EVALUATION OF THE LEVEL OF COMPLIANCE OF VETERINARY MEDICINE PACKAGE INSERTS WITH REGULATORY AUTHORITY GUIDELINES

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ABSTRACT

Background: Veterinary medicines play an imperative role in the diagnosis, prevention and treatment of animal diseases. Many veterinary stock remedies in South Africa are available to the public without the intervention or supervision of a veterinarian or healthcare worker. Therefore, the accompanying package insert with product information and directions for use is central in promoting the safe and effective use of stock remedies. Information such as the dosage, warnings, precautions and storage instructions are essential to assist the user in their treatment decision-making. While local regulatory authority guidelines prescribe and control the minimum information that should be available in the package insert or product label, it is questioned whether the information contained in package inserts of products on the market complies with these regulatory requirements.

Methodology: Using simple random sampling of veterinary stock remedies, 159 package inserts or product labels from various animal health companies were selected and evaluated against the prescribed labelling guidelines of the local regulatory authority responsible for the registration and control of stock remedies. The contents of each package insert or label in the sample were assessed for the presence of the prescribed information statements and were accordingly classified as non-compliant, partially compliant or compliant.

Results: Among the 159 package inserts, 48 were for antimicrobials, 49 for ectoparasiticides, 44 for anthelmintics and the remaining 18 for endectocides. It was observed that none of the package inserts met all of the criteria and that the package inserts were inadequate in many aspects. The average percentage of compliance was 69.43%, with a range of 36.21% to 87.93%.

Conclusion: The study indicated that many package inserts do not fully comply with the prescribed regulatory guidelines and that information related to the safe and appropriate use of stock remedies is insufficient.

Recommendations: It is recommended that registration holders should improve the quantity and quality of the information in their registered stock remedy package inserts to provide users with sufficient information in their decision-making regarding the safe and effective use of veterinary medicines.

KEYWORDS

Patient information, package insert, product labelling, veterinary medicine, medicine labelling, regulatory requirements, stock remedies, patient compliance.

LIST OF ABBREVIATIONS AND ACRONYMS

DAFF: Department of Agriculture, Forestry and Fisheries.

IDR: IVS Desk Reference.

IVS: Index of Veterinary Specialties.

MIMS: Monthly Index to Medical Specialties.

PI: Package Insert.

PPE: Personal Protective Equipment.

SAAHA: South African Animal Health Association.

SAHPRA: South African Health Products Regulatory Authority.

LIST OF DEFINITIONS

Ectoparasiticide:	A substance used to control external parasites such as ticks and fleas.
Endectocide:	A substance to control both internal and external parasites.
Endoparasiticide:	A substance used to control internal parasites such as roundworms, tapeworms, lungworms and liver fluke.
Growth Promoter:	Substance or remedy added to the food or feed of animals to improve feed conversion and animal growth.
IVS Publication:	A 4-monthly publication compromising of abbreviated package insert information of the majority of registered, marketed veterinary medicines available in South Africa.
IVS Desk Reference:	A publication compromising of complete product information on medicines used by veterinarians in South Africa daily. The entries are cross-referenced with the quarterly IVS publication.
LD_{50}	The lethal dose of a substance sufficient to kill half of the test population.
Metaphylactic:	The treatment of a group of animals, including healthy and ill animals, after a part of the group or herd of animals had been diagnosed, with the aim to prevent the infectious disease from spreading.
MIMS Publication:	A reference guide to the pharmaceutical products currently available in South Africa.
Package Insert:	A document included in the packaging of a medicinal product that provides information about the medicine and its use.

Prophylactic:	The preventative treatment of an animal or group of animals before any manifestation of clinical signs of infectious disease, with the intent of preventing disease or infection.
Registration Holder:	The company, applicant or legal entity to whom a registration certificate has been issued in respect of a particular veterinary medicine that may be marketed.
Regulatory Authority:	The official body responsible for medicine regulation to ensure the quality, safety and efficacy of medicines, as well as the accuracy and appropriateness of the medicinal information available to the public.
Stock Remedy:	A substance intended to diagnose, prevent, treat or cure a disease, infection or any unhealthy condition, or to sustain and improve the overall health, growth, production and working capacity to be used in domestic animals, wild animals, livestock, poultry, birds or fish. It excludes any substance that is regulated under the Medicines and Related Substances Control Act, Act 101 of 1965.
UWC:	University of the Western Cape.
Withdrawal Period:	The period of time that should elapse between the administration of veterinary medicine to a food-producing animal and the time when the meat or animal products will be free from medicine drug residue and thus safe for human consumption.
Zoonotic Disease:	An infectious disease caused by a bacteria, virus, fungus or parasite that normally exist in animals but can be transmitted from animals to humans.

DECLARATION

I declare that this mini-thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of this work.

I agree to deposit this thesis in the University of Western Cape's library and Healthcare-Learning's institutional repository and or allow these institutions to do so on my behalf, subject to South African and British Copyright Legislation and the University of Western Cape's conditions of use and acknowledgement.

Signed:  *Dated: 24 February 2021*

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CHAPTER 1: INTRODUCTION

This chapter introduces the research background, providing a broad view of the importance of veterinary medicines focusing on livestock animals. Thereafter, an overall view of package inserts or product information is provided in the context of safe and effective use of veterinary stock remedies available to the public. The rationale for the study is then discussed. In the chapter, the research question, the research problem and the objectives of the study, as well as the study scope and limitations, are also outlined. The chapter ends by presenting a brief structure of this report.

1.1 Background to the study

Veterinary medicines provide exceptional value to society, with animal health and welfare obligations, sustainable food production and food security, as well as the conservation of species. There is a rising demand for veterinary medicines, and it is estimated that the global demand for veterinary drugs will rise to a value of US$ 27,570 million by 2025 from US$ 17,870 million in 2017 (Fortune Business Insights, 2019).

The increased demand for veterinary medicines can be attributed to its role in the prevention and therapeutic treatment of animal disease and the improvement of growth and productivity in food-producing animals (Meseko et al., 2019). Of particular interest is the contributory role that livestock animals play in sustainable food security for people. It is expected that a 70% increase in food production will be required by 2050 to feed an additional two billion people (Tomley and Shirley, 2009; Godber and Wall, 2014). The rising national and global demand for food and animal products increase the focus on animal health and welfare and subsequently, the need for efficient medicinal products.

In addition to the occasional or periodic illness that may necessitate treatment in animals, infectious diseases of food-producing animals are a considerable threat to the health and

welfare of livestock (Meseko et al., 2019). Infectious diseases may be highly contagious with the ability to spread rapidly, especially in intensive livestock production systems, and the management thereof is therefore crucial for the safeguarding of animal health as well as for food security (Meseko et al., 2019). Certain infectious diseases, known as zoonotic diseases, where rabies is a well-known example, may also be transmitted from animals to humans. Threats from both old and new pathogens continue to emerge and are further fuelled by climate and ecosystem changes, as well as the urbanisation of populations, globalisation, and ease of travelling (Tomley and Shirley, 2009). The increased globalisation and population connectivity have also resulted in diseases reaching populations rapidly and widely, and there is therefore a growing incidence of infectious and zoonotic diseases that put not only animal but also human health at risk of disease outbreaks and global pandemics (O'Neill, 2016). A very relevant example of such a new zoonotic virus to have emerged and caused the outbreak of severe illness and disease in humans is the SARS-CoV-2 virus that has resulted in the Covid-19 pandemic. Evidence suggests that the SARS-CoV-2 virus has a zoonotic source and that animals have been involved in the zoonotic transmission of the virus from animals to humans (Ahmad et al., 2020; Mackenzie and Smith, 2020).

Veterinary medicines are commonly classified as products that are used in the diagnosis, prevention, treatment, mitigation, eradication and management of animal diseases (Sykes et al., 2019). Additional purposes of veterinary medicines may include the alteration of any structure or function of the body of an animal, such as the enhancement of reproductive capacity or the improvement of production efficiency, growth promotion or average daily weight gain in food-producing animals (Smith, 2013; Morley et al., 2005).

The scope of veterinary medicines is broad and includes companion animals, livestock, fish and poultry, as well as wild and free animals (Sykes et al., 2019). Categories of animal medication typically include vaccines, antimicrobials, anti-inflammatories, pesticides, feed additives, growth promoters and hormones. There is a range of administration routes for the various formulations, such as a tablet, bolus, drench, dip, pour-on, spray, injection and incorporation into feed and drinking water (Ahmed and Kasraian, 2002).

Before being manufactured, imported or sold in South Africa, veterinary medicines should be registered by the local regulatory authority, as stipulated under the Medicines and Related Substances Act 101 of 1965 and the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act 36 of 1947. Regulatory approval of veterinary medicines is a mandatory and rigorous process to safeguard the quality, safety and efficacy of a new product (Rago and Santoso, 2008), and regulatory authority approval typically takes the form of a methodical, evidence-based evaluation of the documented quality, safety and efficacy information for the product (Smith, 2013). This meticulous approval process ensures that veterinarians, farmers and pet owners can use veterinary medicines with firm assurance that the products are safe and effective in disease prevention and mitigation (Smith, 2013). Two different regulatory authorities are responsible for the regulation of veterinary medicines in South Africa. Applications for scheduled veterinary medicines are submitted to the South African Health Products Regulatory Authority (SAHPRA), while stock remedies are submitted to the Department of Agriculture, Forestry and Fisheries (DAFF) (Eager and Naidoo, 2017). As animals play an essential role in the food chain, this safeguarding is not only for the sake of the animals in need of treatment but also for humans who make use of animal products.

In South Africa, a stock remedy is a veterinary product registered with DAFF to prevent and treat animal diseases. Many of the stock remedies for animal treatment in South Africa are available to farmers and other users from agricultural outlets without veterinarian consultation or control (Sykes et al., 2019). As these products are bought without healthcare advice, the product must be accompanied by adequate patient or product information. Product information for stock remedies usually comes in the form of a printed package insert or as a product label and typically includes information such as indications, directions for use, warnings, precautions and storage instructions.

