240**	**4 262 050**
% Growth year on year	**1,63%**	**2,24%**	**3,04%**

Livestock census figures from 2002 to 2004 were shown in Table 4.4.2 according to the various livestock classes:

Table 4.4.2: Livestock census figures for food animals from 2002 to 2004 obtained from the National Directorate: Animal Health.

Year	Cattle	Sheep	Pigs	Poultry	Ostriches
2002	10 884 446	22 363 296	2 337 017	48 439 104	781 184
2003	10 547 227	27 695 162	1 665 512	67 431 073	586 955
2004	11 547 278	26 575 066	1 836 537	50 792 251	584 594

In elaborating on these livestock census figures, the cattle herd had only rather small variations, in very broad terms around a median of some 11 million head (National Directorate of Animal Health 2005). According to the census figures supplied by the National Directorate Animal of Health, the sheep flock increased substantially by some 21%: from around 22,36 million in 2002 to a median of 27,14 million in 2003-04. The poultry flock increased from 48,44 million birds in 2002 by 39% to 67,43 million birds in 2003, but then fell back to 50,8 million in 2004. Ostriches declined from some 780 000 in 2002 by 25% to a median of some 586 000 birds in 2003-04 (National Directorate Animal Health 2005). The pig herd declined by nearly 29% from some 2,34 million in 2002 to 1,67 million in 2003, only making a small recovery to some 1,84 million pigs in 2004 (a decline of 21,4% against 2002). The postulated percentages of the volumes of medicated feeds were split between the different classes of livestock (Table 4.4.3). The volume of in-feed antimicrobials was calculated from the sales figures provided by the eight pharmaceutical companies.

Table 4.4.3: Postulated percentages of medicated feed sold for each year for each production animal group.

Year	Dairy cows	Slaughter cattle and sheep	Pigs	Layers	Broilers	Broiler breeders
2004	10%	100%	10%	10%	88%	85%
2005	10%	100%	20%	30%	88%	85%
2006	10%	100%	30%	40%	88%	85%

4.5 Value of sales of antimicrobials

The value of sales of antimicrobials (in Rands) were obtained for the years 2002-2004 from the South African Animal Health Association (SAAHA) according to SAAHA's format in Table 4.5.1.

Table 4.5.1: Volume of sales of antimicrobials in Rands from 2002 to 2004

Class of antimicrobials and dosage forms	2002 (R)	2003 (R)	2004 (R)
All Penicillins including streptomycin combinations:			
Injectables:	11 620 851	8 615 039	9 028 252
Tetracyclines: Injectables:			
Long-acting only:	16 902 521	16 698 018	17 886 853
Short-acting only:	6 103 190	5 999 186	6 435 375
Oral (soluble powders, tablets and liquids):	3 095 612	3 264278	3 561 302
Feed additives:	10 230 230	10 500 494	7 161 354
TOTAL:	**331 553**	**36 461 976**	**35 044 884**
Sulphonamides, including potentiated sulphonamides:			
Injectables:	3 087 653	3 176 386	3 044 174
Oral (including soluble powders, tablets and liquids):	5 839 524	9 940 335	10 422 073
TOTAL:	**8 927 177**	**13 116 721**	**13 466 247**
All others			
Injectables:	18 751 748	19 529 758	25 362 462
Orals (powders, tablets and liquids):	2 069 259	10 294 288	9 628120
TOTAL	**20 821 007**	**29 824 046**	**34 990 582**
Growth promoters, including ionophores:	42 658 376	48 143 206	54 173 321
Nitrofurans:	0	0	0
Anticoccidials, excluding ionophores:	35 667 001	32 205 734	12 714 678
Intrauterine antimicrobials:	1 600 939	1 491 371	1 430 613
Topical antimicrobials:	4 570 687	4 287 088	4 570 687
GRAND TOTAL	162 199 591	174 145 181	165 419 264

The comparative bar graph of the sales values of antimicrobials recorded by SAAHA was shown in Figure 4.5.1:

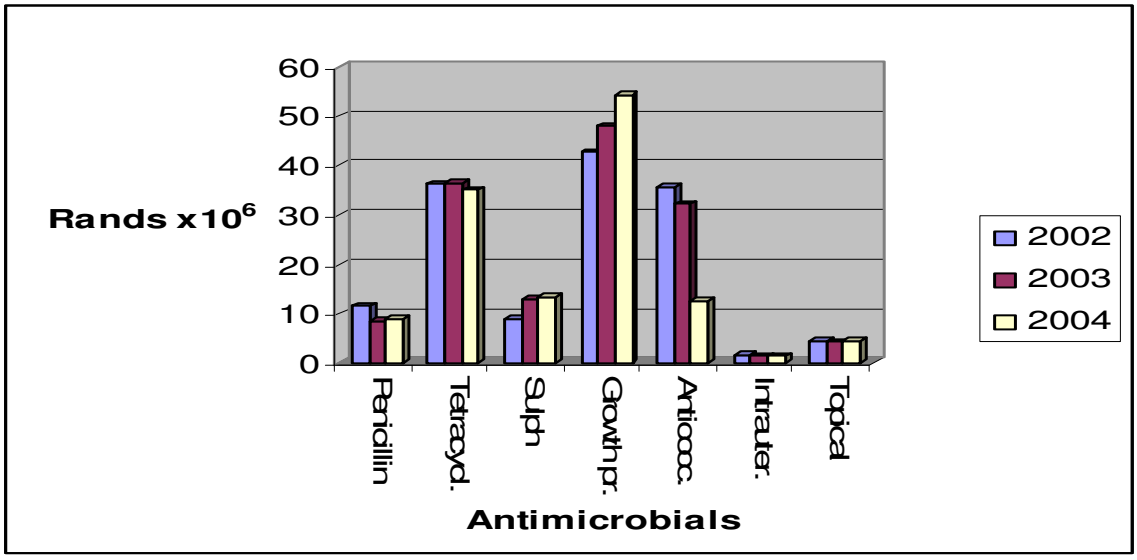

Figure 4.5.1: Values of antimicrobials sold in Rands (x 10^6) from 2002-04.

4.5.1 Correlation of volumes of antimicrobials sold compared with values of sales of antimicrobials

In comparing the values of antimicrobials consumed at this direct level of veterinary pharmaceutical company use with the volumes of sales of antimicrobials, no direct correlation could be made. The highest volumes of sales of classes of antimicrobials, as supplied by SAAHA were the “other” class of antimicrobials, followed by the tetracyclines and then the anticoccidials, excluding the ionophores.

4.6 Potency of antimicrobials versus volumes of antimicrobials sold

Of the veterinary companies who specified the potency of the active ingredients, it was noted that the potency remained the same throughout the three years under review. The volumes of antimicrobials utilized therefore increased or decreased, with potency remaining a constant. Since potency of the antimicrobial actives neither increased nor decreased in these cases, volumes of antimicrobials utilized were accepted as submitted by these companies and were not interpreted in terms of the antimicrobial potency.

CHAPTER 5

5. DISCUSSION

5.1 Introduction

Explanations (where possible) or comments of any marked increased or decreased consumption of the various classes of antimicrobials were only undertaken within the context of the data provided by the eight veterinary pharmaceutical companies. Reasons for upward or downward trends could have been very diverse: ranging for example from more dynamic marketing strategies for certain products to difficulty in sourcing the active ingredients, or possibly increased resistance of bacteria to certain antimicrobials. Indeed, to enter into a detailed analysis of the reasons for increased or decreased use of individual antimicrobials would have constituted a whole investigation on its own. It was however, important to consider general trends of antimicrobial usage and the conclusions that may have been derived within the context of the objectives of this study. It was also important to bear in mind when interpreting and discussing these results, that only eight companies (registration holders of specific classes of antimicrobials) responded, and that there may have been disproportionately more data available for certain classes of antimicrobials than for others. The number of available authorized antimicrobials (Swan editor IVS 2004; Act 36 of 1947 2005; Act 101 of 1965 2005), volumes of feed sold (AFMA 2006), estimated volumes of medicated feed and sales values of antimicrobials (SAAHA 2005) were also interpreted and discussed.

5.2 Antimicrobials authorized for food animal use in South Africa.

The following aspects of antimicrobials authorized for food animal use in South Africa were discussed in order to obtain a complete view of the availability and regulation of authorized antimicrobials in South Africa:

- Classes, types and dosage forms of antimicrobials;
- Differences between regulatory authorities and supply routes in South Africa;
- Use of unregistered antimicrobials in South Africa with respect to compounding, extra-label use and Section 21 use.

5.2.1 Classes, types and dosage forms of antimicrobials

All the main classes and types of antimicrobials were authorized for food animal use in South Africa. These included all the antimicrobial growth promoters, such as the ionophores, macrolides, quinoxalines, polipeptides, streptogramins, glycolipids, oligosaccharides, phosphonic acids and polymeric compounds, all of which were banned for use in the EU (Witte 2000). It could be seen therefore that South Africa does not currently align itself with the EU countries with respect to the use of feed premixes for growth promotion. A discussion of the ongoing use of antimicrobial growth promoters in South Africa will follow later in this chapter. Twenty nine % of all available antimicrobials in South Africa were in the forms of premixes, and represented a large percentage of all the registered antimicrobials. All other dosage forms of antimicrobials such as parenterals, intramammaries, topicals and water solubles were also available for administration to food animals in South Africa. The only types of antimicrobials not available for food animals were chloramphenicol as this may cause aplastic anaemia in humans exposed to residues in food animals (Young & Craig 2001) and nitrofurans such as furazolidone and furaltadone as these were banned in South Africa due to their carcinogenic potential as mentioned earlier.

5.2.2 Differences between regulatory authorities and supply routes in South Africa for veterinary antimicrobials

5.2.2.1 Pre-marketing requirements

The Medicines and Related Substances Control Act, Act 101 of 1965 is responsible for the registration and regulation of all scheduled veterinary medicines. These include scheduled veterinary antimicrobials as determined in the scheduling regulations of Act 101. Scheduled veterinary antimicrobials have a Schedule 4 status[1] (main group prescription medicines). This Act is administered by the National Department of Health and registration of drugs is confirmed at meetings of the Medicines Control Council (MCC) that consists of a panel of experts who have been appointed by the Minister of Health to undertake such a function. Scheduled veterinary antimicrobials are assessed in terms of safety, quality and efficacy and recommendations made to the MCC, in terms of these requirements. These medicines pass through expert committees for registration. These committees comprise the following:

[1]**It must be noted that an applicant can apply for exemption from the scheduling requirements of Act 101 in terms of Section 36 of Act 101 1965.**

- Veterinary Clinical Committee for assessment of safety and efficacy

- Name and Scheduling Committee that confirms the name and scheduling status

- Pharmaceutical and Analytical Committee for validation of the quality of the veterinary medicine (this includes a letter form the MCC Inspectorate that the medicine is distributed or wholesaled according to Good Distributing Practice (GDP) or Good Wholesaling Practice (GWP) or manufactured in compliance with Good Manufacturing Practice (GMP) and that the Applicant has a GMP, GDP or GWP license). The MCC Inspectorate is therefore responsible for ensuring adherence to GMP or GDP or GWP and quality assurance of the product (Act 101 of 1965 2005).The supply route for a scheduled veterinary antimicrobial is indicated in the following diagram:

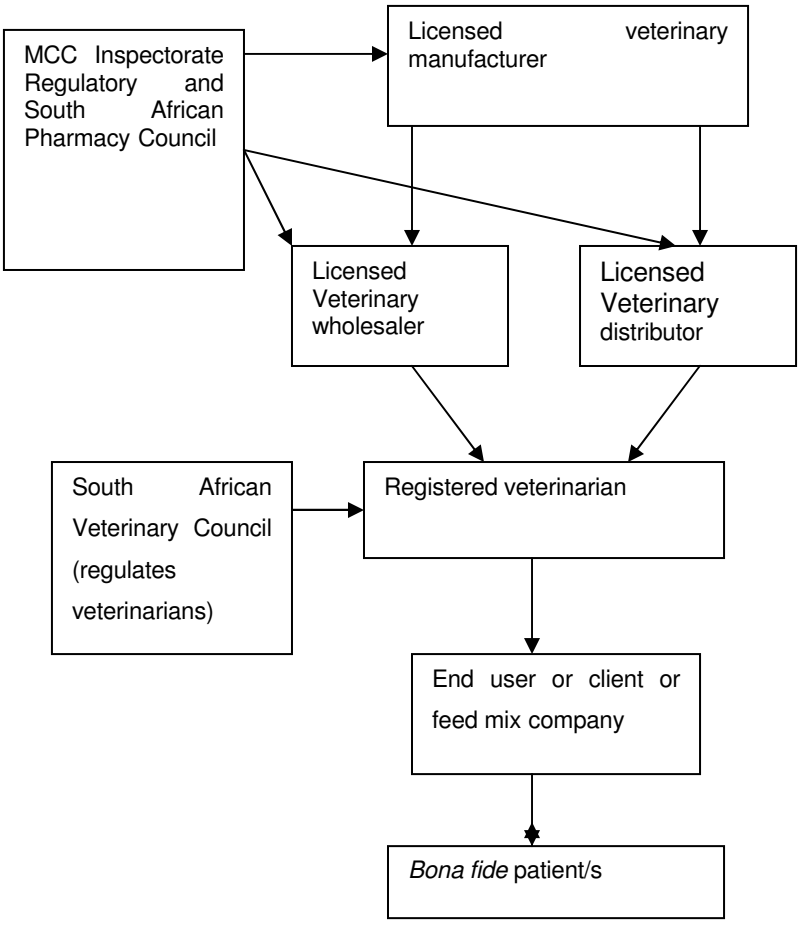

Figure 5.2.2: Supply route of authorized scheduled veterinary antimicrobials

The above diagram is a simplified version of the supply route of a scheduled antimicrobial. It must be noted that all scheduled veterinary antimicrobials are available only on prescription by the responsible veterinarian to the client. The veterinarian may administer the antimicrobial directly to the patient/s, or prescribe and dispense the antimicrobial to the client to administer, or prescribe the antimicrobial to the client who may then obtain the antimicrobial from the veterinary wholesaler or distributor, using a prescription. It must be noted that veterinarians have the privilege to dispense drugs, without having to obtain a dispensing licence, as is the case with medical practitioners. Dispensing of scheduled medicines by veterinarians is controlled in terms of Act 101 of 1965 and the Veterinary and Paraveterinary Professions Act (Act No. 19 of 1982) (SAVC 2000). Act 101 of 1965 determines the availability and requirements for sales of scheduled medicines as discussed earlier. Act 19 of 1982 determines the conditions of use of medicines in animals. No scheduled medicine may be sold in an open shop. An open shop is defined as a place that has unlimited access by the public (SAVC 2000).

Over the counter (OTC) antimicrobials (stock remedies) are controlled by the Fertilizers, Farm Feeds, Stock Remedies and Agricultural Remedies Act 36 of 1947. This Act is administered by the National Department of Agriculture. Stock remedies are also assessed in terms of safety, quality and efficacy. The registration application is assessed by a Technical Evaluator who will evaluate all the relevant parts of the dossier to approve safety, efficacy and quality and make a recommendation to the Registrar: Act 36 of 1947 for registration. Act 36 of 1947 inspectorate is responsible for the regulatory aspect of quality assurance of stock remedies, to ensure that stock remedies are manufactured in compliance with GMP and also distributed and wholesaled in terms of GDP and GWP. OTC stock remedies are distributed to the veterinary wholesalers, distributors, farmers co-operatives, feed mix companies or veterinarians by the veterinary manufacturer. The end-user, for example a farmer, is able to obtain a stock remedy based on his/her observations of the disease condition or indication for which the stock remedy is required and does not need a veterinary prescription. These stock remedies are thus available as over the counter medicaments to the end-user (Act 36 of1947 2005). It must be noted that there are currently no special requirements in terms of either Act 101 of 1965 or Act 36 of1947 to evaluate antimicrobials in terms of risk of cross-resistance to antimicrobials used in human medicine or potential for resistance in both pathogenic and indicator bacterial strains.

5.2.2.2 Post-marketing requirements

Pharmacovigilance is a very important component in the post-marketing monitoring of antimicrobials with respect to adverse drug reactions (ADRs), for example lack of efficacy of antimicrobials at the recommended doses. Provision has been made in the legislation of both Act 101 of 1965 and Act 36 of 1947 that all adverse or suspected adverse drug reactions (ADRs) be reported to the Veterinary Pharmacovigilance Centre, based at the Faculty of Veterinary Science, at Onderstepoort. Reporting all ADRs of veterinary antimicrobials by the relevant role players in the animal health industry is also a useful tool in monitoring antimicrobial resistance and setting out guidelines and establishing polices on prudent use of veterinary antimicrobials. It must be noted that there are certain risks inherent to the whole issue of supply of OTC antimicrobials for the following reasons (Viola & DeVincent 2006):

- There is potential for misuse and abuse of OTC antimicrobials in food animals because there is no direct professional supervision of the use of these products. Without veterinary input, OTC use is largely incompatible with many of the principles of prudent use of antimicrobial drugs for disease treatment and control. Treatments may be administered inappropriately, for the wrong diseases, in insufficient doses, or for incorrect periods of time or routes of administration.