A package insert is a mandatory, approved technical document with written information that is provided with a medicinal product (Sillo et al., 2018). It may also be known as the product label information or prescribing information (Shiyanbola et al., 2017). A good quality package insert is written in such a manner that is not promotional, inaccurate or misleading and that is updated regularly as appropriate pre-clinical and clinical data become available (Ramdas et al.,

2013). It should instruct a patient or user on the correct use of the medicinal product and promote the understanding of its purpose, benefits and risks (Shiyanbola et al., 2017). Knowledge of the proper use of medicines improves their safe and effective use as well as compliance with treatment programmes and recommendations. Smith (2013) explains that medicines should be labelled not only to advise the user of the correct, appropriate and safe use of the product but also to make the user aware of safety considerations such as the withdrawal period, storage and handling procedures.

In South Africa, during the registration of pharmaceuticals, vaccines and stock remedies, registration holders or applicants are obliged to submit the package insert or product labelling information based on scientific evidence to the regulatory authority responsible for product registration (Sykes et al., 2019). Due to the complexity and importance of medicinal information, most regulatory authorities have established technical standards and guidelines that prescribe the format and content for package inserts when submitted for approval (Fasken South Africa, 2018). While there are guidelines for the format, design and wording, there are no specific recommendations regarding the quality or quantity of the presented information.

The incorrect use and inappropriate use of veterinary medicines may cause harm not only to animals but also to humans, both because humans are responsible for the administration of the stock remedies to the animals and because they consume animal products.

1.2 The problem statement

The safe and effective use of veterinary medicines is crucial, not only for animal health and welfare but also for the safety and in the interests of the user who will apply or administer the veterinary medicine and the consumer who will use or consume animal products from treated animals. When medicines are sold and obtained in the marketplace, regulatory and pharmaceutical companies should ensure that the product label or package insert reflects all the necessary product information as this supports good decision-making and compliance by farmers or animal owners in the interest of the animals to be treated.

Although most regulatory authorities have guidelines and requirements to which printed package inserts or product labels are subjected to during the registration approval process, it is questioned whether the printed product information available to consumers or users does indeed include the minimum requirements. Furthermore, it may be asked whether the content of current package inserts is sufficient to support the safe and effective use of medicines as intended by regulatory authorities and pharmaceutical companies.

This study focuses on stock remedies registered by DAFF under the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act 36 of 1947 (Act 36, 1947). To the best of my knowledge, this is the first study in South Africa addressing package inserts or labelling information of veterinary medicines with a specific focus on veterinary stock remedies that are available to the public without veterinarian consultation or supervision.

1.3 Research setting

The research setting is South Africa. The research was conducted through evaluation of package inserts or product labels of veterinary stock remedies registered in South Africa under Act 36 of 1947.

1.4 Research question

The primary research question of this study is whether package inserts or product labels of veterinary stock remedies registered under Act 36 of 1947 comply with the prescribed regulatory guidelines and requirements of DAFF.

1.5 Research design

The research was designed as a descriptive quantitative study using secondary data.

1.6 Research aim

The primary aim of this research was to investigate whether product information or package inserts available for South African veterinary stock remedies comply with the prescribed regulations.

1.7 Research objectives

Primary objectives:

1. To conduct a literature review on the importance of package inserts and patient product information
2. To describe the non-compliance or deficiencies found during the comparison of the investigated package inserts with the regulatory guidelines
3. To report on the findings of this study.

Specific research objectives – Literature review:

- To review literature from around the world on the importance of information found in package inserts available to the public
- To report on the consequences when information on the safe and rational use for veterinary medicines is lacking
- To describe interventions that can improve the information included in package inserts.

Specific research objectives – Empirical investigation:

- To identify and describe the sections of the package insert that are most commonly non-compliant
- To describe potential safety implications when safety data is not provided to the user on the package insert
- To make recommendations for the improvement of the compliance of package inserts with regulatory guidelines.

1.8 Significance of the study

The results of this current research will identify which sections in package inserts are most commonly non-compliant. Furthermore, the study will determine areas on which pharmaceutical companies and regulators could focus on in promoting the safe and effective use of veterinary medicines.

1.9 Limitations and scope of the study

While the main objective of the current research was to investigate the compliance of stock remedy package inserts with regulatory guidelines, it does not establish whether, in practice, users read and understand package inserts. Furthermore, consideration must be given to the fact that the actual printed package insert accompanying the product on the shelf may be different from the package insert found on the pharmaceutical company's website. This may happen in a case where the registration holder has applied for changes or updates to the package insert, after receiving approval from the regulatory authority, and where the information on the website may have been updated, but stock with the old printed version is still in circulation in the market.

Even though the researcher undertook to confirm that the information used in this research was the most updated package insert information available, another limitation of the research is that the researcher had to rely on pharmaceutical companies to publish and print information that is current, relevant and approved by the regulatory authority. As pharmaceutical companies and registration holders self-regulate published and printed packaging, the researcher was able to determine whether the minimum required information, as stipulated by the regulatory authority, was published in the package inserts. However, it was not possible to determine whether additional information appearing on the package inserts was ethically correct as approved by the regulatory authority.

1.10 Structure of the study

A general background to the study having been provided in this Introduction, along with stating the research problem, setting supplementary objectives and describing the research design. Chapter 2 presents the literature review, and Chapter 3 discusses in detail the research design

and methodology selected to address the research problem and objectives. Chapter 4 then presents the results from the research. In Chapter 5, these results are interpreted and discussed to provide a clear picture of the research findings. Finally, the conclusions and recommendations, together with recommendations for future research, conclude this research study in Chapter 6.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter presents the investigation of literature concerning the role that written medicinal information plays in the safe and effective use of medicinal products available to patients or users, as well as in improving compliance. In addition, the literature review examines and discusses the possible consequences of inadequate labelling of information accompanying medicines. The research is contextualised through the legislation and regulation of veterinary medicines in South Africa and includes the applicable Acts, regulations and guidelines. The themes of safe and effective use of medicines provide the foundation on which the research was based.

The researcher conducted the literature review using appropriate databases such as Google Scholar, ScienceDirect and PubMed. The relevant literature was identified by using the keywords of patient information, package insert, product labelling, veterinary medicine, medicine labelling, regulatory requirements, stock remedies and patient compliance.

Due to the lack of studies related to package inserts specifically for veterinary medicine, the researcher had to resort to studies and literature available on package inserts for human medicines.

2.2 The importance of written patient information

Studies from as early as 1979 have indicated that written information is deemed useful in improving patient knowledge and enhancing patient compliance in the treatment of humans (Morris and Halperin, 1979; Bandesha et al., 1996). The importance of written medicinal information is no less relevant today. A review conducted by Sustersic et al. (2016) confirmed that well-written patient information significantly impacts a patient's knowledge and promotes adherence to treatment programmes. Through previous research, it has been assessed that users value the written information that accompanies medicines (Raynor et al., 2004; Fuchs et al.,

2005). Most patients claim that they read package inserts and find them helpful, specifically for instructions on the correct use and possible side-effects of medicines (Koo et al., 2002). Written package inserts are useful as they can be retained and reconsulted when patients' memories for medical information may often be weak and inaccurate, particularly when patients are ill, old or anxious (Kessels, 2003; Adepu and Swamy, 2012).

Even though poor compliance with medicine instructions and treatment programmes is regarded as problematic in human medicines, little attention has been paid to veterinary medicines. While there is a lack of information about veterinary medicine compliance in livestock, it has been established that compliance with veterinary treatments in pet owners falls short of veterinarian's recommendations (Gerrard, 2015; Lavan et al., 2017). Verker et al. (2008) advised that compliance in veterinary medicine involves the consistency and precision with which the client follows the advice offered by the veterinarian. Written confirmation supplements and enhances verbal instructions and will thus have a positive impact on compliance (Chin, 2016). Accurate and reliable medicinal information is essential to advise users on the safe and effective use of medicines (Sykes et al., 2019). The most frequently used source of written medicinal information is the printed package insert (Fuchs et al., 2007).

2.3 A review on package inserts

A package insert is a mandatory, approved technical document with written information that is provided with a medicinal product (Sykes et al., 2019). It may also be known as the product label information or prescribing information. The purpose of the package insert is to increase the patient or the user's awareness of medication-related issues and thereby contribute to the safe and correct use of the particular medicine (Al-Ramahi et al., 2012). Promoting knowledge of the risks, benefits and purposes of medicines encourages users to participate in their safe and effective use, leading to successful therapy (Al-Aqeel, 2012).

Despite the apparent usefulness of package inserts, studies have reported that package inserts are often not read for reasons including (but not limited to) difficulty in understanding the information, presence of excessive information, illegible text, and formats or layouts that are

not user-friendly (Van Dijk et al., 2014). A systematic review by Trevena et al. (2006) suggested that the structured outline of information presented in a logical order is helpful in providing quality package inserts. Adepu and Swamy (2012) confirmed that layout and design are important factors in printed material accompanying human medication and that a well-designed package insert assists patients in finding and understanding the information provided. This would hold true for veterinary medicine package inserts and the information provided to the user or administrator.

While package inserts are regarded as a valuable information resource and are often used to supplement the information obtained from prescribers or pharmacists, special consideration should be given to medicines that are freely available to the public. In contrast to the medicine prescribed by a physician and dispensed by a pharmacist, for which there are opportunities for consultation, medicines that are freely available to the public are often bought without seeking any professional counsel. Self-medication with over-the-counter medicines is an increasing practice due to time constraints, cost constraints and convenience (Limaye et al., 2017), and consumers rely on the product information supplied to expand their understanding of the indications and use (Tong et al., 2014). Hence, adequate and correct information provided with medicine is essential. While package inserts are regulated as mandatory documents with prescribed guidelines and requirements, studies that have evaluated package inserts against regulatory criteria have found that the analysed package inserts failed to adhere to the guideline criteria (Narzaree and Gupta, 2015). Furthermore, studies indicate that package inserts are still criticised worldwide by specialists (Fuchs et al., 2007 and patients (Al-Ramahi et al., 2015; Koo et al., 2002).

2.4 Regulatory control of veterinary medicines in South Africa

The registration and control of veterinary medicines in South Africa are conducted under two different Acts. Applications for scheduled veterinary medicines are submitted to SAHPRA under the Medicines and Related Substances Act 101 of 1965 (Act 101, 1965). Alternatively, stock remedy applications are submitted to DAFF under Act 36 of 1947 (Act 36, 1947).