- Certain combinations of OTC antimicrobials are harmful, for example monensin and tiamulin administered together will have deleterious effects and result in mortalities in food animals.

- There may be deleterious effects on the micro-ecosystem of the environment as a result of easy access to premixes and disposal of the resulting slurry directly into the surrounding environment.

- Irresponsible handling of an OTC antimicrobial may pose a risk for the handler as a result of direct contact with the antimicrobial.

However this must also be weighed up against the advantages and disadvantages of prescription only antimicrobials:

Table 5.2.2: Advantages and disadvantages of prescription only antimicrobials.

Advantages	Disadvantages
More prudent use of antimicrobials (including concomitant use of culture and sensitivity).	Disruption of the current OTC system.
It allows tracking of volumes used (increases or decreases).	Availability of drugs is a problem especially in the rural areas and there is the possibility of a veterinary monopoly.
Veterinary supervision.	Practicality of repeat prescriptions is a problem, especially for in-feed medications.
May limit the selection and co-selection of resistant bacteria.	Veterinary supervision may not necessarily decrease use.

South Africa does not have a best practice system for distributing the antimicrobial drugs used in food animals. This best practice system as laid out by the World Health Organization (WHO 1998) is discussed versus the distributing system applied in South Africa:

1. Antimicrobials according to best practice would be manufactured to GMP or another clear, transparent standard. *South Africa has a dual system of regulating veterinary products so ensuring GMP of antimicrobials is only partially addressed. It is compulsory for veterinary pharmaceutical companies that manufacture Act 101 of 1965 scheduled veterinary antimicrobials to be authorized with a GMP license to do so. This licensing is controlled by the Medicines Control Council Inspectorate and companies must comply with the current GMP requirements to receive such a license. However, this GMP license does not cover the manufacture of antimicrobials classified as stock remedies under Act 36 of 1947. The Act 36 of 1947 Inspectorate inspects veterinary pharmaceutical companies that manufacture stock remedies but does not issue a license in this respect.*
2. Antimicrobials would be evaluated by regulatory authorities for safety (including resistance) and efficacy. *There are clear guidelines established by the regulatory authorities in South Africa with regards to proving both the safety and efficacy of*

veterinary antimicrobials in South Africa. However, more emphasis needs to be placed on the potential resistance development of prospective antimicrobials to be registered in South Africa. There are currently no requirements to evaluate veterinary antimicrobials in terms of cross-resistance with human antimicrobials.

3. The person deciding when and how to use the antimicrobial would be trained, licensed, held to professional standards and not in a conflict of interest (i.e. veterinarian). *The majority of authorized veterinary antimicrobials in South Africa are over the counter stock remedies and as such the end-user is often a layperson administering the treatment to the patient/s.*
4. The person distributing the antimicrobial would be trained, licensed, held to professional standards and not in a conflict of interest (e.g. pharmacist or veterinarian). *All manufacturers, wholesalers, distributors of scheduled veterinary antimicrobials require a pharmacist in terms of the current leglislation to distribute scheduled veterinary medicines. However, many over the counter stock remedies are sold in farmers' co-operatives and these antimicrobials do not require distribution by a pharmacist or veterinarian.*
5. A strong system to ensure compliance and traceability. *Although the legislation is in place to control veterinary antimicrobials in South Africa, there is a lack of human resources across the government departments to ensure compliance and traceability of veterinary antimicrobials.*
6. Antimicrobials available only under prescription. *The majority of authorized antimicrobials in South Africa are over the counter stock remedies and are therefore not under veterinary prescription* ***unless*** *extra-label use of the stock remedy is recommended by a veterinarian (Act 36 of 1947 2005; Act 101 of 1965 2005).*
7. Antimicrobials would be readily available to producers at an economical price. *In South Africa, as a whole, antimicrobials are readily available at an economical price to producers (SAAHA 2005).*

5.2.3 Use of unregistered antimicrobials in South Africa with respect to compounding, importation of unregistered antimicrobials and extra-label use.

5.2.3.1 Compounding

A veterinarian is authorized to compound medicines as stated in Section 14(4) (a) of the Medicines and Related Substances Control Act, 1965 Act No. 101 of 1965). The definition of compounding within this context means to prepare, mix, combine, package and label a medicine for dispensing as a result of a prescription for an individual patient by a person authorized in terms of Act 101 of 1965 (SAPC 2005). It may also include the alteration of the original drug dosage form for ease of administration or because the original drug dosage form is unsuitable for the purpose for which it is intended. Section 14 (4) (a) in Act 101 of 1965 is paraphrased as follows: “compounded in the course of carrying on his or her professional activities by a pharmacist, veterinarian or person who is the holder of a license contemplated in section 22C (1) (a), for a particular patient in a quantity not greater than the quantity required for treatment as determined by the medical practitioner, pharmacist, practitioner or veterinarian.” to further clarify what a veterinarian is authorized to do in terms of compounding by Act 101 of 1965.

A new and worrying issue arises from compounding namely, the mixing of the pure unregistered active antimicrobial directly into the animal feed as opposed to mixing the finished registered antimicrobial into the animal feeds. This practice has not been tested legally, but is considered unethical by the majority of the Animal Health Industry (SAAHA 2007). It is recognized that there is a need for compounding under certain conditions, but this should not be for commercial gain, as is happening currently. Such practices should be undertaken only for the following reasons:

- to the benefit of the patient
- it must address a specific need
- there is no registered alternative available

Compounding needs to be patient driven, for exceptional cases where no alternative is available (SAAHA 2007).At the time of collection of these data, however, this practice did occur, but not to the extent that this practice is now undertaken. It is estimated by SAAHA, that currently 25% of antimicrobial sales in the animal health field, since 2006, is accounted

for by the compounding of raw active antimicrobial directly into the feed. This is cause for concern as such pure actives do not have proven safety, efficacy and furthermore withdrawal times have not been established to prevent unacceptable residue levels in the end food products (SAAHA 2007). Moreover, such practices will exacerbate and increase the incidence of antimicrobial resistance. It will also lead to cross-resistance and other adverse effects from residues such as anaphylactic reactions and deleterious effects on the human gut barrier. The mixing of pure actives directly into the feed is undertaken for economic reasons, as the pure active is cheaper to obtain. However, in the long term such practices will encourage development of antimicrobial resistance (SAAHA 2007). Moreover, to further exacerbate this problem, there is a potential for abuse in the importation of raw actives of antimicrobials because as mentioned earlier, the tariff codes are not specific enough for veterinary antimicrobials and importers do not have to make a specific declaration for the indication of the product (SARS 2004).

The South African Veterinary Council (SAVC) has compiled draft guidelines for the compounding of veterinary medicines. It is recognized that drug compounding is an integral part of veterinary clinical practice. Veterinarians need to prepare remedies for their patients, partly because no suitable formulations exist. However, overall compounded drugs must not harm animals, should not be associated with therapeutic failure resulting from lack of drug potency, should not result in violative residues in food animals and should not be undertaken in order to circumvent the usual drug registration process. The veterinarian using the compounded drug takes full responsibility and liability for its use. The SAVC guidelines on compounding recommend adherence to the following important principles:

- Compounded drugs must only be used on prescription or by a veterinarian registered by the SAVC;

- Must only be used if a valid veterinarian/ client/ patient relationship exists and be applied in accordance with the code of conduct laid down by the SAVC for use of veterinary medicinal products;

- May be used or dispensed only for the treatment and prevention of disease and promote animal health and welfare and not as a tool to improve animal production;

- Needs to be linked to a specific patient or well-defined group of patients for a specific

disease condition;

- Compounding should only be undertaken if there is no alternative registered formulation available;
- Compounded drugs must not be used in food animals that may result in violation of residue parameters;
- The veterinarian must use his/ her professional judgement in accordance with good veterinary clinical practice in ensuring safety and efficacy of the compounded medicine;
- Correct pharmaceutical and pharmacological principles must be applied to ensure good quality of the medicine;
- The compounded drug must be properly and legibly labeled before being dispensed:
    - Name and address of the attending veterinarian;
    - Date dispensed;
    - Active ingredients
    - Identity of the animal/s to be treated, i.e. species, class or group or individual animal;
    - Directions for use;
    - Any additional cautionary statement can be included;
    - Disease condition to be treated
    - Expiry date if applicable
- Compounded drugs must not be advertised or displayed to the public (SAVC 2008).

5.2.3.2 Importation of unregistered antimicrobials

Provision is made by Act 101 of 1965 to import unregistered veterinary medicines in terms of Section 21 of this Act. Unregistered veterinary antimicrobials can therefore be imported into South Africa under special permit conditions, on an **individual** patient basis or to

undertake trial work to register products under Act 101. Applications are processed and authorized by the Veterinary Clinical Committee (VCC) and any special conditions of import and use of the unregistered medicine is stipulated in the Section 21 permit issued to the applicant. In the majority of cases, the applicant is an authorized veterinarian but there may be exceptions, for example a pharmacist or medical doctor may apply for a veterinary Section 21 to facilitate research work undertaken in animals. The applicant thus applying for a Section 21 permit is always a professional person registered with one of the South African medical/ pharmaceutical/ veterinary council bodies regulating such professionals. It is compulsory for the Applicant to report back on the use of the unregistered medicine and the occurrence of any adverse drug reactions or suspected adverse drug reactions to the VCC. The applicant has to motivate the use of the unregistered medicine, for example that there is no other alternative veterinary medicine authorized for use in South Africa. The VCC is aware of the potential for misuse of this system and all Section 21 applications are carefully assessed and a decision is made after consideration of all the facts available and any potential risks inherent in the use of the unregistered medicine. One of the potential risks that the VCC will consider is the potential for development of resistance in bacteria from food animals that can be passed on to humans in the food chain (Act 101 of 1965 2005).

Provision is also made by the Registrar of Act 36 of 1947 to import stock remedies under special conditions. Unregistered antimicrobials may therefore be imported with a permit from Act 36 of 1947 for trial work or other special condition but not for commercial sales. Extra-label use of stock remedies is allowed strictly under veterinary prescription only (Act 36 of 1947 2005).

5.2.3.3 Extra-label use of antimicrobials

"Extra-label use" is defined as the actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses and may include use of human drugs in animals (SAVC 2000). In the light of the international acceptable practice to use medicines in such a manner, the right / obligation for the off-label / extra label use of medicines by veterinary prescribers is recognised by the MCC. It must be noted that the accountability, when this practice is

applied, remains with the prescriber and such a practice must be undertaken in accordance with rational therapeutic principles (SAVC 2000). The onus is therefore upon the prescribing veterinarian, to undertake a risk and benefit assessment in administering an antimicrobial as an extra-label/ off-label indication, especially with regards to the risk of residues of the antimicrobial or selection of resistant bacterial strains in food animals. In many countries, off-label or extra-label use of medicines is prohibited in food animals. This is not the case in South Africa. It is particularly important that special precautions are taken with regards to withdrawal times in food animals – it is best to be very conservative and apply a very long withdrawal period, under normal circumstances a period of 10 biological half-lives following treatment should be sufficient (SAVC 2000).

5.2.4 Comparison between numbers of registered antimicrobials versus the volumes of antimicrobials sold during 2002 to 2004

The top four groups of antimicrobials sold at the supplier level, and available as authorized products in South Africa, namely the macrolides, tetracyclines, sulphonamides and penicillins were the same; even though the order of the classes differed between the two sets of results. As can be deduced, the classes of dosage forms of antimicrobials with the greatest numbers of registrations did not necessarily correlate with the highest volumes of dosage forms of antimicrobials sold; nor indeed, would such a correlation necessarily have been expected. It was important to note that the majority of antimicrobials sold and those registered were Act 36 of 1947 stock remedies and therefore over-the-counter medicaments – as might be expected – since treatments by farmers would have prevented their having to pay professional veterinary fees and would have been convenient in all respects.

5.3 Volumes of antimicrobials consumed

The data obtained in this survey was unfortunately not representative of the volumes of veterinary antimicrobials consumed by food animals in South Africa during 2002 to 2004. As mentioned earlier, only eight veterinary pharmaceutical companies responded to the survey. The volume of 1 538 443 kg was therefore not an accurate reflection of the volumes of veterinary antimicrobials consumed in South Africa. There were 25 veterinary pharmaceutical companies at the time that this survey was undertaken and the volumes consumed by food animals was projected at considerably more than 1 538 443 kg during the three year period from 2002 to 2004. The data collected may have also possibly been skewed, as the pharmaceutical companies that contributed to the survey had more of

certain classes and dosage forms of antimicrobials authorized for use than others. Data also did not include antimicrobials imported under special conditions, such as Section 21 applications, although the latter should have been negligible. In comparing this survey with other surveillance systems undertaken by other countries, the following observations may be made:

- The data recorded by the surveillance systems in Sweden, Denmark, the United Kingdom and Australia are more accurate representations of the volumes of antimicrobials consumed in food animals. In Sweden all antimicrobials are dispensed through pharmacies and these statistics are submitted by Apoteket AB. Products used under special license are also included in the figures (SVARM 2003; SVARM 2007). The information for VETSTAT in Denmark is derived from pharmacies, veterinarians and feed mills (DANMAP 2004). The VMD in the UK obtains antimicrobial use data from the pharmaceutical companies on a voluntary basis, and the data also includes any antimicrobials imported under special conditions (VMD 2008). The TGA in Australia requires that all importers of antimicrobials declare the volume of the antimicrobial, type of antimicrobial, indication for veterinary or human use and whether for treatment or growth promotion. Food animal species information cannot be obtained from this permit (JETACAR 1999). As mentioned earlier, no import data were collected from the South African Revenue Service for veterinary antimicrobials as the tariff codes were not specific enough to describe the different classes of veterinary antimicrobials.

- The information obtained in South Africa was based on the class, type of antimicrobial, kg active ingredient as well as dosage form and indication for species (treatment or prevention of disease or growth promotion). A major deficiency in the data obtained from the 8 companies was that it often could not be established whether the product had been sold for treatment or prevention of disease or growth promotion. Also, where the antimicrobial had an indication for multiple species, the company was not able to trace information on the species for which the antimicrobial was used, including use in non-food animals. Patterns of use at the level of food animal species were therefore not obtained. The data derived are more detailed and are consequently more useful in the surveillance systems established by SVARM and VETSTAT. Patterns of use at food animal species level can be derived to a limited

extent from SVARM because products are intended mostly for pigs and antimicrobials intended for farmed fish are tabulated (SVARM 2003; SVARM 2007). VETSTAT statistics are updated on a monthly basis and the data derived is even more detailed as patterns of use of antimicrobials can be derived on a farm herd level, age-group and diagnostic grouping of the animal, for example treatment of mastitis. The prescribing patterns of the veterinarian can be ascertained from this relational data base (DANMAP 2004). Sales of antimicrobials for each food animal species can also be ascertained by the VMD's surveillance system (VMD 2008).

For the purpose of this study, the sales of the individual classes of antimicrobials were scrutinized and trends were noted and discussed within these different classes and where of interest or where it seemed there were similar overseas trends, compared to results of the overseas surveillance systems mentioned earlier. The increase in penicillin sales over the three years under review could partially be explained by the fact that several registrations of penicillin–containing products were achieved by one specific company during this time (Anonymous 2005), thereby increasing the number of available veterinary penicillins on the market. It must be noted that penicillins such as ampicillin, cloxacillin, and procaine benzylpenicillin in intramammary dosage form, intended for the treatment of mastitis in cattle were exempted from the registration requirements of Act 101 of 1965 (Schedules to Act 90 May 2003). This provision became active in 1983, after the MCC called up veterinary medicines for review. It was concluded by the expert panel at that time that penicillins in intramammary dosage form for mastitis treatment and prevention did not need to be registered under the conditions of Act 101 of 1965. In comparison, the use of penicillins in Sweden to treat mastitis in dairy cows has decreased during the same period as the national dairy cow herd has decreased by 20% (SVARM 2007).

There was no obvious reason for the decreasing/ increasing sales trends of the following classes of antimicrobials:

- cephalosporins;
- tetracyclines
- qunioxalines;

- sulphonamides;
- polipeptides;
- ionophores - In the UK, there was a decrease in sales of ionophores during 2002 to 2004 (VMD 2008) and
- glycolipids.

The reason for the very low sales figure of aminoglycosides was also not immediately apparent but may possibly have been due to no records being maintained in 2002. There was no marked increase or decreased trend of sales of the macrolides, lincosamides and pleuromutilins. Pleuromutilin utilization in the SVARM surveillance system in Sweden decreased sharply during the same period and is ascribed to a successful campaign in previous years in eradicating swine dysentery in the Swedish pig herds, for which the pleuromutilin use is indicated (SVARM 2007). However, in Denmark consumption of the macrolides and tiamulin increased substantially during the same time period. Macrolides and tiamulin are the most commonly prescribed antimicrobials for pigs in Denmark. No data were obtained on the sales of amphenicols.

One of the reasons for the low level of sales of quinolones in both 2002 and 2003 may have been due to increasing concerns about the incidence of cross-resistance between quinolones used in animals and those used in humans. Another factor to consider is that quinolones are classified as scheduled medicines and are available on veterinary prescription only. Interestingly, the results from SVARM during the same period also showed very limited sales due to the legal restriction of use of fluoroquinolones in food animals (DANMAP 2004; SVARM 2007). In Denmark, the consumption of fluoroquinolones decreased sharply during the same time period due to legal restrictions on the use of fluorquinolones in food animals. This was implemented since 2002 due to the concern of selection for resistance for bacterial strains that can affect humans as fluoroquinolones are deemed to be critically important in human medicine (DANMAP 2004). During the same period, sales of fluoroquinolones remained constant at 1 tonne per year in the UK (VMD 2008).

The possible reason that could have been ascribed to the zero sales recorded by the

companies for the nitroimidazoles was the fact that there was only one nitroimidazole (ronidazole) registered for use in what may be termed a minor group of food animals (pigeons). The reason for the negligible sales of nitrofurans was that this group, specifically nitrofuraltadone and nitrofurazone, were banned from use in animals in 1998 by the National Department of Agriculture, as they were seen as a public health risk, due to concerns about the induction of carcinogenic residues in animal tissues.

Various factors could have potentially influenced the volumes of antimicrobials consumed by food animals and should be kept in mind in the assessment of such antimicrobial consumption data. Such external influencing factors could have been as diverse as climactic conditions, farming systems, management practices, availability of antimicrobials and nutrition, to mention but a few.

5.3.1 A comparison between the classes of antimicrobials sold for food animals

The antimicrobial groups showing the largest sales in terms of weight, namely the macrolides and pleuromutilins are used in considerable volumes in the animal health industry, with reference specifically to tiamulin and tylosin. The latter are used for the treatment and prevention of diseases such as mycoplasmosis in poultry and pigs. Mycoplasmosis has been diagnosed increasingly in both layer and breeder poultry houses during the past decade (Anonymous feed-mix company 2006). This group is also indicated as growth promoters in food animals.

The second largest group of antimicrobials sold, the tetracyclines, has many registered products - at the time of collection of these data, the tetracyclines constituted the largest number of registered antimicrobials (Swan editor IVS 2004; Act 36 of1947 2005; Act 101 of 1965 2005). Tetracyclines are broad-spectrum antimicrobials active against *Mycoplasma* spp. and *Chlamydophila* spp. and are also effective against erhlichias, rickettsias, anaplasmas and some protozoa (Prescott 2000).

The third largest group, the sulphonamides, are also readily available due to the number of products registered in terms of Act 36 of 1947 (this class constituted the third largest group of registrations) and also have a wide spectrum of antimicrobial activity, including Gram-positive bacteria, *Chlamydophila* spp. and protozoal disease agents such as coccidia (Prescott 2000; Act 36 of 1947 2005; Act 101 of 1965 2005).

The antimicrobials with the fourth largest sales, the penicillins, are mainly used in the treatment of Gram-positive infections, and are also effective against anaerobes. Penicillins are used extensively in the treatment of soft tissue infections, bovine mastitis and erysipelas in pigs (Prescott 2000). There are many intramammary preparations available containing penicillins. Indeed 63% of the available registered pencillins, are intramammary preparations (Swan editor IVS 2004; Act 36 of 1947 2005; Act 101 of 1965 2005).

Tylosin was the most extensively sold antimicrobial in this study, yet it was one of four growth promoters banned in the EU following recommendations by a WHO meeting in Geneva, in 1997. These four growth promoters namely tylosin, spiramycin, bacitracin and virginiamycin were banned because of their structural relatedness to therapeutic antimicrobials used in humans. The extensive sales of tylosin in South Africa provide cause for great concern because its main route of administration is through the feed and at sub-therapeutic levels as a registered growth promoter, thereby promulgating the potential for resistance to similarly related antimicrobials used in human medicine. All registered tylosin products are available in South Africa as over-the-counter stock remedies under Act 36 of 1947.

Tetracyclines, sulphonamides and penicillins were the next largest groups utilized in the animal health field – there are many analogues of these antimicrobials used in treating people (Snyman editor MDR 2006) These antimicrobials are very important in human health (Mitema *et al* 2001). The previously mentioned antimicrobials all have the potential to lead to development of cross-resistance to antimicrobials used in human health. However to actually quantify the impact of the use of these antimicrobials on human health, a risk assessment for antimicrobial resistance would have to be undertaken, which was not within the scope of this study. There are also other public health concerns in using certain antimicrobials such as the potential genotoxic effects of some growth promoters, the potential cardiotoxic effects of the ionophores (Young & Craig 2001) as well as the potential carcinogenic effects of certain of the nitrofurans.

5.3.2 A comparison between the dosage forms of antimicrobials sold for food animals

5.3.2.1 In-feed antimicrobials sold

In order to better understand the risk that the use of in-feed antimicrobials poses for the selection of antimicrobial resistant bacterial strains in both animals and humans, it is necessary to understand the mechanism by which AGPs exert their growth promoting effect. How antimicrobials improve growth or feed efficiency in farm animals is not fully understood:

- It is understood that the ionophoric antimicrobials shift the production from acetate and butyrate production to propionate production in ruminants, thereby enhancing production (Gustafson & Bowen 1997; McEwen & Fedorka-Cray 2002).

- One possibility is that antimicrobials dampen the effects of subclinical disease on growth and also suppress certain sensitive bacteria that compete with host animals for nutrients.

- Another possibility is that growth promoters enhance the immune system of recipient animals by affecting hormones, cytokines and other immune factors.

- Antimicrobials at sub-therapeutic levels also may modulate the metabolic activity of bacteria in the gut or shift the balance among microbial species, resulting in weight-gain benefits.

- Growth of bacteria that cause low-grade infections or produce toxins, both of which result in thick intestines that do not absorb nutrients well are controlled, i.e. there is a thinning of the gut wall as a result of antimicrobial use that then improves absorption of nutrients.

The class of antimicrobial drugs used and the animal species involved may determine the relative importance of each mechanism (Wegener, Aarestrup, Jensen, Hammerum & Bager 1999). One of the most efficient ways to select for resistance genes in bacteria is to expose bacteria chronically to low doses of broad-spectrum antimicrobial agents. The utilization of in-feed antimicrobials results in a disturbance of the colonization resistance (CR) of the intestinal flora of animals exposed to certain antimicrobials, resulting in a lower minimal

infective or colonization dose of pathogenic or resistant bacteria. These affected animals excrete these bacteria in higher numbers and over a longer period of time compared with animals with an intact colonization resistance. This increased excretion of resistant bacteria thereby enhances the dissemination of salmonellae or resistant bacteria within a group of animals. This may also lead to increased contamination of carcasses with these bacteria during slaughter, thereby exposing humans to zoonotic food-borne disease and resistant bacterial strains. These resistant bacteria can either colonize humans and/ or transfer their resistance genes to other bacteria belonging to the endogenous flora of man. As a result of exposure to antimicrobials, the level of resistance against antimicrobials among bacteria belonging to the normal intestinal flora of humans and animals therefore increases. These bacteria then constitute an enormous reservoir of resistance genes (van den Bogaard & Stobberingh 2000).

Moreover, there is the risk of antimicrobial residues in animal tissues for the human consumer - if residual amounts of these drugs remain in tissues and animal products, low concentrations of the drugs may be ingested by consumers. In recent years, there have been questions concerning the effects of the consumption of subtherapeutic levels of antimicrobial drugs in animal-derived foods on the human intestinal microflora. The presence in the gastrointestinal tract of some antimicrobial drugs at low concentrations may be a selective pressure for the growth of antimicrobial drug-resistant strains of bacteria (Wagner, Johnson & Cerniglia 2008).

The International Committee on Harmonization of Technical Requirements for Registration of Veterinary Products recognizes the importance of considering the effects of antimicrobial drugs in food on colonization resistance. It wrote, "The colonization barrier is a function of the normal intestinal flora that limits colonization of the colon by exogenous microorganisms, as well as overgrowth of indigenous, potentially pathogenic microorganisms. The capacity of some antimicrobial drugs to disrupt this barrier is well established and known to have human health consequences". There are therefore special food safety concerns with respect to veterinary antimicrobial residues. Public health authorities must therefore address the impact of drug residues in food on the selection of resistant bacteria, perturbation of the gut barrier effect within the human intestine, changes in intestinal enzymatic activity, and alteration in intestinal bacteria counts. A perturbation in the human gut barrier effect is of concern because the gut microflora provides a barrier

against the overgrowth and invasion of pathogenic bacteria. When an anti-infective agent destroys this barrier, overgrowth of pathogenic bacteria may occur (Gustafson & Bowen 1997; Woodward 1998; Tollefson & Flynn 2002).

The observation that the in-feed dosage forms constituted 68,5% of the total of antimicrobial dosage forms sold in South Africa, (with tylosin the predominant antimicrobial sold in-feed) is significant for the following reasons. There is a big difference in the way in which medicines are administered to humans and animals. In humans, treatment is directed at the individual patient, but for animals entire groups of animals may be treated with the use of medicated feed. Moreover, the dosages used for growth promotion are usually at low concentrations for extended time periods and both these practices in combination have the potential to accelerate the emergence of resistant bacteria in these animals that can then be passed through contact or via the food chain to infect humans. Tylosin is a selector for resistance to macrolides/ erythromycin and resistance to the macrolide-lincosamide-streptogramin group of antimicrobials has far-reaching consequences for both human and animal health (Wegener 2003). Macrolides have important clinical applications in the treatment and prevention of bacterial diseases in animal health management. Macrolides are also used in human health. Streptogramins are expected to become more important later on in human therapy because of the increasing resistance to other more traditionally used human antimicrobials.

Oxytetracycline had the second highest sales for in-feed antimicrobials. Oxytetracycline is well-known to select for resistant genes in bacteria, following exposure of these bacteria to low doses over an extended period of time. This resistance can develop quickly and extend from that individual to other members of that species as well as by direct contact to people living and working in that environment. However, it is difficult to determine the impact of in-feed use on bacterial resistance in food animals because it is simultaneously being used for therapy and prophylaxis. Due to the concerns expressed above, antimicrobial growth promoters in South Africa should be reviewed in order of priority, relating to the documented evidence to select for antimicrobial resistance to other groups of antimicrobials or because of their structural relatedness to antimicrobials in human medicine.

The following groups should be reviewed in South Africa:

- penicillins;

- tetracyclines;
- macrolides, lincosamides and pleuromutilins;
- streptogramins,
- aminoglycosides; and
- sulphonamides.
- Other groups of AGPs that are mentioned in this study and that should also be reviewed are:
- Quinoxalines – there is only one registered stock remedy, olaquindox which is used as a growth promoter in swine or for the treatment of susceptible intestinal infections, at higher concentrations. Although resistance seems to develop very slowly, the EU banned this AGP in 1999 because of concerns that it was a potential carcinogen. This presents an occupational health hazard to those workers on the farms and at the feed mills who come into direct contact with the product and justifies its review (Wegener 2003).
- Ionophores – these are toxic to many non-target species such as horses and turkeys and there are concerns as to the potential cardiotoxic effects in public health and the interaction with other antimicrobials that exacerbate their toxic effects (Young & Craig 2001).
- Flavophospholipol – there is concern that its use for growth promoting purposes may lead to increased resistance among animal bacteria.
- Avilamycin – There is one registered stock remedy in South Africa, used as a growth promoter in pigs and poultry. There is a human medicine, Ziracin, belonging to the everninomycins, almost identical to avilamycin and resistance to avilamycin will cause cross-resistance to Ziracin (Wegener 2003).
- Fosfomycin – there are 4 registered stock remedies used for a broad spectrum of susceptible infections in pigs and poultry in South Africa. To date, no cross-resistance

with other antimicrobials has been recorded and this antimicrobial has potential for the treatment of other resistant infections. The fact that it is used in feed, justifies its review because of the possible development of resistance.

- Virginiamycin – There is one stock remedy registered for use as a growth promoter in bovines, swine and poultry. This antimicrobial is important because it is known to select for cross-resistance to other streptogramins such as quinupristin, a medicine used in humans for very resistant enterococci in multi-resistant nocosomial infections (Wegener 2003).

5.3.2.2 Antimicrobials sold for water medications

There is not the same concern with antimicrobials administered through the water, as with the in-feed medications, the majority of which are registered as AGPs. This is because the concentrations administered through the water are adequate for the treatment or prevention of bacterial diseases and administered over 3 to 7 days, as opposed to chronically for weeks of the animals' lifespan. However, it is important nevertheless that a standardized monitoring programme for veterinary antimicrobial resistance from animals and foods of animal origin be implemented hand in hand with a monitoring programme surveying the sales of antimicrobials in food animals and patterns of use in order to continuously have feedback on the patterns of resistance in food animals in South Africa and to slow down the emergence of such resistance by means of the rational use of antimicrobials and refinement of the methods of administration of antimicrobials. (Nel *et al*. 2004).

5.3.2.3 Parenteral medications sold

It is not surprising that the penicillins constituted the greatest majority of parenteral dosage forms sold. The penicillins are broad-spectrum and the longer-acting salts facilitate convenient and once-off administration. At the time of collection of this information, there were injectable penicillin dihydrostreptomycin parenterals registered. However, it was noted that none of these combinations were used during the years under review and this may have been due to the fact that there was concern about the stability of these actives in such parenteral formulations (Act 101 of 1965 2005). One of the main concerns about parenteral administration of penicillins is the withdrawal period as any significant residues that end up in the food chain, could, cause overgrowth and invasion of pathogenic bacteria (Gustafson & Bowen 1997; Tollefson & Flynn 2002). Although much has been said about the risk of

anaphylactic reactions in sensitized individuals exposed to veterinary penicillin residues in foods of animal origin, this issue has been reviewed extensively and it was found that the public health threat from this type of exposure is in fact insignificant (Dewdney, Maes, Raynaud, Blanc, Scheid, Jackson, Lens & Verschueren 1991; Dayan 1993)

5.3.2.4 Intramammary preparations sold

In light of the fact that the most common mastitis-causing bacteria are *Streptococcus agalactiae* and *Staphylococcus aureus*, both of which are Gram-positive organisms susceptible to penicillins (Cullor, Tyler & Smith 2001), the result that the greatest majority of intramammaries sold were penicillins or penicillin dihydrostreptomycin combinations was to be expected. In terms of the problem of resistance to antimicrobials in the national dairy herds, resistant *S. aureus* mastitis is a problem in South Africa and it is necessary to holistically assess this type of resistance problem in terms of the management and treatment (Petrovski, Trajcev & Buneski 2006). Resistant *S. aureus* strains may be passed by direct contact to other dairy cows as well as to workers in the dairy and therefore, the treatment and management of a resistant mastitis herd becomes the pivotal issue.

5.4. The percentages of medicated feed consumed for each year

The stock feed sales and livestock census figures are important in the interpretation of the surveillance data. The stock feed sales will be a useful tool in ascertaining the percentages of medicated feed - it is possible to calculate the percentage of medicated feed by correlating the quantities of feed sold with volumes of in-feed antimicrobials sold. However, for this to be accurate, at least the majority of pharmaceutical companies must participate in future surveillance programmes applied in South Africa. Livestock census figures are essential in the calculation of the Defined Daily Dosage, as established in Chapter 3 of the Materials and Methods. However, the majority of pharmaceutical companies need to participate in divulging information on the volumes of antimicrobials consumed annually. It is also possible to ascertain patterns of antimicrobial use at each species level if the information supplied on the volumes of antimicrobials used is both accurate and detailed enough. The feed sales and livestock census statistics did not add value in this survey, due to the paucity of information supplied on volumes of antimicrobials consumed but will be important for future reference. Detailed information on the percentages of medicated feed sold for each year was only available from one feed mix company, from 2004 to 2006 and these were postulated percentages of medicated feed sold per year. Data were requested

from the other feed mix companies, but refused on the grounds that the information requested was too sensitive to disclose. Using this single company as an example, one might be permitted to say that medication of feeds was almost universal in slaughter cattle and very high in broiler chickens. Some trends were also noted within the classes of antimicrobials used in the medicated feed. It was observed that oxytetracycline, chlortetracycline and tylosin were being increasingly used in layer feed. This could be attributed to the fact that while in the past, *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *E. coli* were located in only some houses of some growers, these diseases had spread to the entire layer population on some farms (Anonymous feed-mix company 2006).

In terms of broiler feeds, it was common practice to medicate feeds with oxytetracycline, chlortetracycline and fosfomycin only in winter and spring time. A more recent trend has been that some producers include these medications as a "standard" in the feed consistently throughout the year (Anonymous feed-mix company 2006). In comparing this estimate with the generally accepted estimate of 60% medicated feed, it conclusions cannot be drawn for South Africa since the information received was an estimate. However, the discussion of the percentages of dosage forms of antimicrobials sold by the veterinary pharmaceutical companies can be referred to, in order to obtain an indication of the emphasis on in-feed medicaments. With reference to paragraph 4.3.2.1, 68,5% of all antimicrobials consumed were in the form of in-feed medicaments.