2.4.1 Act 36 of 1947

The control of veterinary medicines in South Africa originated in 1947 when Act 36 of 1947 was promulgated. This Act intended to ensure that farmers had easy over-the-counter access to products registered for use in farm animals or livestock (Sykes et al., 2019; Chanda et al., 2013). Veterinary medicines registered under Act 36 of 1947 are registered as stock remedies.

2.4.1.1 Package insert or labelling requirements

In the context of stock remedies, relevant information may be provided in the form of a printed package insert or, in the case where space permits, a complete product container label. The terms 'package insert' and 'product label' are used interchangeably in the current research.

The Guideline on Labelling of Stock Remedies (Labelling Guideline, 2018) stipulates the mandatory information to appear on a product's package insert in English in addition to one other official language. The information below is required to appear on the package insert in the following format or order:

- The statement 'For (external) animal use only'
- The registered trade name of the stock remedy
- The stock remedy's registration number
- Claims or indications
- A toxicity statement
- Storage instructions
- Composition
- Warnings
- Precautions
- Directions for use
- Efficacy (in the case of anthelmintics)
- Presentations
- The name and address of the registration holder.

It should be mentioned that Act 36 of 1947 makes provision for applicants to use abbreviated labels in the case where product containers such as vaccine vials or intramammary syringes have very limited surface space for the minimum required information. In such cases, abbreviated labels are allowed, but on the condition that the product is accompanied by a printed package insert with the complete information.

In contrast, and different from human medicines, stock remedies such as dips and pour-ons may be sold in large quantities; for example, 25 litres. In such an instance, the full package insert information can be printed on the product or container label.

2.4.2 Act 101 of 1965

Medicine regulation and control in South Africa was first introduced in the 1960s, and in 1965 the promulgation of the Drugs Control Act, 1965 was followed by the creation of the Drugs Control Council responsible for the regulation and control of medicinal products for human use (Keyter et al., 2018). The implementation of a registration procedure in 1968 signified that the Drugs Control Council had to evaluate and approve all human medicines intended for sale in South Africa prior to entering the market. Over the years, several amendments have been made to the Act. In 1974, the name of the Drug Control Council was changed to the Medicine Control Council (MCC), and in 1979 the mandate of the Act was broadened to incorporate the regulatory oversight of veterinary medicines, including the registration and labelling thereof (Keyter et al., 2018). In February 2018, SAHPRA was established and replaced the MCC as the regulatory authority.

Medicines registered under Act 101 of 1965 have a scheduling requirement, and access to these medicines is controlled either as over-the-counter medicine or as prescription medicine through a qualified, practising veterinarian.

2.4.2.1 Package insert or labelling requirements

As stipulated by Regulation 40(1), the following information is mandatory for veterinary medicines registered under Act 101 of 1965 in a minimum of one official language:

- The proprietary name
- Scheduling status
- Dosage form
- Composition
- Pharmacological classification
- Pharmacological action
- Pharmacodynamic and pharmacokinetic properties
- Contra-indications
- Warnings and withdrawal periods in the case of food-producing animals
- Side-effects and special precautions
- Known signs of overdose and particulars of its treatment
- The quantity and strength of the active ingredients per dosage unit
- Storage instructions
- The registration number
- The name and business address of the registration holder.

2.5 Possible consequences when package insert information is insufficient

As indicated in previous sections, clear, accurate and complete product information provided in the form of package inserts assist in improving compliance with treatment programmes. For human medicines, proper information reduces the incidence of incorrect use, adverse events, lack of efficacy, poisoning and accidental exposure (Narzaree and Gupta., 2015; Sykes et al., 2019). Furthermore, it might be said that inaccurate or missing package insert information has the opposite effect on the treatment programmes of patients. An important difference between human and veterinary treatment is that the incorrect use of veterinary medicines has an impact not only on the treated animals but also on humans, whether directly or indirectly (Meseko et al., 2019).

2.5.1 Adverse reactions

The Guideline on Veterinary Drug Adverse Events (MCC, 2004) defines an adverse reaction as a noxious and unintended reaction to veterinary medicine. An adverse reaction may occur at normal prescribed doses or may result from an overdose or misuse of the medicines. It is expected that there is a relationship between the adverse event and the administered product. Adverse reactions typically arise in situations where the product is used or administered outside of the prescribed instructions on the package insert (Naidu, 2013), such as off-label use, administration of dosages other than prescribed, medication errors, misuse, abuse, but adverse reactions also include the lack of efficacy at the prescribed dosage (Kayser, 2014; Sykes et al., 2019). Commonly expected adverse reactions must be stated on the package insert so that users know whether any reactions that they observe are expected, normal and transient or whether veterinarian intervention is needed. Research found that with human medicines, patients considered the adverse reaction information in the package insert as very important. (Fuchs et al., 2007; Al-Ramahi et al., 2015). This reinforces the importance of including adequate information on the possible adverse reactions of veterinary medicines on package inserts.

According to Al-Aqeel (2012), sufficient safety information is provided when the package insert includes a statement about the frequency of adverse events and describes the severity of possible adverse reactions and suitable measures in case they occur. In addition, the following statement (Labelling Guideline, 2018) must be included in the package insert:

> *Although this remedy has been (extensively) tested (under a large variety of conditions), failure thereof may ensue as a result of a wide range of reasons. If this is suspected, seek veterinary advice; notify the registration holder and the Registrar.*

If adverse events are observed, whether expected or unexpected, as with human medicines, farmers and animal owners can report such adverse events or side-effects to the registration holder or to the local regulatory authority (Sykes et al., 2019). For this reason, the registration holder's name must appear on the package insert or product information.

2.5.2 Human exposure

With veterinary medicines, there is always a risk that the user may be exposed to the product, whether directly or indirectly. This section examines such risks.

2.5.2.1 Direct exposure

During the handling of veterinary stock remedies, there is always a possibility that humans may come into contact with the veterinary product, which may lead to unintended and unwanted reactions. Direct exposure or contact may occur during the storage of the product or preparation of the remedy, during the application or even after application, or when a person may come into contact with the treated animal. Examples of routine tasks that may lead to exposure include the storage of the product, mixing or diluting the product for administration, during administration, cleaning of administration equipment, and disposal of the surplus product or empty receptacles (EMA, 2010).

Human exposure to veterinary pesticides is of particular concern, as there are serious health risks and effects associated with pesticide exposure especially. These health effects depend on the particular pesticide used, the route of exposure, the application method and the contact time (MacFarlane et al., 2013). While dermal exposure is the most common, other routes of exposure include oral and inhalation (Damalas and Koutroubas, 2016). Acute toxicity is most often observed after a single exposure and has effects such as irritation of the skin, eyes or respiratory tract. Repeated and more prolonged exposure may lead to chronic effects, including neurological effects, mutagenic or reproductive effects, endocrine effects and cancer (MacFarlane et al., 2013). Based on the toxicity of products and their risk for exposure, it is essential that package inserts not only warn users to avoid contact with the product but also recommend measures to follow if accidental contact does occur (Sillo et al., 2018). Furthermore, package inserts should advise users, when necessary, about the personal protective equipment (PPE) required for skin, eye or respiratory protection (Sykes et al.,2019).

2.5.2.2 Indirect exposure

When veterinary medicines are used to treat food-producing animals intended for human consumption or to improve the productivity of these animals, there is always a risk that the medicines may pose a health hazard to consumers (Meseko et al., 2019), as there is a danger that residues may be found in the animal products. Residues may comprise of the parent compound or its metabolites (Smith, 2013). While many factors influence the occurrence of medicine residues in animal products, the most likely reasons are improper medicine usage and the failure to abide by the prescribed withdrawal period (Beyene et al., 2015).

The withdrawal period for animal meat, eggs, offal or milk is the interval between the time of the last administration of the veterinary medicine and the time when the animal products are considered safe to consume. A survey conducted by Rana et al. (2019) indicated that antibiotics, parasiticides and anti-inflammatory medicines that are broadly used in livestock are associated with the presence of residues in animal products like meat, milk and eggs. To ensure that veterinary medicine residues in edible animal products do not pose a threat to consumers' health, the withdrawal period should be stated on the package insert as the first bulleted warning, in accordance with Act 36 of 1947 (Labelling guideline, 2018).

2.5.3 Incorrect storage of stock remedies

The proposed or recommended storage conditions for medicines are based on stability studies that the product had been subjected to under controlled temperature and humidity conditions (Küpper et al., 2016). If the stock remedy is stored outside of these proposed conditions, the quality, safety or efficacy of the product may be affected (Aziz Ali et al., 2016). Küpper et al. (2016) explained that exposing a medicinal product to higher temperatures than those under which it was tested may cause degradation of the product, which decreases the efficacy.

The most common storage instructions included on labels based on the conditions under which the product was tested are listed in Table 1 (EMEA, 2007).

Table 1: Storage condition statements (EMEA, 2007)

Testing conditions under which the product was stable	Required label storage instructions
25°C/60% RH* (long term) 30°C/60% or 65% RH (intermediate) or 30°C/65% RH (long term)	Do not store above 30°C Store below 30°C
25°C/60% RH (long term)	Do not store above 25°C Store below 25°C
5°C ± 3°C (long term)	Store in a refrigerator (+2°C to +8°C)

*RH: Relative Humidity

To ensure that veterinary stock remedies are stored under the correct storage conditions, the package insert should indicate the temperatures for storage (Sykes et al., 2019). Furthermore, it should include whether the medicine should be protected from light or moisture for products that are sensitive to these environmental factors (Ondrak et al., 2015).

2.5.4 Antimicrobial resistance

Increasing levels of resistance to last-line antibiotics and other antimicrobials mark one of the most significant global threats to public health. Animals play a significant role in the global food production sector and many antimicrobials widely used in livestock, such as tetracyclines, penicillin and sulphonamides available without a prescription, are identical or very closely related to antimicrobials used in humans (Falowo and Akimoladun, 2019). In animals, antimicrobials are not only used for the treatment of disease but also as metaphylaxis where the detection of disease signs and symptoms in one animal results in the mass treatment of the entire herd with sick and healthy animals (Founou et al., 2016; Eager and Naidoo, 2017), and as prophylaxis, where sub-therapeutic doses are administered to prevent disease especially during high-risk periods (Meseko et al., 2019). Also, antimicrobials are used as growth promoters in food-producing animals when administered through feed to increase efficiency in

food uptake (Chanda et al., 2013). The incorrect and inappropriate use of veterinary medicines may cause harm not only to the animals but also to humans, as it may lead to unsafe drug residues in food-producing animals (Beyene et al., 2015) and accelerate the occurrence of antibiotic resistance (Eager and Naidoo, 2017). Antimicrobial resistance amid food-producing animals is an intensifying concern with consequences for both animal and human health (Boireau et al., 2017).