It must be born in mind that there are specific concerns that medicated feeds pose for South Africa, with regards to the control and regulation of in-feed mixing practices by feed-mix mills. The mixing of in-feed antimicrobials in overseas countries is strictly monitored and accountability of persons responsible for in-feed mixing is precisely defined. Feed-mix mill facilities also need a license to use feed additives and are monitored to ensure compliance with Good Manufacturing Practice. However, in South Africa, there is a dual system of regulating veterinary products, with veterinary medicines falling under Act 101 of 1965 and stock remedies falling under Act 36 of 1947. For a scheduled in-feed medicament, the veterinarian will write a prescription for the feed-mix mill. However, the risk that this practice poses is that there are no clearly defined guidelines on how the in-feed mixing of antimicrobials is monitored, especially with regard to ensuring the correct inclusion levels. There is also potential for abuse in how long a veterinary prescription is valid for a feed-mix

company, a feed-mix company may for example be using an expired veterinary prescription to obtain scheduled in-feed medicaments. This system therefore needs to be urgently reviewed.

5.5. Correlation of volumes of antimicrobials sold compared with values of sales of antimicrobials

The reason for the discrepancy between the statistics supplied by SAAHA and the data supplied by individual companies can be explained as follows: Two of the companies were not members of SAAHA at the time of collection of these data and therefore did not contribute to the quarterly statistics supplied by SAAHA. The prices of the different dosage forms of the antimicrobials could have no direct correlation with the utilization of the raw actives of the antimicrobials and therefore these two sets of data could not be an accurate reflection of each other. One set of data was measured in kg and the other in Rands and therefore no direct comparison can be made. This is because the categories of antimicrobials described in the SAAHA sales statistics were very broad, covering for example all the injectable penicillins and therefore these sales statistics were comprised of various pharmaceutical companies' inputs with prices varying for the different companies' formulations. The format of presentation of these SAAHA statistics was also somewhat different to the proposed format submitted under Materials and Methods and some antimicrobial classes were omitted from the statistics. This information was therefore not of any value. The only significant finding from these sales figures was that there were increased sales of AGPs from 2002 through to 2004.

5.6 Potency of antimicrobials

The relative potencies may be calculated according to the Defined Daily Dosage per food animal species as set out in Materials and Methods. However, clarification needs to be sought as to how to calculate these relative potencies in South Africa so that the maximum value may be extracted from such figures, especially in the light of the decision by the WHO Collaborating Centre for Drug Statistics Methodology that the ATCvet Working Group's terms of reference are not clear. The role of such a unit may differ between disciplines such as epidemiological studies or statistics on a national or an international level. In the comments submitted from the contributors, a thorough discussion on how to express drug usage data in veterinary medicine for the various purposes, e.g., linkage with antimicrobial drug resistance data, was requested. Furthermore, it was highly recommended to involve

relevant experts, representatives of relevant international organizations as well as from various countries in the decision making process in order to cover the diversity of veterinary prescribing practices and to ensure transparency. The ATCvet Working Group supported these opinions and concluded that further international discussions will be necessary. The ATCvet Working Group decided not to terminate, but to postpone the assignment of DDD_{animal}. It must be emphasized that the term DDD is an international unit of measurement linked to the ATC classification system for human medicines, with international values for the ATC codes assigned by the WHO International Working Group for Drug Statistics Methodology. The DDD_{animal} is the corresponding unit for veterinary medicines and should be linked to the ATCvet classification system. DDD_{animal} is a copyright of the WHO Collaborating Centre for Drug Statistics Methodology. In order to avoid confusion, this term should not be used as an expression for other, similar units. Within the South African context, it is necessary to obtain accurate census figures of the food animal groups, establish patterns of use of the actives and dosage forms in each food animal group and at least most of the veterinary pharmaceutical companies must provide accurate sales figures of the active ingredient of antimicrobials in order for DDD_{animal} to be of value. In the context of this study undertaken from 2002 to 2004, unfortunately, the available information on sales of active ingredient of the antimicrobials is not sufficient to calculate valid $DDD_{animal.}$ Please refer to Addendum V, for the temporary Defined Daily Dosages.

5.7 Conclusions on the most appropriate type of surveillance system for South Africa

In discussing the best surveillance system to apply in South Africa, the different types of surveillance systems available in Denmark, Sweden, United Kingdom and Australia were reviewed and compared. It was very difficult to obtain data on the volumes of antimicrobials sold by the veterinary pharmaceutical companies. Industry perceived these data to be too sensitive to divulge but this information is essential to establish a good surveillance programme which will be beneficial in many ways as mentioned earlier. Existing legislation regulating veterinary products needs to be reviewed in order to include a mandate for annual veterinary surveillance data from the pharmaceutical companies, or such data requirements should be included in prudent use policies for antimicrobials and formally adopted by the relevant stakeholders in the animal health industry. In assessing the animal health situation in South Africa it would be of value to obtain import statistics of veterinary antimicrobials from SARS. The tariff codes established by SARS would have to be revisited

and made much more specific for the different classes of veterinary antimicrobials. The undertaking of such a task would have to be initiated between the Regulatory Authorities for veterinary products and SARS, in order to establish common ground in the regulation and import control of veterinary antimicrobials. As in Australia, importers of veterinary antimicrobials should also declare the indication of such antimicrobials, whether for therapy, prophylaxis or growth promotion. In a parallel exercise, a similar undertaking could be initiated for human antimicrobials. To establish and sustain such data systems as found in Scandinavia in a country like South Africa, is currently impractical as legislation controlling veterinary products is currently very fragmented and the interests of the relevant stakeholders in animal health are very diverse, not to mention the human, financial and technical logistics of initiating and sustaining such an exercise. In scrutinizing the feasibility of data that could be submitted by the veterinary pharmaceutical companies as well as the information that was possible from this survey, the most applicable type of information systems could be adapted from the Veterinary Medicines Directorate (VMD) surveillance reports and include the following information for food animals:

- Annual sales volumes (kg) of antimicrobials by chemical grouping;
- Annual sales volumes (kg) of antimicrobials by dosage form ie premixes, water soluble powders, injectables etc.;
- Annual sales volumes (kg) of therapeutic and prophylactic antimicrobials;
- Annual sales volumes (kg) of antimicrobial growth promoters;
- Annual sales volumes (kg) of ionophoric coccidiostats;
- Annual sales volumes (kg) of non-ionophoric coccidiostats;
- Sales of antimicrobials with indication of therapy, prophylaxis or growth promotion for each food animal species. (In establishing patterns of use for each species, each company would be able to give the trade name of the antimicrobial sold, which in turn will give the authorized indications for use in South Africa and at least give some idea of patterns of use. A separate study to better establish and trace patterns of use in each of the food animal species would be relevant to undertake as well).

- Annual sales volumes (kg) of antimicrobials under Section 21 importation or Act 36 of 1947 permit importation.

It is of course recognized that a surveillance system is a dynamic information system that on an ongoing basis will need to be changed to better adapt to changing trends of antimicrobial consumption and resistance patterns. It is very important that this surveillance system of consumption of antimicrobials is paired with an antimicrobial resistance surveillance and monitoring programme, in order to better facilitate the slowing down of resistance and the problems associated with resistance by recognizing trends of antimicrobial resistance and applying rational use of antimicrobials accordingly.

CHAPTER 6

6. RECOMMENDATIONS AND CONCLUSIONS

It was very difficult to obtain data on the sales volumes of veterinary antimicrobials in South Africa. Nevertheless, in spite of the limitations encountered during this study, the results submitted by the eight pharmaceutical companies who did respond are still worthwhile in determining trends of antimicrobial sales and in serving as a pilot study towards the establishment of a national monitoring programme for the sales and usage of antimicrobials. Such a programme can then also be used later on to establish the patterns of use of antimicrobials in the actual food animal groups.

In focusing upon the conclusions and making recommendations, it is relevant to revisit the objectives and ascertain whether these have all been met. Within the context of the objectives of the study it was found that:

- Although only eight veterinary pharmaceutical companies responded with figures of volumes of antimicrobials utilized, this sample was sufficiently representative to establish certain indications of trends of antimicrobial consumption.

- The number of authorized antimicrobials available in South Africa was recorded in full during 2002 to 2004.

- The total volumes of animal feedstuffs sold during 2002 to 2004 was established.

- The percentage of medicated feed was not established during 2002 to 2004 but it was calculated that 68,5% of the antimicrobials recorded in this study, were sold as in-feed dosage forms.

The difficulty in obtaining this information was that companies were not obliged by any existing legislation to submit such data. One way to overcome this obstacle would be to centralise this information at government level. As part of the policy to initiate prudent use of antimicrobials, it could be recommended that within the regulations of the revised appropriate legislation (Act 36 of 1947 and Act 101 of 1965) or within the precepts of a Prudent Use of Antimicrobials Policy, that all veterinary pharmaceutical companies and feed

mix companies must submit the annual consumption of antimicrobials in kg or the percentages of medicated feeds. This information could also be compared to import figures of antimicrobials compiled by SARS.

It would be logical for the Regulatory Authorities to collect this information for future surveillance studies as they would be responsible for establishing future policies and revising legislation for prudent antimicrobial use. Act 36 of 1936 and Act 101 of 1965 are the legal frameworks responsible for antimicrobial registration and would set the requirements specifically for registering antimicrobials, based on the data of antimicrobial consumption collected. All the relevant stakeholders, at every level in the animal health field would be consulted on such an initiative and industry and government would work together closely to establish feasible policies and regulations for the prudent use of antimicrobials. An example, very simplistically of such a model could be as follows in Figure 6.1.

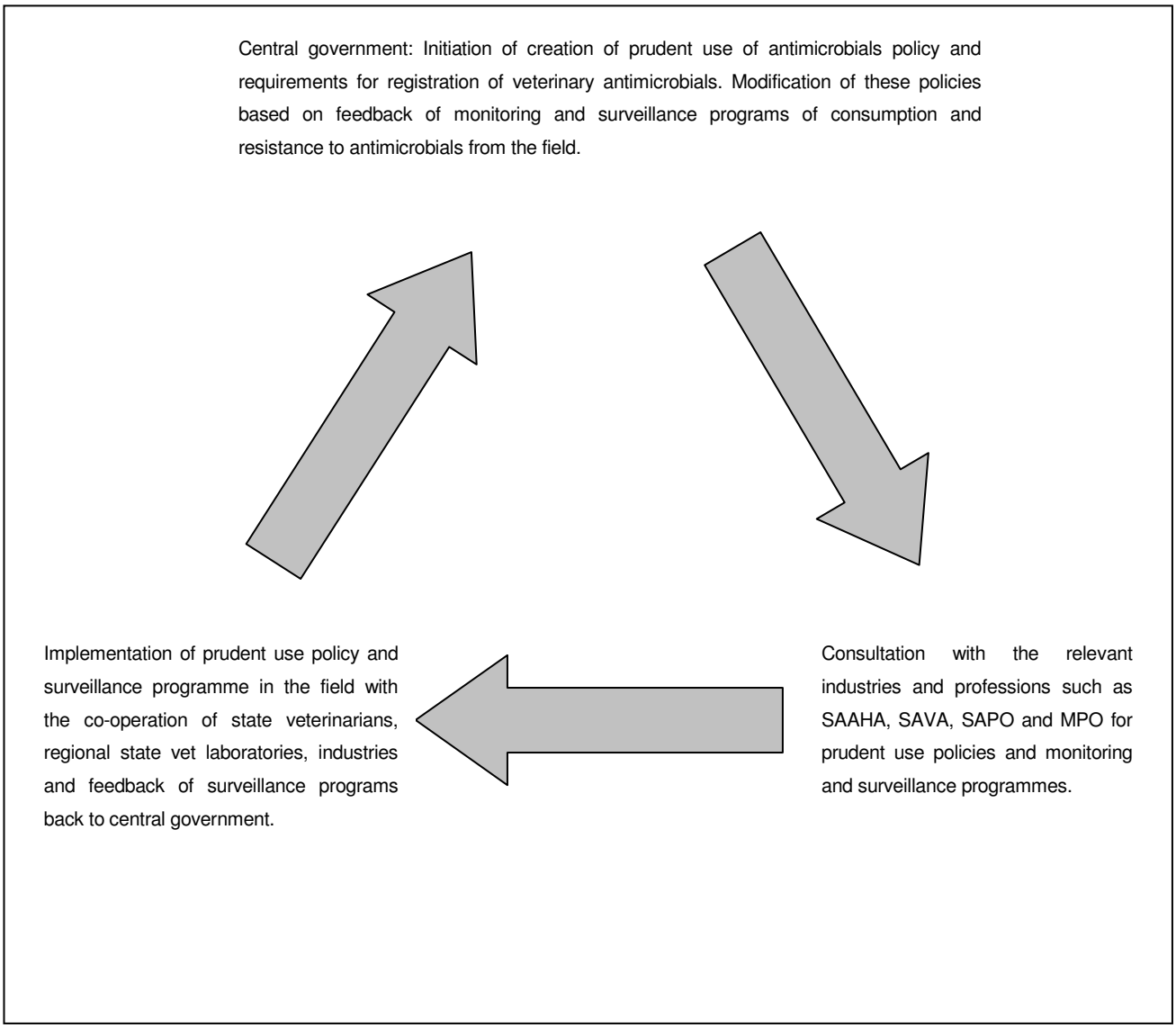

Figure 6.1: Postulated model for prudent antimicrobial use policy and surveillance programmes for antimicrobial consumption and resistance.

This study was an initial effort towards contributing to the provision of databases for policy recommendations for future prudent antimicrobial use.

These data can also be correlated with the National Agricultural Residue Monitoring Plan (NARMP), in foods of animal origin, run by the National Department of Agriculture to assess any violations of antimicrobial residue limits in animal tissues and establish the compliance and prudent use of antimicrobials in food animals, from this perspective.

This study has uncovered certain trends of antimicrobial sales from the reasonable sample of eight veterinary companies who volunteered the relevant data. A significant observation is the very large volume of antimicrobials sold as in-feed dosage forms. The in-feed administration of antimicrobials needs to be scrutinized and decreased in order to minimize the risk of development of antimicrobial resistance in both the human and animal health fields. This type of recommendation needs to be addressed in future prudent use policies, created as a joint venture, based on objective and scientific risk assessments of antimicrobial consumption and antimicrobial resistance between both Industry and Government. The Regulatory Authorities need to establish a review process for registered antimicrobial feed additives in South Africa. This process should be focused on the basis of the actives, rather than the products as the documented evidence points towards the fact that antimicrobials should not be used as growth promoters, if they are known to select for cross-resistance to the human therapeutic antimicrobial equivalents. The time to act and establish these systems, is now, in order to preserve the future efficacy of antimicrobials in animal health and the medical field in South Africa.

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A d d e n d a e

ADDENDUM I

MATERIALS AND METHODS

ADDENDUM I:

3.4 DATA COLLECTION/ OBSERVATIONS

3.4.1 Availability of Antimicrobials for Food Animal use in South Africa

Class	Trade names	API	Dosage Form and strengths	Indication (specie and whether for treatment, prophylaxis or growth promotion)	ACT*	Withdrawal period
Penicillins		ampicillin amoxicillin benzylpenicillin cloxacillin				
Cephalosporins		ceftiofur cephalonium cephalexin cefuroxime				
Tetracyclines		oxytetracycline doxycyline chlortetracycline				
Aminoglycosides		neomycin kanamycin streptomycin spectinomycin				
Macrolides, lincosamides and pleuromutilins		tylosin, kitasamycin tilmicosin spiramycin, tiamulin lincomycin				
Amphenicols		florfenicol				
Quinolones		danofloxacin enrofloxacin sarafloxacin norfloxacin				
Quinoxalines		olaquindox				
Sulphonamides		sulphonamide analogues and potentiators				
Polipeptides		colistin, bacitracin polimixin				
Nitroimidazoles		dimetridazole				
Nitrofurans		nitrovin				
Ionophores		monensin salinomycin lasalocid, naracin				
Steptogramins		virginiamycin				
Glycolipids		flavophospholipol				
Oligosaccharides		avilamycin				
Phosphonic acids		fosfomycin				
Polymeric compounds		poly 2-propenal 2-propenoic acid				

***ACT denotes whether the antimicrobial is controlled in terms of Act101/1965 or in terms of Act 36/1947.**

ADDENDUM I CONTINUED:

3.4.2 Volumes of antimicrobials sourced at the Veterinary Pharmaceutical Company Level from 2002-2004

Class of antimicrobial	Active Pharmaceutical Ingredient (API)	Kg of active ingredient	Dosage form*	Indication (species and if for treatment, prophylaxis or growth promotion)
Penicillins	ampicillin, amoxycillin, benzylpenicillin, cloxacillin			
Cephalosporins	ceftiofur, cephalonium, cephalexin, cefuroxime			
Tetracyclines	oxytetracycline, doxycyline, chlortetracycline			
Aminoglycosides	neomycin, kanamycin, streptomycin, spectinomycin, gentamicin			
Macrolide, lincosamides and pleuromutilins	tylosin, kitasamycin, tilmicosin, spiramycin, tiamulin, lincomycin			
Amphenicols	florfenicol			
Quinolones	danofloxacin, enrofloxacin, sarafloxacin, norfloxacin,			
Quinoxalines	olaquindox, carbadox			
Sulphonamides	sulphonamide analogues and potentiators			
Polipeptides	colistin, bacitracin, polimixin			
Nitroimidazoles	dimetridazole			
Nitrofurans	nitrovin			
Ionophores	monensin, salinomycin, lasalocid, naracin			
Glycolipids	flavophospholipol			

Dosage forms in this survey included: parenteral injection, tablets, enteral solutions, water solubles for mixing into the drinking water, premixes, intramammary preparations, intrauterine preparations and topical preparations.

ADDENDUM I CONTINUED:

3.4.4 Sales of feed from 2002-2004[1]

TYPE OF FEED FOR 2002/03; 2003/04; 2004/05 AND % GROWTH:

Dairy cows	Slaughter cattle sheep & goats	Pigs	Layers	Broilers	Broiler breeders	Ostriches	Aquaculture (fish) freshwater	Other	Total

[1]There was a study deviation here. Please refer to Addendum III.

3.4.5 The percentages of medicated feed sold for each year[2].

Year	% Antimicrobial used per final feed	Dairy cows % feed medicated	Slaughter cattle and sheep % feed medicated	Pigs % feed medicated	Layers % feed medicated	Broilers % feed medicated	Broiler Breeders % feed medicated
2004							
2005							
2006							

[2]There was a study deviation here. Please refer to Addendum III.

ADDENDUM II

AVAILABILITY OF ANTIMICROBIALS

CONTENTS TO ADDENDUM II: AVAILABLE REGISTERED ANTIMICROBIALS

LIST OF ABBREVIATIONS

B	Bovine
Cap	Caprine
D	Days
E	Equine
Hr	Hours
Liv.	Liver
Mkgs	Milkings
O	Ovine

P	Porcine
Qtr	Quarter
Rx	Treatment
Std.	Standard
Wk	Weeks
WP	Withdrawal period

ANTIMICROBIALS AUTHORIZED FOR FOOD ANIMAL USE IN SOUTH AFRICA

B-LACTAMS

PENICILLINS

CLASS	API	TRADE NAMES	DOSAGE FORMS AND STRENGTHS	INDICATION (SPECIE AND WHETHER FOR TREATMENT, PROPHYLAXIS OR GROWTH PROMOTION)	ACT *	WP
			INJECTABLES			
	Amoxycillin	Synulox RTU	Injection Amoxycillin 140mg/ml Clavulanic acid 35mg/ml	Bovine Treatment (Rx) of infections caused by susceptible organisms: soft tissue, metritis, masitis, respiratory and urinary tract infections.	101/1965	Meat: 28 days (d) Milk 24 hours (hr)
		Clamoxyl RTU	Injection Amoxycillin 150mg/ml	Bovine (B); Ovine (O); Porcine (P) Rx of acute and severe wound infections, skin infections.	101/1965	Meat 30d Milk 72 hr
	Ampicillin	Ampitac	Injection Ampicillin 150mg/ml	B; Equine (E) ;O Rx of sensitive infections	101/1965	Meat: 10d Milk: 24hr
Penicillins (long-acting)	**Procaine benzyl penicillin**	Depocillin Aqueous Suspension for Injection	Injection 300mg/ml	B; O; P Rx of penicillin-sensitive infections	101/1965	Meat B; O 4 days P: 5 d Milk: 5 milkings (mkgs)

PENICILLINS

Procaine benzyl penicillin and benzathine benzyl penicillin	Duplocillin Aqueous Suspension for Injection	Injection proc.benzyl penic. 150 000iu benza.benzyl penic. 150 000iu	B; O; P Rx of infections including swine erysipelas, and wound infections	101/1965	Meat: 14d Milk 3 d
	Peni LA Phenix	Injection proc.benzyl penic. 150 000mg benza.benzyl penic. 126 mg/ml	B; O; Caprine (Cap); P; Rx of infections	101/1965	Meat: 30d Milk 4d
Procaine penicillin and benzathine penicillin	Lentrax	Injection proc. penic. 150 000iu benza. penic. 112,5mg/ml	All species Rx of infections	101/1965	Meat:30 d Milk: 3 d
	Procapen LA	Injection proc. penic. 150 mg/ml benza. penic. 112,5mg	All species Rx of infections	101/1965	Meat:30 d Milk: 72 hr
		INJECTABLE COMBINATIONS			
Procaine benzyl penicillin and dihydrostreptomycin	Depomycin Aqueous Suspension for Injection	Injection Proc. Benzyl penicillin 200mg/ml Dihydrostreptomycin 200mg/ml	B;E;O;P Rx of infections	101/1965	Meat: 14d Liver/ Kidney B;P: 21d O: 35d Milk: 4milkings
	Pendistrep 20/20	Injection Proc. Benzylpenicillin 200000iu Dihydrostreptomycin 200 mg/ml	All species Rx of bacterial infections	101/1965	Meat: 7d Milk: 3d

PENICILLINS

	Procaine penicillin and dihydrostreptomycin	Procastrep	Injection Procaine penicillin 200mg/ml Dihydrostreptomycin sulphate 250mg/ml	All species Rx of infections	101/1965	Meat:18d Milk: 60hr
	Amoxycillin and colistin	Potencil	Injectable Amoxycillin 10g/100 ml Colistin sulphate 25 million iu	All species Rx of susceptible infections	101/1965	Meat: 21d
Penicillins (short-acting)	**Amoxycillin trihydrate**		**WATER SOLUBLE POWDERS**			
		Avimox 10	Powder 150mg/g	Poultry Rx of infections	101/1965	Meat and eggs: 24 hours
		Avivet	Powder 40g/100g	Pigeons and cage birds Treatment of infections	36/1947	Meat of pigeons: 5 days

PENICILLINS

INTRAMAMMARY PENICILLINS

Semi-synthetic penicillins	**cloxacillin & ampicillin**	Bovaclox DC	Intramammary Cloxacillin 500 mg ampicillin 250mg/ 4,5g syringe	B Rx and prevention of mastitis in dry cows	101/1965	Meat: 28d Milk 30d
		Curaclox DC	Intramammary Cloxacillin 500 mg ampicillin 250mg/ syringe	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 60 hr post-calving
		Curaclox DC Xtra	Intramammary Cloxacillin 600 mg ampicillin 300mg/ syringe	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 96 hr post-calving
		Dri-cillin	Intramammary Cloxacillin 500 mg ampicillin 250mg/ syringe	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 60 hr post-calving
		Masticillin DC	Intramammary Cloxacillin 500 mg/ single dose	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 28 d plus 10 milkings post-calving

PENICILLINS

Semi-synthetic penicillins	**cloxacillin & ampicillin**	Masticlox DC	Intramammary Cloxacillin 500 mg/ single dose in a long-acting base	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 60 hr post-calving
		Masticlox Plus DC	Intramammary Cloxacillin 500 mg ampicillin 250mg	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 60 hr post-calving
		Masticlox Plus DC Xtra	Intramammary Cloxacillin 600 mg ampicillin 250mg in a long-acting base	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 96 hr post-calving
		Noroclox DC	Intramammary Cloxacillin 500 mg/ 4,5 syringe	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 96 hr post-calving
		Noroclox DC Xtra	Intramammary Cloxacillin 600 mg/ 4,5 syringe	B Rx and prevention of mastitis in dry cows	36/1947	Meat: 28d Milk 96 hr post-calving

PENICILLINS

INTRAMAMMARY COMBINATIONS

Semi-synthetic penicillins	**cloxacillin & ampicillin**	Orbenin Xtra DC Infusion	Intramammary Cloxacillin 600 mg	B Rx and prevention of mastitis in dry cows	101/1965	Meat 4 weeks (wk) Milk 4 d
		Pendiclox Blue DC Infusion	Intramammary Sodium cloxacillin 200mg Sodium ampicillin 75 mg	B Rx and prevention of mastitis in dry cows	36/1947	Meat 4 wk Milk until blue dye disappears and 24 hr thereafter
		Cloxamast LC	Intramammary Sodium cloxacillin 200mg Sodium ampicillin 75 mg	B Rx of mastitis in lactating cows	36/1947	Meat 7 d Milk 72 hr
		Count- Down LC	Intramammary Sodium cloxacillin 200mg Sodium ampicillin 75 mg	B Rx of mastitis in lactating cows	36/1947	Meat 7 d Milk 72 hr
		Curaclox LC	Intramammary Sodium cloxacillin 200mg Sodium ampicillin 75 mg	B Rx of mastitis in lactating cows	36/1947	Milk 72 hr after last infusion

PENICILLINS

INTRAMAMMARY COMBINATIONS

procaine penicillin & albamycin	Albadry Plus	Intramammary Procaine penillin 200000 iu albamycin 400mg	B Rx and prevention of mastitis in dry cows	101/1965	Meat: 30d Milk 72 hr post-calving
procaine penicillin & dihydrostreptomycin	Dispolac Dry Cow injection	Intramammary Procaine benzyl penicillin 4,9% m/m dihydrostreptomyin 6,5 % m/m	B Rx and prevention of mastitis in the dry period	36/1947	Meat: 7d Milk 24 hr
procaine penicillin	R x 4 B Injection	Intramammary Procaine penicillin 487 000 iu dihydrostreptomycin 530 000 iu	B Rx of mastitis	36/1947	Meat: 7d Milk 24 hr
procaine penicillin & dihydrostreptomycin & nafcillin	Napenzal DC	Intramammary Benzyl penicillin 300 000 iu dihydrostreptomycin 300 mg/3g nafcillin 300mg/ 3g	B Rx and prevention of mastitis in dry cows	101/1965	Milk: 3mkg Organs: 5wk

PENICILLINS

Benzyl penicillin & dihydrostreptomycin & nafcillin	Napenzal MC	Intramammary Benzyl penicillin 300 000 iu dihydrostreptomycin 100 mg/3g nafcillin 100mg/ 3g	B: Rx of mastitis	101/1965	Meat 24hr Milk treate qtr 6 mkgs Milk untre qtr 3mkgs Udder 3d Kidney/liv. 3 d
procaine penicillin & neomycin	Neo-Mastitar Dry Cow	Procaine penicillin 500 000 iu neomycin base 300mg/8g	Rx and prevention of mastitis in dry cows	101/1965	Meat 5wk Milk 5wk
Procaine penicillin G Novobiocin Polymixin B sulphate Dihydrostreptomycin	Special Formula 17900 Forte	Intramammary Procaine penicillin G 100 000iu Novobiocin 150 mg Polymixin B sulphate 50 000 iu Dihydrostreptomycin 100mg/10 ml	B Rx of mastitis	101/1965	Milk 72hr
Procaine penicillin G dihydrostreptomycin	Streptocillin	Intramammary Procaine penicillin G 300 000iu dihydrostreptomycin 500mg	B Rx of mastitis	36/1947	Meat 24hr Milk 24 hr
procaine penicillin & dihydrostreptomycin & nafcillin	Napenzal DC	Intramammary Benzyl penicillin 300 000 iu dihydrostreptomycin 300 mg/3g nafcillin 300mg/ 3g	B Rx and prevention of mastitis in dry cows	101/1965	Milk:3mkgs Organs: 5wk

CEPHALOSPORINS

INJECTABLES

Cephinome	Cobactan Intramuscular Injection	Cephinome 25mg/ml Injection	B Rx of respiratory tract infections, including P. multocida and Mannheimia haemolytica	101/1965	Meat: 5d
Ceftiofur	Excenel Injection	Ceftiofur 50 mg/ml Injection	B; P Rx of infections Respiratory disease and bovine footrot	101/1965	Meat:24hr

INTRAMAMMARY CEPHALOSPORINS

Cephapirin	Cephudder	Cephapirin 300 mg Intramammary	B Rx and prevention of mastitis	101/1965	Meat: 21d Milk:2mkg provided that the dry period has lasted longer than 35 days
Cephalonium	Cepravin Dry Cow	Cephalonium 250 mg/3g Intramammary	B Treatment and prevention of mastitis	101/1965	Meat 21 d Milk 4 d after calving

CEPHALOSPORINS

Cefuroxime	Spectrazol Milking Cow	Cefuroxime 250 mg Intramammary	B Treatment of mastitis	101/1965	Meat:60hr Milk: 1 d
		INTRAMAMMARY COMBINATIONS			
Cepalexin & neomycin	Rilexine 200 LC injection	Cephalexin 100 mg neomycin 100 mg Intramammary	B Treatment of mastitis	101/1965	Meat 96hr
	Rilexine 500 DC Injection	Cephalexin 250 mg neomycin 250 mg Intramammary	B Treatment of mastitis	101/1965	Milk: 4 weeks

TETRACYCLINES

Oxytetracycline

INJECTABLES

Alamycin LA 300	Injection Oxytetracycline dihydrate 300mg/ml	B;O; Cap; P Rx of infections such as heartwater, anaplasmosis, pneumonia, foot-rot, joint-ill and navel-ill	36/1947	Meat: Std dose: B; Cap; O; 28 d P: 14 d High dose: B;Cap;O: 35d P: 28 d Milk: 7d
Alamycin 10 Injection	Injection	B;O;Cap;P;E B: Rx of infections	36/1947	Meat: 7d Milk: 2d
Ecomycin Dual Purpose	Injection Oxytetracycline 135 mg/ml	E;B;O;Cap;P Rx of infections	36/1947	Meat: 28d Milk: 7d
Ecomycin LA	Injection Oxytetracycline HCl 230 mg/ml	B; O;Cap; P Rx of infections.	36/1947	Meat: 28d Milk: 5d

TETRACYCLINES

Oxytetracycline

INJECTABLES

Engemycin 10% Injectable solution	Injection Oxytetracycline HCl 100 mg/ml	E;B;O;Cap;P Rx of infections.	36/1947	Meat: 14d Milk: 60hr
Hexasol HB Injection	Injection Oxytetracycline 300mg/ ml	B: Rx of infections	101/1965	Meat: 21d
Hi-Tet 120 Injection	Injection Oxytetracycline HCl 120mg/ ml	B;E; Cap; O; P Stock: Rx of infections	36/1947	Meat: 7d Milk: 2d
Hi-Tet 200 LA Injection	Injection Oxytetracycline HCl 200mg/ ml	B;E; Cap; O; P Rx of infections.	36/1947	Meat: 28d Milk: 6d
Linacycline LA	Injection Oxytetracycline HCl 200mg/ ml	B;Cap;O;P Rx of infections	36/1947	Meat: 21d Milk: 15d

TETRACYCLINES

Oxytetracycline

INJECTABLES

Oxytetracycline	Hi-Tet 300 LA Injection	Injection Oxytetracycline HCl 300mg/ ml	B;E; Cap; O; P Rx of infections.	36/1947	Meat: Std dose: B: 28d Cap; O:P 14d Higher dose: B: 35 d Cap;O:P: 28d Milk: 7d
	Langa Mycin LA	Injection Oxytetracycline 200mg/ ml	B;O;Cap;P Rx of infections	36/1947	B: Meat: 30d Milk 6d O: Meat 22d Milk 6d Cap: Meat: 30d Milk 8d P: 22d
	Liquamycin LA	Injection Oxytetracycline HCl 200mg/ml	B;O;P;Cap Rx of infections	101/1965	Meat: 28d Milk 5d
	Miltet	Injection Oxytetracycline HCl 120mg/ml	B;E;O;Cap;P Rx of infections	101/1965	Meat: 7d Milk: 2d

Oxytetracycline

TETRACYCLINES

Noromycin LA	Injection Oxytetracycline dihydrate 200mg/ml	B;O;Cap;P Rx of infections.	36/1947	Meat: 21d Milk: 7d
Obermycin 125	Injection Oxytetracycline HCl 125mg/ml	B;E;O;Cap;P Rx of infections.	36/1947	Meat: 7d Milk: 48h
Oxytet 12,5%	Injection Oxytetracycline HCl 125mg/ml	B;E;O;Cap;P Rx of infections.	36/1947	Meat: 7d Milk: 48h
Oxytetra LA	Injection Oxytetracycline HCl 200mg/ml	B;O;Cap;P Rx of infections.	36/1947	Meat: 8w Milk: 5d
Reverin 100	Injection Oxytetracycline 100mg/ml	B;Cap;E;O;P Rx oxytetracycline-sensitive organisms	36/1947	Meat: 14d Milk: 60h
Reverin LA	Injection Oxytetracycline 200mg/ml	B;Cap;O;P Rx of infections.	36/1947	Meat: 28d Milk: 5d
Tenaline LA	Injection Oxytetracycline 200mg/ml	B;Cap;O;P Rx of infections.	36/1947	Meat: 21d Milk: 15d
Terralon 100	Injection Oxytetracycline HCl 100mg/ml	B;Cap;O;P Rx of infections.	36/1947	Meat: 14d Milk: 4d
Terramycin 100	Injection Oxytetracycline HCl 100mg/ml	B;Cap;O;P;E Rx of infections.	36/1947	Meat: 7d Milk: 48h