2.5.5 Pesticide resistance

Like resistance to antimicrobial stock remedies, resistance to pesticides is also a current and growing problem. For example, acaricides are used to a great extent to control tick populations in South Africa, but acaricide failure is rising as acaricide resistance emerges. *Rhipicephalus microplus* (Southern cattle tick) is an ectoparasite of great veterinary and economic significance and has been shown to develop resistance to major commonly used chemical classes of acaricides (Robbertse et al., 2016). *Rhipicephalus microplus* resistance against organophosphate and amidine acaricides in South Africa was reported as early as 1979 (Baker et al., 1979) and more recently against amitraz, chlorfenvinphos and cypermethrin (Ntondini et al., 2008). While genetic factors play a key role in the development of parasite resistance, operational factors that often contribute to the development of acaricide resistance include the prolonged use of the same acaricide without changing to another class, the selection of a different class with possible cross-resistance, the frequency of treatment and underdosing or over-dilution (Abbas et al., 2014). Operational factors can be controlled by educating farmers and users about the rational use of acaricides.

In addition to the emerging resistance in ectoparasite remedies, anthelmintic resistance is also posing a threat. *Haemonchus contortus* (Barber's pole worm), another economically important parasite, is a blood-sucking nematode causing anaemia, weight loss and even death in ruminant animals (Wang et al., 2017). South Africa was the first country where it was reported that a population of *H. contortus* was resistant to all five of the anthelmintic active ingredient groups available for the control of this endoparasite (Wang et al., 2017).

2.5.6 Environmental impact

While veterinary medicines have many benefits for the health and welfare of animals, these products may contaminate the environment during treatment or disposal. Veterinary medicines or pesticides are likely to enter the environment through direct contact, spillage or improper disposal of unused medicines or medicine containers (Boxall, 2004; Kaczala and Blum, 2016). Pesticides are known to be highly persistent in the environment, often remaining in the environment and interacting with non-target organisms in various ways (Lushchak et al., 2018). In particular, as fish are highly sensitive to pyrethrin and pyrethroid products, which are often found in pesticides, the contamination of water sources should be avoided.

2.6 Discussion

The rational use of veterinary medicines has many advantages, such as increased efficacy, fewer and less intense adverse reactions, reduced residues in animal products and the combatting of stock remedy resistance.

The safe and effective use of veterinary medicines is crucial, not only for animal health and welfare but also for the safety and in the interests of the farmer or user, the consumer and the wider global population. When products are available in the marketplace, regulators and pharmaceutical companies should be convinced that the product labelling or package insert accurately reflects the essential information, as this supports good decision-making and compliance in medicine use.

2.7 Conclusion

The literature review has investigated the importance of accurate and thorough product information to the users of veterinary stock remedies, as well as the possible consequences when package inserts do not comply with prescribed regulatory guidelines. Although package inserts are subjected to regulator authority scrutiny during the registration process, it is not guaranteed that printed package inserts available to the farmer or user do indeed contain all the mandatory information. Several sources in the literature highlighted compliance issues associated with package inserts and the dangers that these pose to both animals and humans.

Therefore, imposing regulation does not mean that manufacturers or registration holders comply in practice. This challenges researchers to conduct further empirical research at the level of the South African market into the extent of compliance with veterinary stock remedy package guidelines, and the next chapter discusses the methods and processes that were followed in the current study to meet this challenge.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction

This chapter outlines and discusses the methods, processes and procedures that were used in the present study. The study was quantitative and descriptive in nature and made use of secondary data to answer the research questions on whether package inserts or product labels of registered stock remedies do comply with the prescribed guidelines of the regulatory authority, DAFF. The research design, sampling processes, data collection, data collection tools and analysis are outlined, and the research ethics that guided the study are discussed. The chapter starts with the identification of the population and study setting.

3.2 Study setting and population

The South African Animal Health Association (SAAHA) is a non-profit association representing 90% of South Africa's animal health product importers, manufacturers and suppliers (SAAHA, n.d). Member companies of SAAHA undertake to comply with the SAAHA code of conduct that sets standards for the production, manufacturing and marketing of veterinary health products. Each of the 19 member companies with registered pesticides and antimicrobials was included in the study.

3.3 Study design

The study was designed as quantitative descriptive secondary research. It made use of pre-existing available data; package inserts were collected for various stock remedies from companies registered with SAAHA. The package inserts were obtained from animal health pharmaceutical company websites, or the Monthly Index to Medical Specialties (MIMS) publication, the Index of Veterinary Specialties (IVS) Desk Reference (IDR) 2017/2018 and IDR 2019/2020. The contents of each package insert were compared with the Act 36 of 1947 Labelling Guidelines. The research design was aimed at describing compliance levels quantitatively, as determined by its research objectives. The study was also designed in a cross-sectional mode, as it aimed to collect and analyse data at a single point in time (Kumar, 2011).

3.4 Sampling

A simple random sampling method was used to select research candidate package inserts for the research project. For each of the SAAHA member companies with registered stock remedies that complied with the selection criteria, all available package inserts were collected from the pharmaceutical company websites or the IDR 2019/2020. In some instances, products that were advertised on company websites did not appear in the 2019/2020 edition of the IDR, and, in such cases, the researcher reverted to the previous 2017/2018 edition. All the package inserts obtained for stock remedies, with the exclusion of the product categories listed below, were listed alphabetically on a Microsoft® Excel® for Office 365 ProPlus 2021 (Version 16.0.1257.21504) spreadsheet and were numbered from 0 to 270, representing the study population. As the purpose of sampling in quantitative research is to draw inferences and a generalised conclusion about the study population (Kumar, 2014), a predetermined sample size representative of the population was established. For researchers lacking solid mathematical skills, various online sample size calculators are available to accurately calculate the required sample size (Burmeister and Aitken, 2012; Sathian et al., 2014). Thus, to calculate the sample size that will achieve statistical significance, the researcher utilised an online sample size calculator to obtain the required sample size of 159 package inserts.

In order to prevent bias and randomly select the required 159 sample package inserts from the 270 collected package inserts, the researcher made use of randomizer.org, a computerised random number generator. The choice of the randomised generator was based on the research by Tu and Benn (2017) that identified randomizer.org as one of the top five utilised generators, and it is also recommended by Saghaei (2011). The sample was selected with the aim of achieving a 95% confidence level and a 5% margin or error. With the required information entered into the random number generator, the researcher was provided with 159 random numbers between 0 and 270. The package inserts corresponding to the random 159 numbers were selected to be used in the research.

The focus of the study was on registered stock remedies and, in particular, on pesticides and antimicrobials used in livestock and food-producing animals, as the incorrect use of stock

remedies in food-producing animals may have consequences for the animal as well as the administrator or consumer. Scheduled medicines, hormones, vaccines, steroid growth promoters, vitamins, supplements, nutraceuticals and complementary medicines were excluded from the study. Package inserts for these excluded products were not collected and did not form part of the initial 270 package inserts, of which the 159 package inserts were selected in the end. Scheduled medicines are typically handled and administered by veterinarians, and, in the event that a veterinarian provides scheduled medicines to a user, it is presumed that their dispensing is accompanied by proper directions for use, warnings and precautions. Hormones were not included because many of these products are often not available to the public as they usually require technical advice to users and form part of a vaccination, breeding or feeding programme. Vitamins, supplements, nutraceuticals and complementary medicines were not included on the assumption that they have a smaller risk profile than registered stock remedies. In addition, companion animal products were also excluded, as it was assumed that most people take their pets to the veterinarian during times of illness, and the veterinarian dispenses medicines when necessary.

3.5 Data collection

Data for this research was obtained from the information available on the sample package inserts collected. The standardised collection template (Appendix A) was used to compare each package insert with the Act 36 of 1947 guidelines. Data collection involved printing out the package insert of the randomly sampled medicines and entering relevant information from it onto the data collection tool. The data were extracted by the author twice at different times to minimise the possibility of missing information.

The inclusion criteria for the package inserts were:

- The product is currently marketed in South Africa
- The product is a registered stock remedy under Act 36 of 1947
- The product is either an antimicrobial or parasiticide.

Package inserts for the following types of products were not included:

- Vitamins
- Supplements
- Nutraceuticals
- Complementary medicines
- Vaccines
- Steroid growth promoters
- Hormones.

3.6 Data collection tool

The first step in this study was to develop a data collection tool (Annexure A) according to the criteria stipulated by Act 36 of 1947 for package inserts of stock remedies. The standardised data collection tool was used to compare the information on the collected package inserts with the requirements of Act 36 of 1947 Labelling Guideline. The template was developed by taking information from the regulatory authority's guideline and by establishing the sections that were addressed in the guidelines.

The data collection tool had two major sections. The first section collected data that identified and described the product under analysis: the product number, source, generic name, dosage form, strength, product category and target species.

The second section rated the compliance of the product with thirteen aspects:

- The statement 'For (external) animal use only'
- The registered trade name of the stock remedy
- The stock remedy's registration number
- Claims or indications
- A toxicity statement
- Storage instructions

- Composition
- Warnings
- Precautions
- Directions for use
- Efficacy (in the case of anthelmintics)
- Presentations
- The name and address of the registration holder.

The data collection tool used a rating scale from 0 to 1 for each of the 13 package insert aspects or headings, with a score of 0 for non-compliant, 0.5 for partially compliant, and 1 for compliant observations. There was also a space for non-applicable observations. A pilot study was performed through the review of five package inserts, and minor changes were made to the data collection tool. The first checklist contained a list of the requirements but not necessarily in the order as prescribed in the labelling guidelines. The most significant change made to the data collection tool was to organise the 13 package insert aspects for evaluation in the same order as they appear in the labelling guidelines. Also, the first data collection tool listed different medicine storage temperatures to select from. To avoid numerous different storage temperature descriptions by registration holders and to ease the data analysis, the data collection tool was modified only to indicate whether a specific temperature range was indicated on the package insert, but it was not necessary to indicate the temperature range. Lastly, a section was added to the data collection tool to indicate whether the package insert information was obtained from the company website or the IDR. The five package inserts used for the trial were not excluded from the data analysis as the reorganisation of the data collection tool did not influence the data collected.