TETRACYCLINES

Oxytetracycline		**INJECTABLES**			
	Terralon LA	Injection Oxytetracycline dihydrate 200mg/ml	B;Cap;O;P Rx of infections.	36/1947	B: Meat:30d Milk: 6d P: Meat:22d O: Meat:22d Milk: 6d Cap: Meat:30d Milk:8d
e					
	Terramycin LA	Injection Oxytetracycline 200mg/ml	B;Cap;O;P Rx of infections.	36/1947	Meat: 28d Milk: 5d
	Triple Two LA	Injection Oxytetracycline HCl 230mg/ml	B;O;Cap;P Rx of infections.	36/1947	Meat: 56d Milk: 5d
Doxycycline	Doxymycin QA	Injectable Doxycycline hyclate 100mg/ml	B;E;O;Cap;P Rx of infections.	36/1947	Meat: 14d Milk: 4d
	Mildox	Injection Doxycycline hyclate 100mg/ml	B;E;O;Cap;P Rx of infections.	36/1947	Meat: 14d Milk: 2d

TETRACYCLINES	**Oxytetracycline**		**WATER SOLUBLE POWDERS**			
		Vitamycin	Powder Oxytetracycline 55mg/g	B;O;P; Poultry Rx: Oxytetracycline-sensitive infections	36/1947	Meat: 14d Eggs: 4d
		Oxytetracycline 5,5%	Powder Oxytetracycline HCl 5,5%	Poultry Rx: Bacterial infections sensitive to oxytetracycline	36/1947	Meat: 7d
		Phenix Oxphen 20%	Powder Oxytetracycline base 20%	Poultry Rx: Secondary bacterial infecions following respiratory disease	36/1947	Meat: 14d Eggs: 4d
		Terramycin Animal Formula	Powder Oxytetracycline HCl 55mg/g	B;O;P;Poultry Calves,lambs,P: Rx Bacterial Respiratory and gastrointestinal infections Poultry: Rx Respiratory infections	36/1947	Meat: 14d Eggs: 4d
		Langa Oxyvet 5%	Oral powder Oxytetracycline base 5% m/m	B;O;P; Poultry Rx secondary bacterial infections following respiratory disease	36/1947	Meat: 14d Eggs: 4d
		Phenix Oxyvit 5%	Powder Oxtetracycline base 5%	B;O;P;Poultry Rx: Secondary bacterial infecions following respiratory disease	36/1947	Meat: 14d Eggs: 4d

TETRACYCLINES	**Oxytetracycline**		**WATER SOLUBLE POWDERS**			
		Contramycin	Oral powder Oxytetracycline HCl 55mg/g	B;O;P, Poultry Rx of infections.	36/1947	Eggs: 4 d Meat:14d
		Terravit	Powder Oxytetracycline HCl 55mg/g	B;O;P;Poultry Rx of infections.	36/1947	Meat: 14d Eggs: 4d
		TM-200	Powder Oxytetracycline dihydrate 200g/kg	B;O;P;Poultry Rx of bacterial infections.	36/1947	Meat: 7d
	Doxycycline	Doxyveto-50 S	Powder Doxycycline HCl 500mg/g	Poultry Rx of infections.	36/1947	Meat: 12d
		Ostri-Dox	Powder Doxycycline HCl 125mg/g	Ostriches Rx of susceptible infections.	36/1947	
		Doxyvit 100	Powder Doxycycline HCl 100mg/g	Poultry Rx susceptible bacterial infections.	36/1947	Meat: 7d
		Pulmodox 50 OSP	Powder Doxycycline HCl 500mg/g	Poultry Rx of infections.	36/1947	Meat: 12d
	Tetracycline	TFC	Powder Tetracycline disodium salt phosphate complex 100g/kg	Calves;P;Poultry Rx of sensitive infections	36/1947	Meat: 7d

PREMIXES

TETRACYCLINES	**Oxytetracycline**	Phenix Oxytetracycline 20% FG	Premix Oxytetracycline 20% m/m	B;O;P;Poultry Rx of infections.	36/1947	Meat: 7d
		Oxytet FG	Premix Oxytetracycline 200g/kg	B;O;P;Poultry Rx of infections.	36/1947	Meat: 7d Eggs: 2d
		Oxytetracycline 20%	Premix Oxytetracycline 200g/kg	P; Poultry Rx: Bacterial infections sensitive to oxytetracycline	36/1947	Meat: 5d
		Oxytetracycline 10%	Premix Oxytetracycline 100g/kg	P; Poultry Rx: Bacterial infections sensitive to oxytetracycline	36/1947	Meat: 5d
			Premix Oxytetracycline HCl 100g/kg	B;P;Poultry Rx of infections	101/1965	Meat: 5d
		Protet 20%	Premix Oxytetracycline 200g/kg	B;O;P;Poultry Rx: Secondary bacterial infecions	36/1947	Meat: 7d Eggs: 2d
		Protet 10%	Premix Oxytetracycline 100g/kg	B;O;P;Poultry Rx: Secondary bacterial infecions	36/1947	Meat: 7d Eggs: 2d
		Phenix Oxytetracycline 10% FG	Premix Oxytetracycline 10% m/m	B;O;P;Poultry Rx of infections.	36/1947	Meat: 7d

PREMIXES

TETRACYCLINES	**Chlortetracycline**	Aurofac 100	Premix Chlortetracycline 10% m/m	B;Calves; P; Poultry Rx: Respiratory, enteric, systemic and local infections.	36/1947	Meat: 7d
		Phenix CTC 20%	Premix Chlortetracycline 20%	B;P;Poultry Prevention and control of disease sensitive to chlortetracycline	36/1947	Meat: P: 7 days Poultry:4d
		Chlortet FG200	Premix Chlortetracycline 200g/kg	B;P;Poultry Rx respiratory and other infections caused by organisms susceptible to chlortetracycline	36/1947	

COMBINATION PREMIXES

Neo-Terramycin 50/50	Premix Oxytetracycline HCl 50mg/kg Neomycin 50mg/kg	Calves, Lambs, P; Rx susceptible bacterial infections	101/1965	Meat: 5d
Aureo-S-700	Premix Chlortetracycline HCl 77g/kg Sulphamethazine 77g/kg	B;P Rx gram-positive and gram-negative infections.	36/1947	Meat: 7d

INTRAUTERINE PREPARATIONS

TETRACYCLINES	**Oxytetracycline**	Obermycin Foaming Pessaries	Pessary Oxytetracycline HCl 2250 mg/25g	B;O;Cap;P Rx of bacterial infections	36/1947	Meat: 7d
		Terramycin Super	Pessary Oxytetracycline HCl 2000 mg/pessary	B; Cap; P Rx of bacterial infections.	36/1947	Meat: 7d Milk: 72 hr
		Terra-Fizz Super Afterbirth	Pessary Oxytetracycline HCl 2000 mg/pessary	B Rx of vaginal and uterine infections.	36/1947	Meat: 7d Milk: 72 hr
		Eco Afterbirth Pessaries	Pessary Oxytetracycline 375 mg Sulphadimidine 125 mg Sulphathiazole 125 mg Sulphadiazine 125 mg	B;E;O;Cap;P Rx of bacterial infections of vagina and uterus.	36/1947	Meat: 7d
		Antrovet Afterbirth Pessaries	Pessary Oxytetracycline 375 mg Sulphadimidine 125 mg Sulphathiazole 125 mg Sulphadiazine 125 mg	B;E;O;Cap;P Rx of bacterial infections of vagina and uterus.	36/1947	Meat: 7d

AEROSOLS

TETRACYLINES	**Oxytetracycline**	Alamycin aerosol	Aerosol Oxytetracycline HCl 3,6% m/m	B;O Rx of Footrot, Topical infections	36/1947	
		Necrospray NF	Aerosol Oxytetracycline HCl 40mg/g	All species Rx all topical infections	36/1947	
		Engemycin Spray	Spray Oxytetracycline HCl 5g/ 200ml	All species Rx of topical infections.	36/1947	

OPHTHALMIC/ AURAL AGENTS

	Oxytetracycline	Terramycin Eye Powder	Ophthalmic Oxytetracycline HCl 20mg/g	All species Rx bacterial eye infections.	36/1947	
		Terra-Cortril Eye/Ear Suspension	Ophthalmic/Aural Oxytetracycline 10mg/ml	All species Rx bacterial eye and ear infections.	36/1947	

OPHTHALMIC / AURAL AGENTS (COMBINATION)

	Doxycycline	Doxymycin Eye Powder	Ophthalmic Doxycycline 1% Sodium sulphacetamide 5%	B;E;Cap;E; P Rx Ophthalmia	36/1947	Meat: 5d

TETRACYCLINES	**Doxycycline**		**TABLETS**		
		Doxybird	Tablet 7,5 mg	Pigeons	36/1947
			INTRAMAMMARY PREPARATIONS (COMBINATION)		
	Tetracycline & Neomycin & Bacitracin	Mastijet Fort	Intramammary Tetracycline HCl 200mg neomycin 250 mg bacitracin 2000 iu	B Rx of mastitis caused by susceptible organisms 101/1965	Meat: 2d Organs: 42d Milk: 8 milkings Untreated quarters: 1 milking

AMINOGLYCOSIDES

Gentamicin		**INJECTABLES**			
	Genta 50	Injectable Gentamicin base 50 mg/ml	E; P E: Rx of infections.	101/1965	Meat: 7 d Milk: 2 d Piglets: Meat: 6wk
Kanamycin	Kanamyn	Injectable Kanamycin base as sulphate: 100mg/ml	All species Rx acute and chronic infectons	101/1965	Meat: 7d Milk: 2d
		INJECTABLE COMBINATIONS			
See injectable combinations for penicillins					
Neomycin		**WATER SOLUBLE POWDER**			
	Biosol 70%	Powder Neomycin 490 g/kg	B;O;P; Poultry Rx of bacterial enteritis	101/1965	Meat: B: 30d P;O: 20d Turkeys, Layers: 14d Broilers: 5d

AMINOGLYCOSIDES

See oxytetracycline premix combinations.

**See penicillin intramammary combinations.
and tetracycline intramammary combinations.**

PREMIX COMBINATIONS

INTRAMAMMARY COMBINATIONS

MACROLIDES, LINCOSAMIDES AND PLEUROMEUTILINS

MACROLIDES

Tylosin		**INJECTABLES**			
	Tylan 200	Injectable Tylosin 200mg/ml	B; Cap; O; P Rx of infections.	101/1965	Milk: B: 72hrs Cap;O:48h
	Tylo 200	Injectable Tylosin base 200 mg/ml	B; P; Poultry Rx of infections.	101/1965	Meat: 12d Milk: 5d
Tylosin tartrate		**WATER SOLUBLE POWDERS**			
	Tylobiotic	Powder Tylosin tartate 10% m/m	Pigeons Prevention of mycoplasmosis	36/1947	Meat: 3d
	Tylosin Tartrate Water Soluble Powder	Powder Tylosin tartate 800g/kg	Poultry Prevention of mycoplasmosis in replacement pullets and broilers.	36/1947	Meat: 1d
	Tyloveto-S-Soluble	Powder Tylosin tartrate 1000mg/g	Poultry Prevention of mycoplasmosis	36/1947	Meat: 3d

WATER SOLUBLE POWDERS

MACROLIDES	**Tylosin tartrate**	Aivlosin Water Soluble Powder Acetyl-isovaleryl-tylosin tartrate 850 mg/g		Poultry Prevention of mycoplasmosis in replacement pullets and broilers.	36/1947	Meat: 5d
		Tylan Soluble	Powder Tylosin Tartrate 77-95%	Poultry Prevention of mycoplasmosis in replacement pullets and broilers.	36/1947	Meat: 3d
	Kitasamycin tartrate	Kitasamycin Water Soluble Powder	Powder Kitasamycin tatrate 1g/g	P; Poultry P:Prevention and treatment of swine dysentery and pneumonia Poultry: Prevention and treatment of chronic respiratory disease.	36/1947	
	Spiramycin	Suanovil 50	Powder Spiramycin adipate 1,5 million iu/g	Poultry Treatment of mycoplasmal infections	36/1947	Meat: 10d Eggs: 3d
	Josamycin	Tri-Alpucine	Powder Josamycin 18 million iu/100g Trimethoprim 10g/100g	Poultry Prevention and Rx of infections.	101/1965	

PREMIXES

MACROLIDES	**Tylosin**	Promote	Premix Tylosin phosphate 10% m/m	P; Poultry Improves mass gain and feed efficiency.	36/1947	
		Tyleco FG 250	Premix Tylosin phosphate 25% m/m	B;P; Poultry Improved growth rate and feed conversion efficiency.	36/1947	Meat: P: 15d Poultry:3d B: 0 d
		MDB Tylosin	Premix Tylosin phosphate 10% m/m	B;O;Cap;P;Poultry Growth promotant	36/1947	
		Tylosin 10% premix	Premix Tylosin phosphate 10% m/m	P improves mass gain and feed converson.	36/1947	Meat: 3wk

PREMIXES

MACROLIDES	**Tylosin**	Tylan 100	Premix Tylosin phosphate 10% m/m	B;P; Poultry 36/1947 B: prevents liver abscesses in feedlot cattle, improves mass gain and feed conversion efficency. P: Prevents porcine proliferative enteropathies associated with *Lawsonia intracellularis*. Improves mass gain and feed converson. Broilers: Improves mass gain and feed conversion efficiency. Layers: Improves feed conversion efficiency and egg production.
	Kitasamycin	Kitasmycin 10% Premix	Premix Kitasamycin 10% m/m	P;Poultry 36/1947 P: growth promotion prevention and Rx dysentery, feed efficiency in swine enzootic pneumonia. Poultry:Growth promotion Rx and prevention of chronic respiratory disease.
	Tylosin tartrate	Aivlosin FG 50 Acetyl-isovaleryl-tylosin tartrate 50g/kg	Premix	Poultry; P 36/1947 Meat: 5d Prevention of mycoplasmosis in replacement pullets and broilers. Prevention of swine enzootic pneumonia.

PREMIX COMBINATIONS

MACROLIDES	**Sulpha and Tylosin**	Tylan 100 plus Sulpha	Premix Tylosin 100g/kg Sulphamethazine 100g/kg	P For prevention and Rx susceptible respiratory and enteric infections. Improves growth rate and feed conversion efficiency.	101/1965	Meat:5d

LINCOSAMIDES

		INJECTABLES			
Lincomycin	Lincocin Sterile Solution	Injectable Lincomycin 100mg/ml	P Rx Infectious arthritis and mycoplasmal pneumonia.	101/1965	Meat:48hr
	Linco-Spectin	**INJECTABLE COMBINATIONS**			
		Injectable Lincomycin 50mg Spectinomycin 100mg	Calves; Cap;O;P; Poultry Rx of susceptible infections.	101/1965	Meat: 14d Milk: 48hr
		WATER SOLUBLE POWDER COMBINATIONS			
	Linco-spectin 100 Soluble Powder	Powder Lincomycin HCl 33,3g Spectinomycin SO4 96,7g	P;Poultry P: Rx swine dysentery, bacterial enteritis, infectious arthritis. Poultry: Prevention and Rx Mycoplasmal CRD, coliform infections	101/1965	Meat: P: 8d Poultry:2d
		PREMIX COMBINATIONS			
	Linco-Spectin	Premix Lincomycin 22g/kg Spectinomycin 22g/kg	P Rx and prevention of Swine dysentery and bacterial enteritis	101/1965	Meat:24hr

PLEUROMUTILINS

Tilmicosin		**INJECTABLES**			
	Micotil 300	Injectable Tilmicosin 300mg/ml	B Rx Bovine Respiratory Disease	101/1965	Meat:28d
		ORAL SOLUTIONS			
	Pulmotil AC Solution	Solution Tilmicosin 250mg/ml	Poultry Rx and prevention of diseases	101/1965	Meat: 12d
		PREMIXES			
Tiamulin	Pulmotil 200 Premix	Premix Tilmicosin 200g/kg	P Prevention of disease.	101/1965	Meat: 14d
	Tiamutin 10%	Premix Tiamulin hydrogen fumarate 100g/kg	P;Poultry P: Prevention and treatment infections. Feed conversion efficiency and growth promotion. Poultry:Prevention and treatment of disease.	101/1965	P: Meat: 3d

AMPHENICOLS

Florfenicol		**INJECTABLES**			
	Nuflor	Injectable Florfenicol 300mg/ml	B;P	101/1965	B: IM inject. 30d s/c inject. 44d P: Meat: 21d
			B: Rx Bovine respiratory disease and footrot. P: Rx respiratory infections and infections due to florfenicol-sensitive bacteria.		

QUINOLONES

INJECTABLES

Enrofloxacin	Baytril 10% Injectable Solution	Enrofloxacin 100mg/ml	B Rx of Gram-positive and Gram-negative infections and mycoplasma.	101/1965	Meat: 7d Milk: 3d
	Baytril 100	Injectable Enrofloxacin 1g/ 10ml	B: Rx of infections.	101/1965	Meat: 14d Milk: 3d
Norfloxacin	Quinabic 7% Injectable Solution	Injectable Norfloxacin nicotinate 70mg/ml	B;P Rx of infections.	101/1965	Meat: 4d
Danofloxacin	Advocin	Injectable Danofloxacin 25mg/ml	B;P B: Rx respiratory and enteric disease. P: Rx respiratory disease.	101/1965	B: Meat: 5d Milk: 96 hr P: Meat: 21d
	Advocin 180	Injectable Danofloxacin 180mg/ml	B Rx of respiratory disease caused by *M. haemolytica*, *P. multocida* and *H. somni.*	101/1965	Meat: 5d Milk: 96 hr

			WATER SOLUBLE POWDERS			
QUINOLONES	**Norfloxacin**	Quinabic	Powder Norfloxacin nicotinate 1000mg/g	Poultry Rx of infections.	101/1965	Meat: 4d
			ORAL SOLUTIONS			
		Menorox Liquid Concentrate	Oral Solution Norfloxacin 100 mg/ml	Poultry Rx of norfloxacin -sensitive bacterial and mycoplasmal infections.	101/1965	Meat and eggs: 4d
	Enrofloxacin	Baytril 10% Oral Solution	oral solution Enrofloxacin 100mg/ml	Poultry Rx of infections.	101/1965	Meat: 7d Milk: 3d

QUNIOXALINES

PREMIXES

Olaquindox	Olaquindox 10%	Premix Olaquindox 100g/kg	P;Poultry Antimicrobial growth promotant.	36/1947	Meat: 2d
Carbadox	Mecadox 11%	Premix Carbadox 11%	P Rx swine dysentery and growth promotion	36/1947	Meat: 35d

SULPHONAMIDES AND POTENTIATORS

INJECTABLES

Sulpadimethypyrimidine Trimethoprim	Amphoprim Sulphadimethypyrimidine 200mg/ml Trimthoprim 40mg/ml	Injectable	E;B;B;O Rx of bacterial infections.	101/1965	Meat: 7d Eggs: 3d
Sulphadimethoxine	Disulfox LA Sodium sulphadimethoxine 40% m/v	Injectable	B;Cap;O;E;P Rx of bacterial infections.	36/1947	Meat: 7d Milk: 48hr
Sulphadimethoxine	Ecosulf LA Sodium sulphadimethoxine 40% m/v	Injectable	B;E;O Rx of infections.	36/1947	Meat: 7d Milk: 48hr
Sulphamethoxazole Trimethoprim	Kyrotrim Sulphamethoxazole 200mg/ml Trimethoprim 40mg/ml	Injectable	B;O;P Rx sulphonamide-sensitive infections.	36/1947	Meat: 5d Milk: 3d
Sulphadiazine Trimethoprim	Norodine Sulphadiazine 200mg/ml Trimethoprim 40mg/ml	Injectable	B;E;O;Cap;P Rx of infections.	36/1947	Meat: 28d Milk: 72hr
Sulphadiazine Trimethoprim	Norotrim 24 Injection Sulphadiazine 200mg/ml Trimethoprim 40mg/ml	Injectable	All species Rx of bacterial infections.	36/1947	Meat: 3d Milk: 48hr
Sulphamethoxypyridazine Trimethoprim	Sulfatrim 240 Sulphamethoxypyridazine 200mg/ml Trimethoprim 40 mg/ml	Injectable	B;P Rx of bacterial infections.	101/1965	Meat: 12d Milk: 5d
Sulphadimidine sodi	Sulfazine 33,33% Injection Sulphadimidine sodium 33,33%	Injectable	B;E;O;P;Cap Rx of infections.	36/1947	Meat: 7d Milk: 48hr

SULPHONAMIDES AND POTENTIATORS

INJECTABLES

Sulfazine 16%	Sulphadimidine sodium 16%	B;E;O;P;Cap	36/1947	Meat: 7d	
Sulphamethoxazole Trimethoprim	Sulmethotrim	Injectable Sulphamethoxazole 200mg/ml Trimethoprim 40mg/ml	B;O;P Rx bacterial infections.	101/1965	Meat: 12d Milk: 5d
Sulphamethoxazole Trimethoprim	Sulmetrim Plus	Injectable Sulphamethoxazole 200mg/ml Trimethoprim 40mg/ml	B;O;P Rx of sulphonamide-sensitive infections.	36/1947	Meat: 5 d Milk: 3 d
Sulphamethazine		Sulphamethazine 33% Sulphamethazine 16%	B;E;O;P;Cap Rx of infections.	36/1947	Meat: 7d Milk: 48hr
Sulphathiaxole Sulphadiazine Sulphamerazine	Trimeto Tad Pro	Injectable Sulphathiaxole 40mg/ml Sulphadiazine 60mg/ml Sulphamerazine 100mg/ml	B;P Rx primary and secondary infections.	101/1965	Meat: 8 d Milk: 5 d
Sulphadoxine Trimethoprim	Trivetrin	Injectable Sulphadoxine 200mg/ml Trimethoprim 40mg/ml	B;O; P;E Rx: gram-pos and gram-neg infections.	36/1947	Meat: 3 d Milk: 48hr

WATER SOLUBLE POWDERS

Sulphamethoxypyridazine Trimethoprim	Colimix Plus	Powder Sulphamethoxypyridazine 69% Trimethoprim 21%	Poultry Rx of infections.	36/1947	Meat:72hr Eggs:72hr

SULPHONAMIDES AND POTENTIATORS **WATER SOLUBLE POWDERS**

Sulphonamides Potentiated and non-potentiated	Coccistop 2000	Powder Na-sulphaguanidine 40g/200g Na-sulphadimethoxine 4g/200g	Poultry Coccidiostat	36/1947	Meat: 5 d Eggs: 3 d
Sulphachloropyridaz Trimethoprim	Cosumix Plus	Powder Sulphachloropyridazine 100g/kg Trimethoprim 20g/kg	B;P;Poultry Rx of bacterial and digestive infections. *E. coli* infections	36/1947	Meat: Calves: 2d P: 4 d Poultry:1d Eggs: 3 d
Sulphachloropyrazin	ESB3	Powder Sulphachloropyrazine-Na 300g/kg	Poultry Rx coccidiosis and infectious coryza	36/1947	Meat: 7d Eggs: 3 d
Sulphaguanidine Sulphadiazine Phthalylsulphathiazole	Stoplaks NF Diarrhoea Powder	Powder Sulphaguanidine 1,50% Sulphadiazine 1,50% Phthalylsulphathiazole 1,50%	B Rx of bacterial scours	36/1947	Meat: 7d
Sulphanilamide	Sulphanilamide Powder	Powder Sulphanilamide 100% m/m	B;E;O;P;Cap Rx of infections.	36/1947	Meat: 7d Milk: 48hr

SULPHONAMIDES AND POTENTIATORS

WATER SOLUBLE POWDERS

	Trimeto Tad	Powder	B;P, Poultry	101/1965	Meat: 10d
Sulphathiazole		Sulphathiazole 1,3 mg/100g	Rx of infections.		
Sulphadiazine		Sulphadiazine 0,7 mg/100g			
Sulphamerazine		Sulphamerazine 1,3 mg/100g			
Trimethoprim		Trimethoprim 0,7 mg/ 100g			
	Triple Sulfa Powder	Powder	Poultry	36/1947	Meat: 7d
Na-sulphamerazine		Na-sulphamerazine 27,2g	Rx coccidiosis and		Eggs: 3d
Na-sulphamethazine		Na-sulphamethazine 27,2g	Haemophilus coryza.		
Na-sulphathiazole sequihydrate		Na-sulphathiazole sequihydrate 29,85g			
Sulphadiazine	Tucoprim 40%	Powder	E:	36/1947	
Trimethoprim		Sulphadiazine 12,5g/ 37,5g	Rx Respiratory, urinary, genital,		
		Trimethoprim 2,5g/ 37,5g	GI-tract infections and wounds.		

ORAL SOLUTIONS

Sulphathiazole	Avisol	Solution	Poultry	36/1947	Meat: 7d
		Sulphathiazole 20%	Rx of infections.		Eggs: 3 d
Sulphadiazine sodiu	Biaprim	Solution			
Trimethoprim		Sulphadiazine sodium 20g/100ml	Poultry	36/1947	Meat: 3 d
		Trimethoprim 4g/100ml	Rx of infections.		
Na-sulphachloropyridazine	Coliprim	Solution	Calves, P, Poultry	36/1947	Meat: 5 d
Trimethoprim		Na-sulphachloropyridazine 10%	Rx of infections.		
		Trimethoprim 2%			

SULPHONAMIDES AND POTENTIATORS **ORAL SOLUTIONS**

Sulphaquinoxaline	Embazin	Solution Sulphaquinoxaline 9,61% m/m	Poultry Rx coccidiosis	36/1947	Meat: 7 d Eggs: 3 d
Sulphamethoxazole Trimethoprim	Methoxasol-T	Solution Sulphamethoxazole 10% Trimethoprim 2%	P; Poultry Rx GI-tract, respiratory and urogenital tract infections.	36/1947	Meat: P: 3 d Poultry:4d
Sulphadimine sodiun	Sulfazine 16%	Solution Sulphadimine sodium 16%	Poultry, calves, lambs, kids ,rabbits Rx of infections.	36/1947	Meat: 7d Eggs: 3 d
Sulphadimine sodiun	Sulphamethazine 16% Solution	Sulphadimine sodium 16%	B;Cap;O; Poultry Rabbits Rx of infections.	36/1947	Meat: 7d Eggs: 3 d Milk: 48 hr

SULPHONAMIDES AND POTENTIATORS

PREMIXES

Sulphadiazine Trimethoprim	Tucoprim	Premix Sulphadiazine 125g/ kg Trimethoprim 25g/ kg	P;Poultry Rx of infections.	36/1947	Meat: P: 5 d Poultry:1d

PREMIX COMBINATIONS

See Chlortetracycline and Tylosin combinations.

TABLETS

Sulphapyridine	M & B 693	Tablets Sulphapyridine 82,5%	B;O;Cap;E;P Rx of infections.	36/1947	Meat: 7 d

SULPHONAMIDES AND POTENTIATORS

INTRAUTERINE PREPARATIONS

Sulphafurazole Sulphadimidine	Afterbirth Pessaries	Pessary Sulphafurazole 5% Sulphadimidine 5%	B Treatment of bacterial infections of the vagina and uterus.	36/1947	Meat: 7d

INTRAUTERINE PESSARY COMBINATIONS

See oxytetracycline intra-uterine pessary combinations.

TOPICAL PREPARATIONS

Sulphanilimide	Acrisulph	Ointment Sulphanilimide	All species Treatment of wounds and burns	36/1947
	MUPS Lotion	Lotion Sulphanilimide 2%	All species Wound cleanser and antiseptic	36/1947

POLIPEPTIDES

		INJECTABLE COMBINATIONS			
Colistin	Potencil	Injectable Amoxycillin 10g/100 ml Colistin sulphate 25 million iu	All species Rx of susceptible infections	101/1965	Meat: 21d
		WATER SOLUBLE POWDERS			
Colistin	Colistine 1200	Powder Colistin sulphate 120000 iu/g	B;P Rx GIT infection, cystitis, nephritis, pneumonia and bronchitis	101/1965	Meat: 1d Milk: 1d
Bacitracin	BMD Soluble 50%	Powder Bacitracin methylene disalicyclate 10%	P;Poultry Poultry: An aid in the prevention of necrotic enteritis and the improvement of growth and feed conversion efficiency. P: Prevention of swine dysentery and improvement of growth and feed conversion efficiency.	36/1947	

POLIPEPTIDES

PREMIXES

Bacitracin

Zn bacitracin 15% (Virbac)	Premix Zinc bacitracin 10% m/m	Calves;P;Poultry Antimicrobial performance enhanc	36/1947
Zinc bacitracin 15% (Ceva Anchorpharm)	Premix Zinc bacitracin 15% m/m	Calves;P;Poultry Antimicrobial performance enhanc	36/1947
BMD Granulated 10%	Premix Zinc bacitracin 15% m/m	Calves;lambs; P;Poultı Antimicrobial performance enhanc	36/1947
Albac-150	Premix Zinc bacitracin 15%	B;P;Poultry Improved feed efficency and live mass gain. Layers: increased egg production.	36/1947
Pay-Bac 250	Premix Zinc bacitacin 20g/250g nitrovin 12g/250g	Poultry Growth promotant for broilers.	36/1947
Logos Zn bacitracin 10%	Premix Zinc bacitracin 10% m/m	Calves;P;Poultry Antibiotic Performance promoter	36/1947

INTRAMAMMARY COMBINATION

See tetracycline intramammary combinations.

NITROIMIDAZOLES

Ronidazole

WATER SOLUBLE POWDERS

Medizole	Powder Ronidazole 10% m/m	Pigeons Prevention and Rx trichoniasis and hexamitosis	36/1947	Meat: 3d

NITROFURANS

Nitrovin

PREMIXES

Nitrovin 24%	Premix Nitrovin 24%	P; Poultry Growth promoter	36/1947
Nitrovin 50%	Premix Nitrovin 50%	P; Poultry Growth promoter	36/1947

PREMIX COMBINATIONS

See Zinc bacitracin premix combinations.

IONOPHORES

Monensin

PREMIXES

Ancoban 100	Premix Sodium monensin 10% m/m	Poultry Coccidiostat in poultry.	36/1947
Ancoban 200	Premix Sodium monensin 20% m/m	B;Poultry Coccidiostat in poultry. Growth promotant in B; poultry	36/1947
Elancoban 200	Premix Monensin sodium 200g/kg	Poultry Coccidiostat in poultry.	36/1947
Ecox 200 MG	Premix Monensin sodium 200g/kg	B Improved feed efficiency in feedlot cattle.	36/1947
MDB Monensin 20	Premix Sodium monensin 20% m/m	B;O; Cap; Poultry Coccidiostat for poultry and production enhancer for both poultry and cattle.	36/1947
Poulcox Premix	Premix	B;Poultry Coccidiostat for poultry and production enhancer for both poultry and cattle.	36/1947

IONOPHORES	**Monensin**	Rumensin 200	Premix Monensin sodium 200g/kg	B;Cap;O B: Improved feed efficiency, mass gain, milk production, reduced severity of ketosis, coccidiostat. O; Cap: Coccidiostat, improved feed efficiency and mass gain.	36/1947	
			CAPSULES			
		Rumensin CR Capsules	Capsule Monensin sodium 32g/ capsule	B Dairy cows: increased milk production, reduction of ketosis in lactation. Cattle: Mass gain and reduces the incidence of bloat.	36/1947	
	Salinomycin		**PREMIXES**			
		Bio-Cox 120 G	Premix Salinomycin sodium 120g/kg	P; Poultry Improvement of live mass gain and feed conversion efficiency.	36/1947	Meat: 5d
		Coxistac 12%	Premix Salinomycin sodium 120g/kg	P; Poultry Poultry: prevention of coccidiosis. P: Growth promotant.	36/1947	Meat: 5d Eggs: 7d

IONOPHORES	**Salinomycin**	Coxistac G 12%	Premix Salinomycin sodium 120g/kg	P; Poultry Poultry: prevention of coccidiosis. P: Growth promotant.	36/1947	Meat: 5d Eggs: 7d
		MDB Salinomycin 12	Premix Salinomycin sodium 120g/kg	B;Cap; O; P; Poultry O; Broilers: coccidiostat B;Cap;P: Growth promotant.	36/1947	Meat: 5d
		Procoxacin	Salinomycin sodium 120g/kg	Poultry Coccidiostat	36/1947	
		Sacox 120	Premix Salinomycin sodium 120g/kg	B;O;Cap;P;Poultry; Rabbits Improved mass gain and feed conversion efficiency.	36/1947	Meat: P: 3d
		Salecox 120	Premix Salinomycin sodium 120g/kg	B;O;Cap;P;Poultry; Improved mass gain and feed conversion efficiency.	36/1947	Meat: P: 3d Poultry:5d
		Virbacox	Premix Salinomycin sodium 120g/kg	Poultry Prevention of coccidiosis	36/1947	Meat: 5d
	Lasalocid		**PREMIXES**			
		Taurotec	Premix Sodium lasolocid 15%	B;O;Cap Improved mass gain and feed conversion efficiency.	36/1947	

IONOPHORES	**Lasolacid**	Avatec	Premix Sodium lasolocid 15%	Poultry Prevention and treatment of coccidiosis	36/1947	
	Narasin		**PREMIXES**			
		Maxiban 160	Premix Narasin 80g/kg Nicarbazin 80g/kg	Poultry Coccidiostat	36/1947	Meat: 5d
		Monteban 100	Premix Narasin 100g/kg	Poultry Coccidiostat	36/1947	

PHOSPHONIC ACIDS

		WATER SOLUBLE POWDERS	
Fosfomycin	Fosbac Powder	Powder Fosfomycin 25%	P; Poultry; Ostriches 36/1947 Rx Gram-positive and Gram-negative infections.
Fosfomycin and Tylosin	Fosbac Plus T Powder	Powder Fosfomycin 20% Tylosin 5%	P; Poultry; Ostriches 36/1947 Rx gram-positive and gram-negative infections and mycoplasmosis.
		PREMIXES	
Fosfomycin	Fosbac Premix	Premix Fosfomycin 25%	P; Poultry; Ostriches 36/1947 Rx Gram-positive and Gram-negative infections.
Fosfomycin and Tylosin	Fosbac Plus T Premix	Premix Fosfomycin 20% Tylosin 5%	P; Poultry; Ostriches 36/1947 Rx gram-positive and gram-negative infections and mycoplasmosis.