3.7 Validity and reliability of data

The data used in this research study was obtained either from the pharmaceutical company's website or from the MIMS publication, IDR 2017/2018 or IDR 2019/2020. While every effort was made to ensure that the information used in this research was up to date, the researcher relied on the fact that pharmaceutical companies have an obligation to ensure that information available to users are current and relevant.

Thus, validity was ensured through the use of regulatory standards that are used to guide and evaluate package insert compliance, while reliability was enhanced through a data collection tool that ensured consistency in recording the sampled products' data. The pilot test of the data collection tool further enhanced validity, as this ensured the collection of the right type of data through necessary improvements.

3.8 Data-collection process

Data were collected by reviewing the sample package inserts from the sampled sources, as explained earlier. The researcher recorded all of the findings using the pre-developed data collection tool. Data were anonymised and analysed.

3.9 Data analysis

The data collection tool was used to compare the sample package inserts with the regulatory guidelines to establish compliance with the guideline requirements. The data obtained were entered into a Microsoft® Excel® for Office 365 ProPlus 2021 Version 16.0.1257.21504 spreadsheet and analysed.

First, each package insert was classified in terms of its source, generic name, dosage form, strength, product category and target species. Thereafter, the content of each of the package inserts in the sample was evaluated according to the required headings and information and classified as compliant, partially compliant or non-compliant.

As stated above, the second section of the data collection tool had 13 subsections. Each package insert was screened and evaluated according to the subsection on the checklist and was scored 0 if the information was non-compliant, 0.5 if partially compliant, and 1 if compliant. A total score of 29 was assigned to all of the evaluated package inserts except in the case of stock remedies indicated for anthelmintic use. Endectocide and endoparasiticide package inserts were assigned a total score of 32, as these anthelmintics had three additional criteria. After each

section was scored, the total for each package insert was calculated. The data was presented in a tabular format on an Excel spreadsheet.

The number of package inserts that met each quality criterion was calculated. The results were expressed as both absolute numbers and percentages, and the percentages were used to describe the package insert compliance.

The presence of information in the package insert was evaluated firstly for appearing under the relevant heading or elsewhere in the package insert, but then also for the completeness of the information. The presence of information on each package insert was scored as '1' if it was present, '0' if it was absent, and '0.5' if the information was either present in a section other than the required heading or if the information did appear under the correct heading but was inadequate. The scores for each of the headings were calculated by adding the assigned scores. The total score for each package insert was expressed as an absolute number as well as a percentage.

3.10 Statistical analysis

Microsoft® Excel® for Office 365 ProPlus 2021 Version 16.0.1257.21504 was used to assist with the general calculations for the data obtained in this research and to describe and summarise the data.

3.11 Ethical considerations

The investigator ensured that the study was conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords greater protection to the subject. The study commenced only once approval had been granted from the Faculty of Natural Science Research Committee from the University of the Western Cape (UWC) (number 20/4/21). The study was granted an exemption from requiring ethical approval.

3.11.1 Permission

Package information used in the research was publicly available. No permissions were needed from the manufacturers of veterinary stock remedies to conduct the research. UWC Natural Sciences Faculty Research Committee provided approval for the study (number 20/4/21).

3.11.2 Informed consent

No informed consent was needed for the research study because it did not have human subjects as participants or respondents (Kumar, 2011).

3.11.3 Anonymity

In the data analysis phase, the researcher did not disclose the identity of any of the package inserts or the corresponding pharmaceutical animal health company. The researcher ensured that no information could be used to trace the information back to the corresponding product or company.

3.11.4 Confidentiality

The confidentiality of pharmaceutical animal health companies was maintained throughout the data analysis phase. Data was kept confidential, and it was impossible to link a company's identity to its data set. Companies and their specific package inserts were identified through a generated number. Data collection forms were kept in a locked location at the School of Pharmacy, UWC. Electronically stored data was password protected.

3.11.5 Anticipated risks and precautions

There were no risks encountered during this research: the researcher is of the opinion that any findings from this study would only be beneficial in its contribution to the safe and effective use of veterinary stock remedies.

3.12 Funding

The researcher required no funding for the research. Administrative support was provided by the School of Pharmacy (UWC).

CHAPTER 4: RESULTS

4.1 Introduction

In this chapter, the researcher presents the results based on the research question of this current study. The research question of this study is whether stock remedy package inserts available in the South African market comply with the guidelines and requirements as stipulated by the local regulatory authority, DAFF. Through random sampling, a sample of 159 package inserts was selected to be included in this study from the overall 270 available package inserts obtained from pharmaceutical company websites or from the IDR 2017/2018 and IDR 2019/2020.

4.2 Package insert evaluation results

Each of the 159 package inserts was screened and evaluated according to the 13 sections identified from the Act 36 of 1947 Labelling Guideline (2018). Each requirement was scored 0 if the information was missing or non-compliant, 0.5 if the information was partially compliant, and 1 when compliant. A total score for each package insert was calculated and expressed as an absolute number and a percentage. A graphical representation of the data from the 159 package inserts that were evaluated is shown in Figure 1 to illustrate how each package scored in the compliance evaluation.

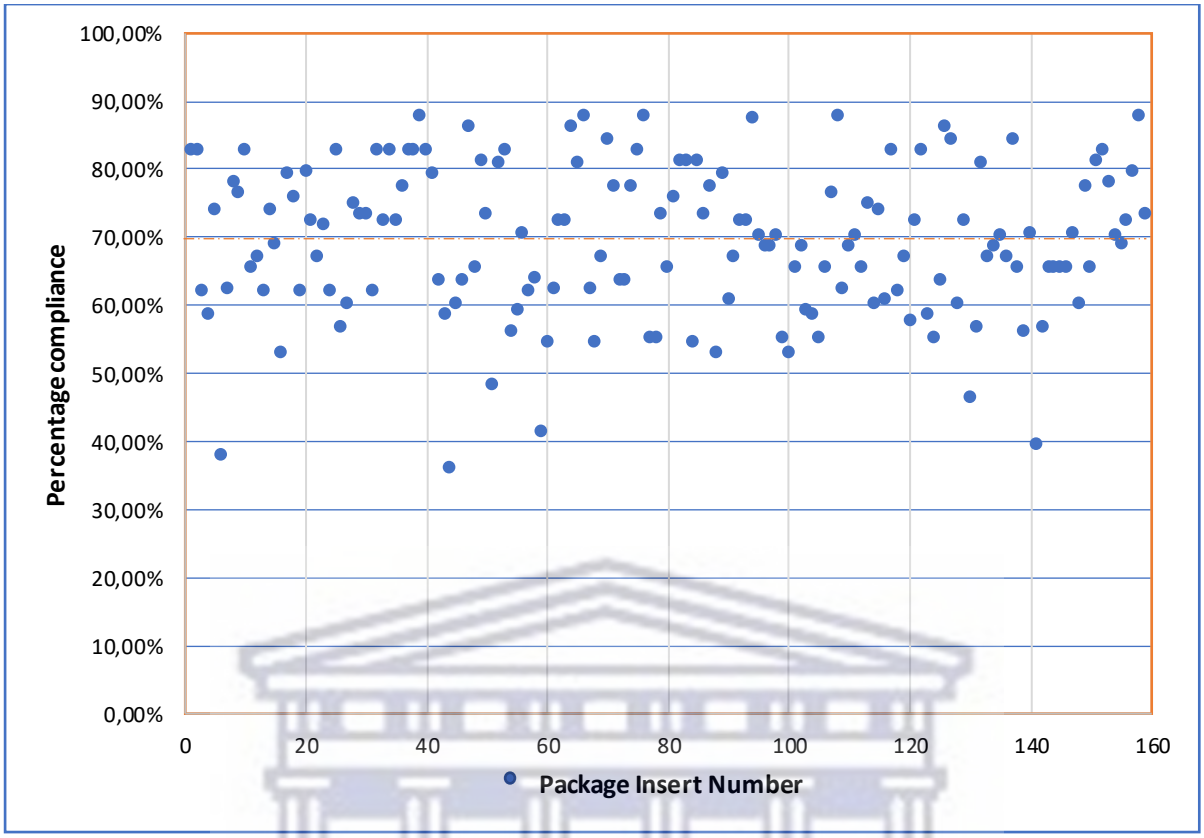

Figure 1: Percentage compliance of the 159 evaluated package inserts

The average percentage compliance was 69.43%. Of the 159 package inserts, the highest percentage was 87.93%, achieved by 4 of the studied package inserts, while the lowest level of compliance was from 1 package insert, which scored 36.21%.

Regarding the individual subsections of the 13 requirements as displayed in Table 2, it can be seen that the requirements for the package insert to display the trade name, claims or indications, and composition were all 100% complied with. On the contrary, precautions (30.74%) and warnings (44.65%) were the two subsections with the least compliance.

Table 2: Overall percentage compliance of each evaluated package insert heading

	Non-Compliant (%)	Partially Compliant (%)	Fully Compliant (%)
1. For (external) animal use only (n = 159)	1.89	0.63	97.48
2. Trade name (n = 159)	0	0	100
3. Registration number (n = 159)	0.63	0.42	98.95
4. Claims or indications (n = 159)	0	0	100
5. Toxicity statement (n = 159)	45.28	1.26	53.46
6. Storage instructions (n = 159)	9.43	45.92	44.65
7. Composition (n = 159)	0	0	100
8. Warnings (n = 159)	27.43	14.78	57.79
9. Precautions (n = 159)	55.74	13.52	30.74
10. Directions for use (n = 159)	1.58	0.31	98.11
11. Anthelmintic efficacy (n = 62)	39.79	0.53	59.68
12. Presentations (n = 159)	8.18	0	91.82
13. Registration holder (n = 159)	0.63	3.14	96.23

4.2.1 The statement 'For (external) animal use only'

Of the 159 evaluated package inserts, only 3 (1.89%) did not indicate that the stock remedy was for (external) animal use only. In Figure 2, it can be seen that 1 package insert only partially fulfilled the requirement, and 3 were non-compliant.

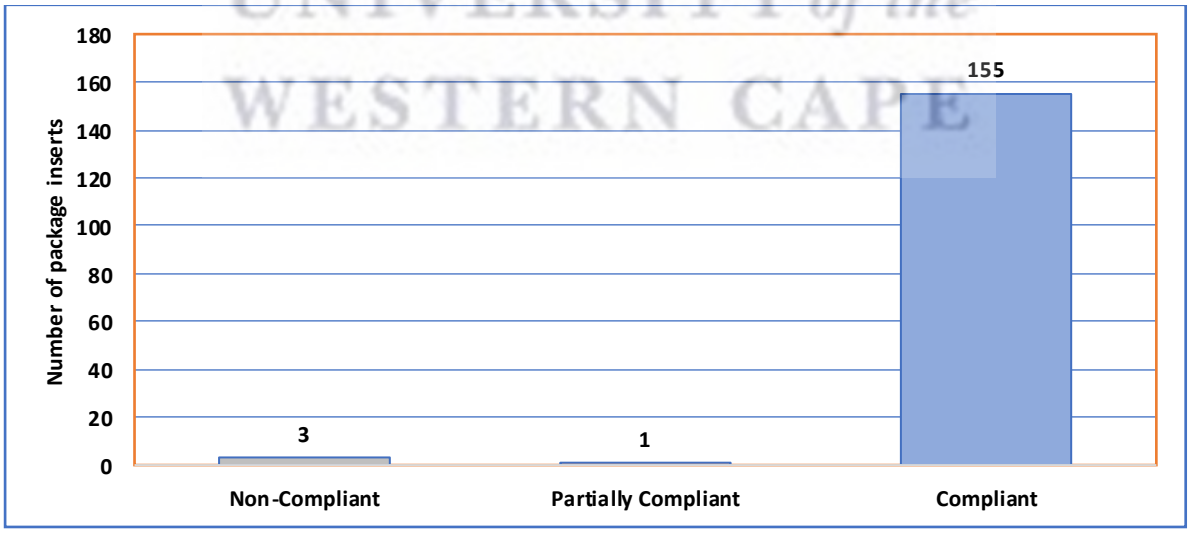

Figure 2: Compliance of package inserts (n = 159) in terms of inclusion of the statement 'For animal use only'

4.2.2 The trade name of the stock remedy

Figure 3 shows that all the package inserts evaluated displayed the stock remedy's trade name.

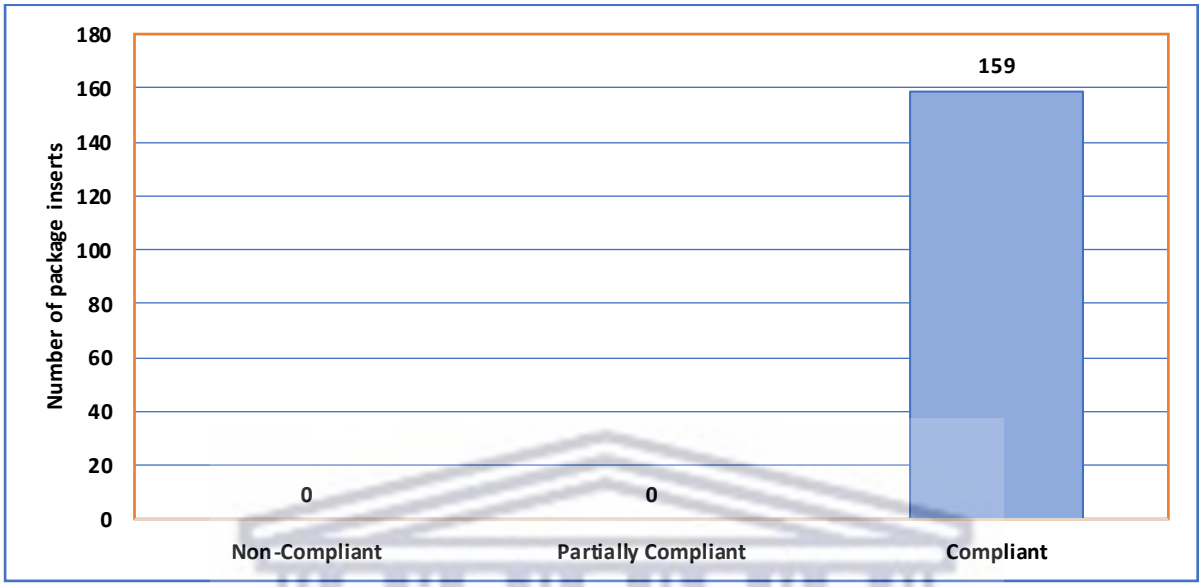

Figure 3: Compliance of package inserts (n = 159) in terms of inclusion of the trade name of the stock remedy

4.2.3 The registration number of the stock remedy

Figure 4 illustrates the results for the requirements with regards to the registration number of the stock remedy. The registration number as allocated under Act 36 of 1947 appeared on 158 of the 159 package inserts. Only one package insert did not comply.

The requirement that the registration number should be followed by the words 'Act 36 of 1947' was met by 158 of the package inserts, while 1 was partially compliant. One hundred and fifty-six package inserts complied with the requirement that the registration number should appear directly below the tradename; 2 of the package inserts were non-compliant, and 1 was partially compliant.

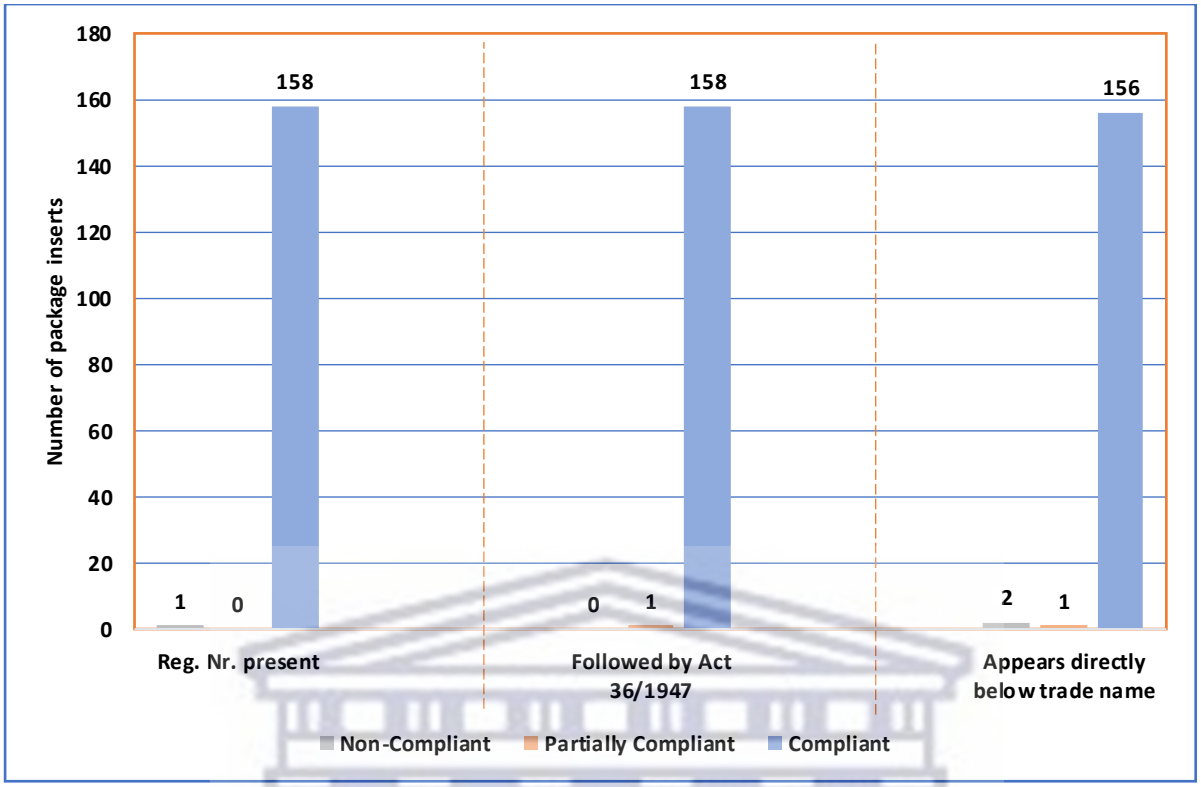

Figure 4: Compliance of package inserts (n = 159) in terms of inclusion of the registration number of the stock remedy

4.2.4 Claims or indications

All 159 package inserts stated the indications or claims (Figure 5).

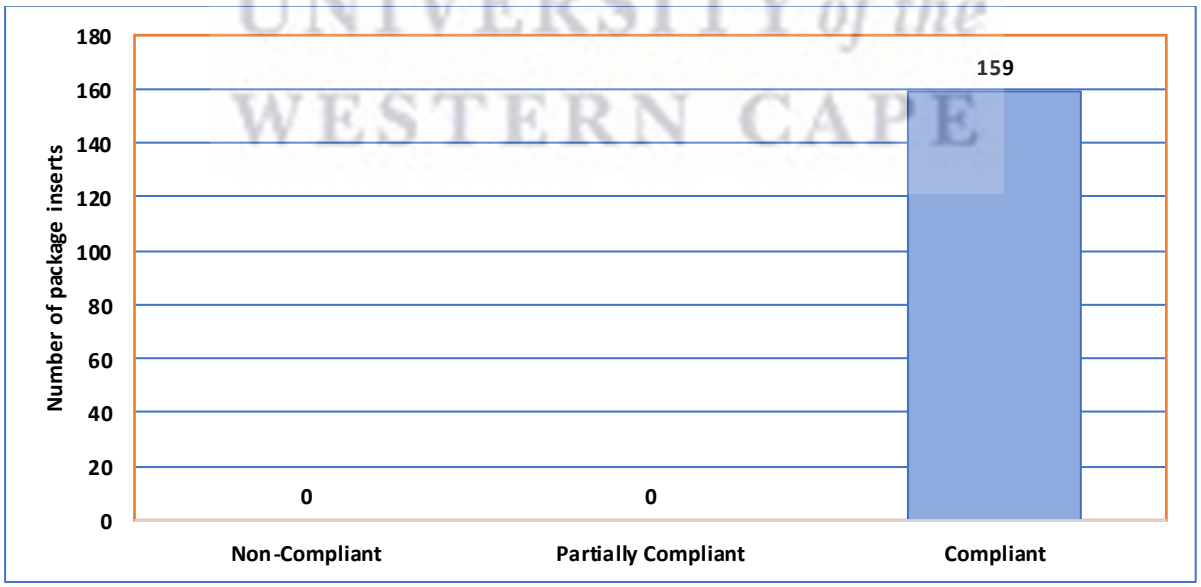

Figure 5: Compliance of package inserts (n = 159) in terms of inclusion of the claims or indications of the stock remedy

4.2.5 Toxicity statement

Of the 159 package inserts, 72 (45.28%) had no toxicity statement or indication, while 85 (53.46%) complied fully with the requirements. As indicated in Figure 7, 2 of the 159 package inserts partially adhered to the requirement to indicate the toxicity statement.