GLYCOLIPIDS

PREMIXES

Flavophoshpolipol	Bambermycin 2% Flavophospholipol 2%	Premix	B;P;Poultry Growth promotant	36/1947	0 days
	Bambermycin 4% Flavophospholipol 4%	Premix	B;P;Poultry Growth promotant	36/1947	0 days
	Flaveco 40 Premix Flavophospholipol 4%	Premix	B;P;Poultry Growth promotant	36/1947	0 days
	Flaveco 80 Premix Flavophospholipol 80g/kg	Premix	B;P;Poultry Growth promotant	36/1947	0 days
	MDB Flavo 4 Flavophospholipol 4%	Premix	B;O;Cap;P;Poultry Growth promotant	36/1947	0 days
	Flavomycin 8% Flavophospholipol 80g/kg	Premix	B;O;Cap;P;Poultry Growth promotant	36/1947	0 days
	Pharmastim 4%	Flavophospholipol 4%	B; P	36/1947	0 days
	Pharmastim 8%	Flavophospholipol 80g/kg	Growth promotant	36/1947	0 days

STREPTOGRAMINS

PREMIXES

Virginiamycin	Stafac 500	Premix Virginiamycin 500g/kg	B;P;Poultry Growth promotant	36/1947	0 days

OLIGOSACCHARIDES

Avilamycin	Surmax	Premix Avilamycin 10% m/m	P;Poultry Growth promotant	36/1947	0 days

POLYMERIC COMPOUNDS

ORAL SOLUTIONS

Poly 2-propenal 2-propenoic acid	Chemeq Polymeric Antimicrobial for Broilers	Oral solution 55g/litre	Poultry	36/1947	0 days
	Chemeq Polymeric Antimicrobial for Pigs	Oral solution 55g/litre	Pigs	36/1947	0 days

ADDENDUM III

STUDY DEVIATIONS

ADDENDUM III
Study Deviations
Study deviation 1:
3.4.3 The percentages of medicated feed sold for each year.

In the original study protocol completed by the author in 2004, the information was going to be collected from 2002-04 as follows for each of the species:

	Dairy cows	**Slaughter cattle and sheep**	**Pigs**	**Layers**	**Broilers**
Percentages of feed medicated with each production enhancement antimicrobial and therapeutic antimicrobial	monensin	bacitracin monensin salinomycin flavomycin, tylosin lasalocid virginiamycin tetracyclines	bacitracin, salinomycin avilamycin, flavomycin nitrovin, carbadox, tylosin olaquindox, tetracyclines virginiamycin, dimetridazole	salinomycin monensin tetracyclines lasalocid	bacitracin nitrovin monensin salinomycin avilamycin flavomycin tylosin olaquindox tetracyclines virginiamycin fosfomycin avilamycin
% of medicated feeds (all anti-microbials)					
	Broiler breeders	**Ostriches**	**Aquaculture (fish)** **freshwater**	**Other**	
Percentages of feed medicated with each production enhancement antimicrobial and therapeutic antimicrobial	salinomycin monensin tetracyclines	tetracyclines olaquindox	Tetracyclines, potentiated sulphadimethoxine		
% of medicated feeds (all antimicrobials)					

ADDENDUM III CONTINUED:

However, due to the perceived sensitivity of the information by the feed mix companies, the author obtained postulated percentages, presented in the following format:

Year	Dairy cows % feed medicated	Slaughter cattle and sheep % feed medicated	Pigs % feed medicated	Layers % feed medicated	Broilers % feed medicated	Broiler Breeders % feed medicated
2004						
2005						
2006						

Moreover, the actual in-feed antimicrobial dosage form quantities and percentage were calculated in this study from the information supplied by the eight veterinary pharmaceutical companies.

Study deviation 2

3.4.5 Volumes of Sales of antimicrobials 2002-2004:

In the original study protocol, it was stipulated that the volumes of sales of antimicrobials for each of the three years under review would be collected in kg and stratified according to the thirteen antimicrobial classes and the dosage forms as follows:

- Penicillins
- Cephalosporins
- Tetracyclines
- Aminoglycosides
- Macrolides

- Amphenicols
- Quinolones
- Sulphonamides
- Polipeptides
- Nitroimidazoles
- Nitrofurans
- Ionophores
- Glycolipids
- Oligosaccharides
- Polymeric compounds
- Phosphonic acids
- Streptogramins
- However, these data were only available in Rands from SAAHA, hence the title was changed to **Values of Sales of Antimicrobials**, and only available in their format as follows:

- **INJECTABLE ANTIMICROBIALS**

  Tetracyclines (Long-acting)

  Tetracyclines(short-acting)

Sulphonamides

Sulphonamides/ potentiated sulphonamides

All penicillin & streptomycin

All others

- **ORALS (SOLUBLE POWDERS/ TABLETS & LIQUIDS**

Tetracyclines

Sulphonamides & poentiated sulphonamides

Nitrofurans

Other oral/ soluble powders – poultry

All others

- **ANTIMICROBIAL FEED ADDITIVES**

Tetracyclines

Tylosin

Nitrofurans

Growth promotants excluding ionophores

Anticcoccidials

Ionophores excluding anticoccidials

All others

- **INTRAMAMMARIES**

Lactating cow (Act 36/197)

Lactating cow (Act 101/1965)

Dry cow (Act 36/197)

Dry cow (Act 101/1965)

- **OTHER ANTIMICROBIALS**

Intrauterine

Topical

Eye/ ear

Capsules/ tablets/ drops

ADDENDUM IV

STATISTICAL ANALYSIS OF RESULTS

Addendum IV: STATISTICAL ANALYSIS

RESULTS OF VETERINARY ANTIMICROBIALS CONSUMED FROM 2002 TO 2004 IN KG

Descriptive calculations of the quantities of antimicrobials will be made such as the determination of means, standard deviations and minimum and maximum values.

	2002	2003	2004	TOTAL		
	49465	55676	59688	165170	*	164829
	113.667	113.667	113.667			
Penicillins	49578.7	55789.7	59801.7	165170		
	5468	3321	3316	12105		12105
	0	0	0			
Cephalosporins	5468	3321	3316	12105		
	58342	71991	59130	256502	*	189463
	22346.3	22346.3	22346.3			
Tetracyclines	80688.3	94337.3	81476.3	256502		
	2	242	268	1048	*	512
	178.667	178.667	178.667			
Aminoglycosides	180.667	420.667	446.667	1048		

		204325	221275	223412	651690	*	649012						
Macrolides and		892.667	892.667	892.667									
lincosamides		205218	222168	224305	651690								
Amphenicols		No data were accessible											
		30625	27050	31530	90053	*	89205						
		282.667	282.667	282.667									
Quinolones		30907.7	27332.7	31812.7	90053								
		35041	76539	80059	199965	*	191639						
		2775.33	2775.33	2775.33									
Sulphonamides		37816.3	79314.3	82834.3	199965								
Polipeptides		27011	26985	42191	96188		96187						
Nitroimidazoles		0	0	0	0								
Nitrofurans		6	0	0	6		6						
Ionophores		14736	6086	43950	70600		64772						
		362	425	706	4203	*	1493						
		903.333	903.333	903.333									
Others		1265.33	1328.33	1609.33	4203								

	Penicillin	Cephalos	Tetracycli	Aminogly	Macrolide	Quinolon	Sulphona	Polipeptic	Nitroimida	Nitrofuran	Ionophore	Others
2002	49578.67	5468	80688.33	180.6667	205217.7	30907.67	37816.33	27011	0	6	14736	1265.333
2003	55789.67	3321	94337.33	420.6667	222167.7	27332.67	79314.33	26985	0	0	6086	1328.333
2004	59801.67	3316	81476.33	446.6667	224304.7	31812.67	82834.33	42191	0	0	43950	1609.333
TOTAL	165170	12105	256502	1048	651690	90053	199965	96188	0	6	70600	4203
								96187		6	64772	

APPENDIX IV; STATISTICAL ANALYSIS CONTINUED

Descriptives(a)

			Statistic	Std. Error
Pen	Mean		55056.66667	2973.797
	95% Confidence Interval for Mean	Lower Bound	42261.45253	
		Upper Bound	67851.88081	
	5% Trimmed Mean		.	
	Median		55789.66667	
	Variance		26530399	
	Std. Deviation		5150.766836	
	Minimum		49578.66667	
	Maximum		59801.66667	
	Range		10223	
	Interquartile Range		.	
	Skewness		-0.627421015	1.224745
	Kurtosis		.	.
Ceph	Mean		4035	716.5015
	95% Confidence Interval for Mean	Lower Bound	952.1430638	
		Upper Bound	7117.856936	
	5% Trimmed Mean		.	
	Median		3321	
	Variance		1540123	
	Std. Deviation		1241.016922	
	Minimum		3316	
	Maximum		5468	
	Range		2152	
	Interquartile Range		.	
	Skewness		1.732019178	1.224745
	Kurtosis		.	.
Tetra	Mean		85500.66666	4424.185
	95% Confidence Interval for Mean	Lower Bound	66464.93409	
		Upper Bound	104536.3992	
	5% Trimmed Mean		.	
	Median		81476.33333	
	Variance		58720244.33	
	Std. Deviation		7662.913567	
	Minimum		80688.33333	
	Maximum		94337.33333	
	Range		13649	
	Interquartile Range		.	

	Skewness		1.711468276	1.224745
	Kurtosis		.	.
AminoG	Mean		349.3333334	84.66667
	95% Confidence Interval for Mean	Lower Bound	-14.95793109	
		Upper Bound	713.6245978	
	5% Trimmed Mean		.	
	Median		420.6666667	
	Variance		21505.33333	
	Std. Deviation		146.6469684	
	Minimum		180.6666667	
	Maximum		446.6666667	
	Range		266	
	Interquartile Range		.	
	Skewness		-1.671000668	1.224745
	Kurtosis		.	.
MacLincos	Mean		217230	6037.765
	95% Confidence Interval for Mean	Lower Bound	191251.5954	
		Upper Bound	243208.4046	
	5% Trimmed Mean		.	
	Median		222167.6667	
	Variance		109363806.3	
	Std. Deviation		10457.71516	
	Minimum		205217.6667	
	Maximum		224304.6667	
	Range		19087	
	Interquartile Range		.	
	Skewness		-1.651038549	1.224745
	Kurtosis		.	.
Quin	Mean		30017.66667	1367.684
	95% Confidence Interval for Mean	Lower Bound	24132.99925	
		Upper Bound	35902.33409	
	5% Trimmed Mean		.	
	Median		30907.66667	
	Variance		5611675	
	Std. Deviation		2368.897423	
	Minimum		27332.66667	
	Maximum		31812.66667	
	Range		4480	
	Interquartile Range		.	
	Skewness		-	1.224745

			1.452019661	
	Kurtosis		.	.
Sulfas	Mean		66655	14455.09
	95% Confidence Interval for Mean	Lower Bound	4459.755613	
		Upper Bound	128850.2444	
	5% Trimmed Mean		.	
	Median		79314.33333	
	Variance		626849121.3	
	Std. Deviation		25036.95511	
	Minimum		37816.33333	
	Maximum		82834.33333	
	Range		45018	
	Interquartile Range		.	
	Skewness		-1.693614709	1.224745
	Kurtosis		.	.
Polipep	Mean		32062.33333	5064.339
	95% Confidence Interval for Mean	Lower Bound	10272.24176	
		Upper Bound	53852.4249	
	5% Trimmed Mean		.	
	Median		27011	
	Variance		76942585.33	
	Std. Deviation		8771.692273	
	Minimum		26985	
	Maximum		42191	
	Range		15206	
	Interquartile Range		.	
	Skewness		1.732033688	1.224745
	Kurtosis		.	.
Nitrofurans	Mean		2	2
	95% Confidence Interval for Mean	Lower Bound	-6.605305459	
		Upper Bound	10.60530546	
	5% Trimmed Mean		.	
	Median		0	
	Variance		12	
	Std. Deviation		3.464101615	
	Minimum		0	
	Maximum		6	
	Range		6	
	Interquartile Range		.	
	Skewness		1.732050808	1.224745
	Kurtosis		.	.

Ionophores	Mean		21590.66667	11455.14
	95% Confidence Interval for Mean	Lower Bound	-27696.80821	
		Upper Bound	70878.14154	
	5% Trimmed Mean		.	
	Median		14736	
	Variance		393660465.3	
	Std. Deviation		19840.87864	
	Minimum		6086	
	Maximum		43950	
	Range		37864	
	Interquartile Range		.	
	Skewness		1.369107143	1.224745
	Kurtosis		.	.
Others	Mean		1401	105.7423
	95% Confidence Interval for Mean	Lower Bound	946.0273916	
		Upper Bound	1855.972608	
	5% Trimmed Mean		.	
	Median		1328.333333	
	Variance		33544.33333	
	Std. Deviation		183.1511216	
	Minimum		1265.333333	
	Maximum		1609.333333	
	Range		344	
	Interquartile Range		.	
	Skewness		1.504357038	1.224745
	Kurtosis		.	.

a Metronidazole is constant. It has been omitted.

ADDENDUM V

TEMPORARY DEFINED DAILY DOSAGES

Addendum V: TEMPORARY DEFINED DAILY DOSAGES

Temporary DDD_{animal} (expressed per kg bodyweight)

			Cattle				*Swine*				*Chicken*	
			DDD_{cattle}	*unit*	*Route of administration*	*comments*	*DDD_{swine}*	*unit*	*Route of administration*	*comments*	*$DDD_{chicken*}$*	*unit*
QJ01A A	*Tetracyclines*											
	01	demeclocycline										
	02	doxycycline	10	mg	O		12.5	mg	O			
	03	chlortetracycline	25	mg	O		25	mg	O		50	mg
	04	lymecycline									(oral)	
	05	metacycline										
	06	oxytetracycline	10	mg	P		10	mg	P			
			20	mg	O	May be low	20	mg	O	May be low	50	mg
	07	tetracycline	20	mg	O		10	mg	P		(oral)	
							20	mg	O			
	08	minocycline										
	09	rolitetracycline										
	10	penimepicycline										
	11	clomocycline										
	20	combinations of tetracyclines										
	53	chlortetracycline, combinations	25	mg	O	Based on the DDD_{cattle} for chlortetracycline						
	56	oxytetracycline, combinations	20	mg	O	Based on the DDD_{cattle} for oxytetracycline	20	mg	O	Based on the DDD_{swine} for oxytetracycline		
QJ01F A	*Macrolides*											
	01	erythromycin	4	mg	P		4	mg	P		30	mg

	02	spiramycin	7.5 20	mg mg	P O	Based on the treatment of mastitis	10	mg	P		(oral) 20	mg
	03	midecamycin										
	05	oleandomycin										
	06	roxithromycin										
	07	josamycin										
	08	troleandomycin										
	09	clarithromycin										
	10	azithromycin										
	11	miocamycin										
	12	rokitamycin										
	13	dirithromycin										
	14	flurithromycin										
	90	tylosin	10 7.5	mg mg	P O		10 7.5	mg mg	P O		75	mg
	91	tilmicosin	10 25	mg mg	P O		 16	 mg	 O		(oral) 20	mg
	93	kitasamycin									(oral)	
QJ01M A	***Fluoroquinolones***											
	01	ofloxacin										
	02	ciprofloxacin										
	03	pefloxacin										
	04	enoxacin										
	05	temafloxacin										
	06	norfloxacin										
	07	lomefloxacin										
	08	fleroxacin										
	09	sparfloxacin										
	10	rufloxacin										

11	grepafloxacin										
12	levofloxacin										
13	trovafloxacin										
14	moxifloxacin										
15	gemifloxacin										
16	gatifloxacin										
90	enrofloxacin	2.5	mg	P, O	Based on the treatment of respiratory infections	2.5	mg	P, O		10	mg
92	danofloxacine	1.25	mg	P		1.25	mg	P		(oral)	
93	marbofloxacin	2	mg	P		2	mg	P			
94	difloxacin									10	mg
95	orbifloxacin									(oral)	
96	ibafloxacin										

* The dose depends on the amount of drinking water. We have chosen 130 ml/day