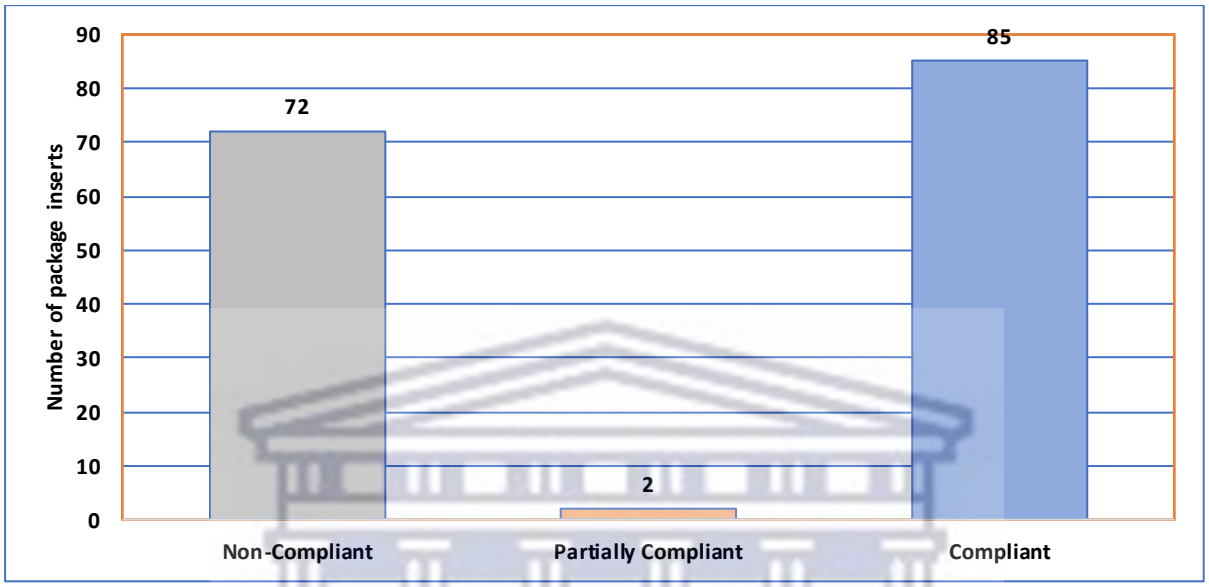

Figure 6: Compliance of package inserts (n = 159) in terms of inclusion of a toxicity statement of the stock remedy

4.2.6 Storage instructions

Of the 159 package inserts evaluated, 15 (9.43%) did not display any indication of storage instructions (Figure 7). Seventy-one package inserts complied with the storage instruction requirements, while the remaining 73 (45.91%) were found to be partially compliant.

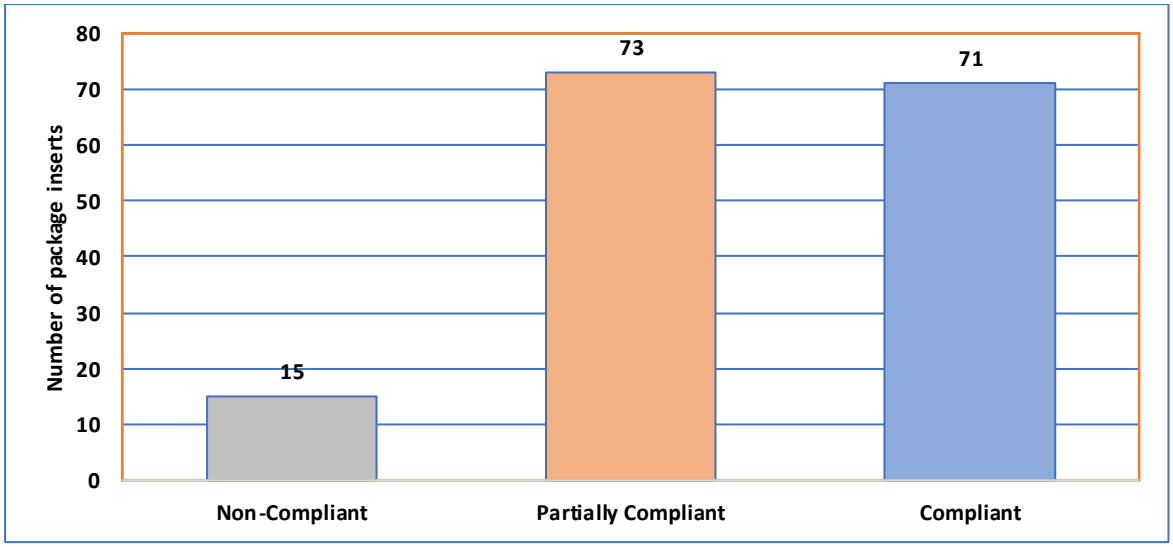

Figure 7: Compliance of package inserts (n = 159) in terms of inclusion of storage instructions for the stock remedy

4.2.7 Composition of the stock remedy

The composition of the stock remedy showed 100% compliance in that all the stock remedies displayed the composition of the active ingredients (Figure 8).

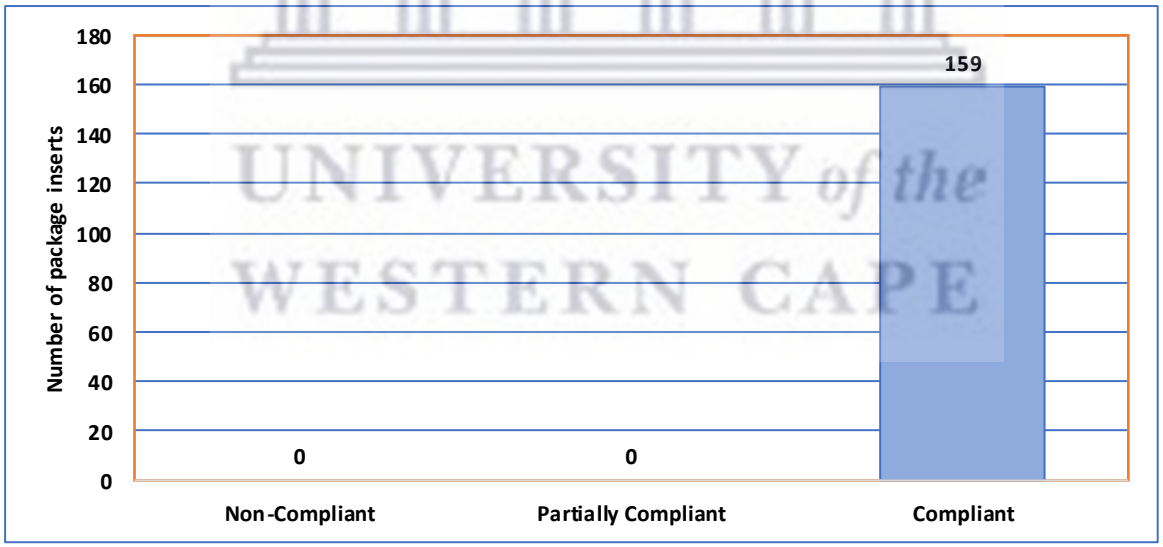

Figure 8: Compliance of package inserts (n = 159) in terms of inclusion the composition of the stock remedy

4.2.8 Warnings

As displayed in Figure 9, the overall results from the evaluated warnings section indicated that the majority of the package inserts (156; 98.11%) included warnings, but not all of the required statements were equally adhered to. In general, the most frequent warning included in the package inserts was the recommendation to report suspected failure (155; 97.48%), followed by the instruction to keep out of the reach of children, uninformed persons and animals (149; 93.71%).

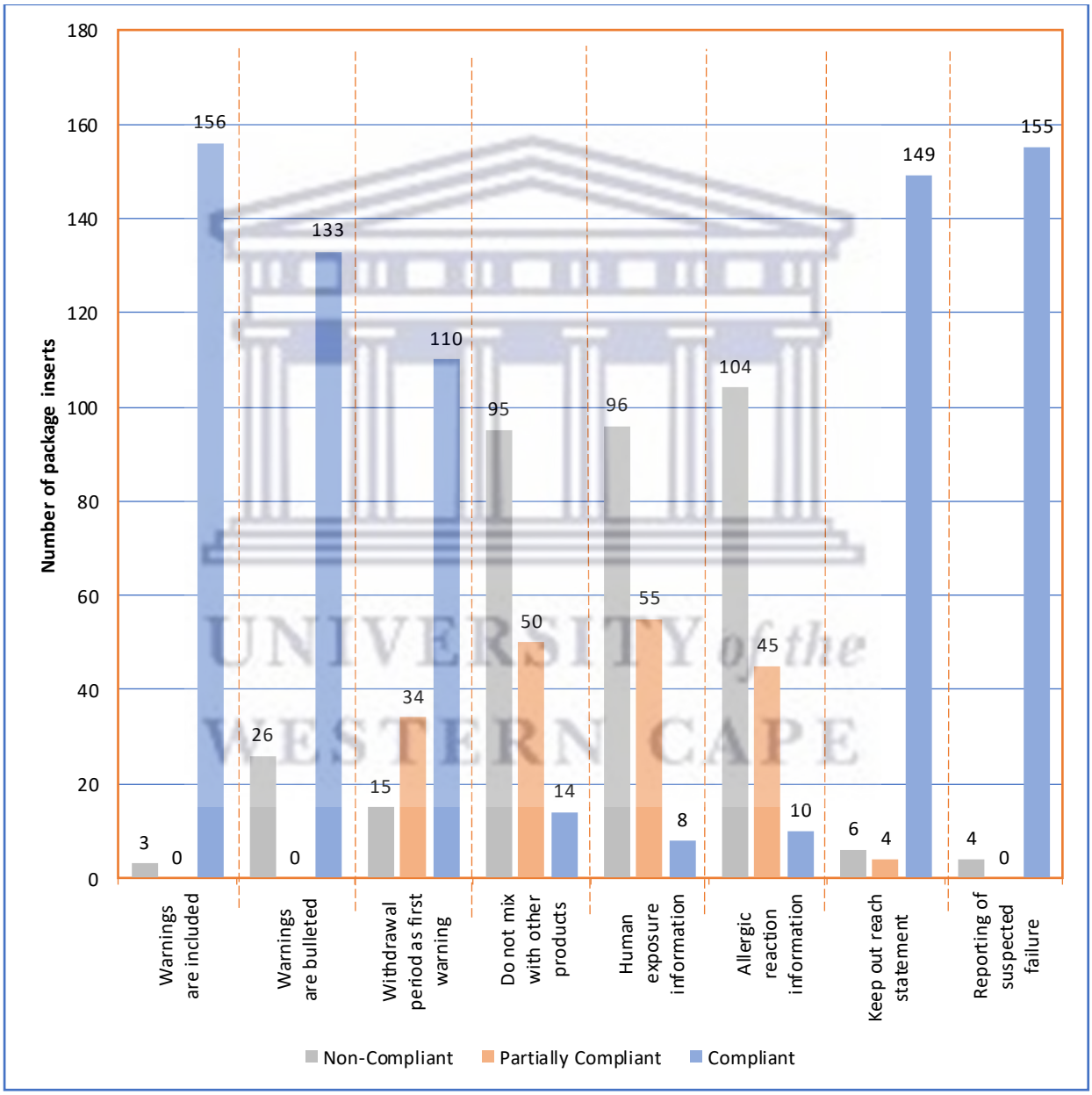

Figure 9: Compliance of package inserts (n = 159) in terms of inclusion of warnings for the stock remedy

4.2.8.1 Warning must be included

Three package inserts contained no warnings in the required format and the warnings were also not included as part of the other sections. The remaining 156 package inserts all included warnings for the user to read.

4.2.8.2 Warnings must be bulleted

The majority of the package inserts (133; 83.65%) complied with the requirement that warnings must be bulleted. Only 26 of the 159 package inserts (16.35%) did not have the warnings presented in a bulleted manner.

4.2.8.3 The withdrawal period must be listed as the first bulleted warning

Of the 159 package inserts, 110 (69.18%) conformed to the requirement to list the withdrawal period of the stock remedy as the very first listed and bulleted warning. Thirty-four package inserts (21.39%) partially complied, in that they did state the withdrawal period of the stock remedy, but it was not the first warning. The remaining 15 inserts (9.43%) did not indicate any withdrawal period.

4.2.8.4 Do not mix with other products

The required statement to not mix the stock remedy with any other products appeared on only 14 of the 159 package inserts evaluated (8.80%). Most package inserts (95; 59.75%) did not comply with this requirement, while 50 package inserts (31.45%) partially complied.

4.2.8.5 Information on human exposure

Overall, this section had the worst compliance. Of the 159 evaluated package inserts, only 8 (5.03%) complied with stating sufficient information. Fifty-five package inserts (34.59%) provided some information, making them partially compliant, while the majority (96; 60.38%) had no information on human exposure.

4.2.8.6 Information on allergic reactions

Information about allergic reactions was the second-least met requirement in the overall warning section. Only 6 package inserts (3.77%) provided sufficient warnings about allergic reactions. A total of 104 of the package inserts (65.41%) completely lacked this information, while the remaining 45 (28.30%) contained some information, although it was not adequate.

4.2.8.7 Keep out of reach of children, uninformed persons, and animals

Only 6 of the 159 package inserts (3.77%) did not contain the 'keep out of reach' warning, while the majority (149 of 159; 93.71%) did comply with the regulatory requirements. The remaining 4 package inserts were partially compliant.

4.2.8.8 Reporting of suspected failure

As the second-most included warning in the overall warning section, the statement to report suspected failure appeared on 155 package inserts, giving a 97.48% compliance rate. The remaining 4 package inserts (2.52%) failed to include the statement.

4.2.9 Precautions

Figure 10 displays the overall compliance of the precaution section. Overall, 108 of the 159 (67.92%) package inserts evaluated included precautions in the written product information. However, 48 package inserts (30.19%) did not bear any precautions, while 3 (1.89%) were partially compliant in this area.

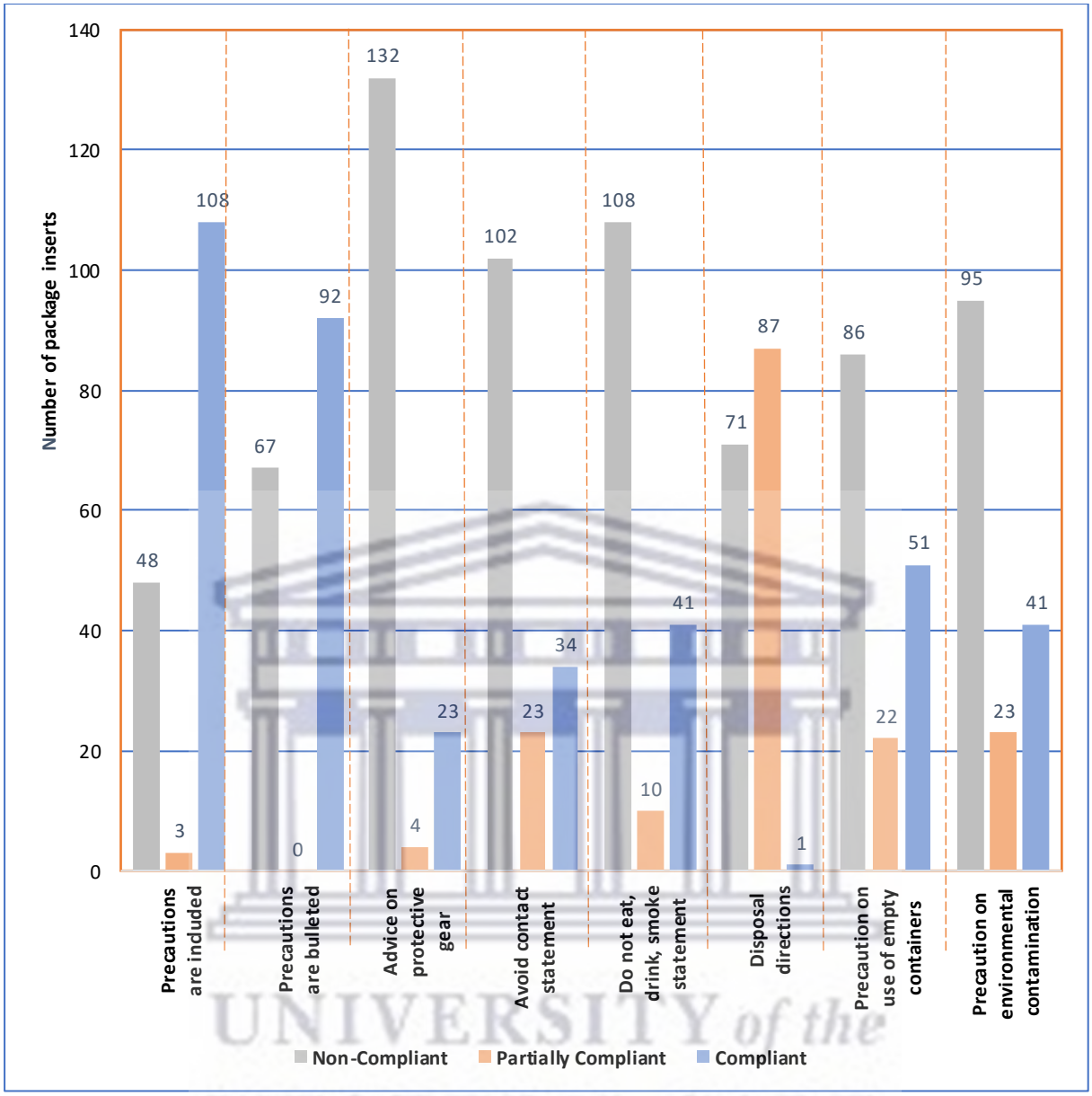

Figure 10: Compliance of package inserts (n = 159) in terms of inclusion of precautions for the stock remedy

4.2.9.1 Precautions must be included

From the overall chart (Figure 11), it can be seen that this requirement was the most frequently complied with: 108 of the 159 (67.92%) package inserts evaluated included precautions in the written product information, 48 (30.19%) did not bear any precautions, and 3 partially complied.

4.2.9.2 Precautions must be bulleted

The requirement that precautions should be bulleted was adhered to by 92 (57.86%) package inserts. On the contrary, 67 package inserts (42.14%) did not have bulleted precautions.

4.2.9.3 Advice on protective gear

Advice on protective gear was the precaution section with the least compliance as 132 of the 159 package inserts (83.02%) did not state any form of advice on protective gear. Only 23 package inserts (14.47%) supplied sufficient advice on protective gear to be utilised during the use of the stock remedy. Four of the package inserts (2.51%) were found to be partially compliant.

4.2.9.4 Avoid contact with the stock remedy

The requirement to provide information that contact with the remedy should be avoided was lacking in most of the package inserts, with 102 of the 159 (64.15%) omitting the precaution. Of the 159 package inserts, only 34 (21.38%) fully complied, while 23 (14.47%) partially complied.

4.2.9.5 Do not eat, drink or smoke while handling the stock remedy

The precaution to not eat, drink or smoke while handling the stock remedy was not available in 108 (67.92%) of the package inserts. Only 41 (25.79%) contained the precaution. Partial fulfilment of the required precaution was demonstrated in the remaining 10 package inserts (6.29%).

4.2.9.6 Disposal directions

While 87 of the package inserts (54.72%) were partially compliant with disposal instruction requirements, only 1 (0.63%) was fully compliant. Seventy-one package inserts (44.65%) contained no instructions on how to safely dispose of the stock remedy or empty containers.

4.2.9.7 Precaution on future use of empty containers

The majority of package inserts (86; 54.08%) omitted the precaution that the stock remedy containers should not be used for any other purposes. Fifty-one (32.08%) package inserts did instruct users to not reuse containers, and 22 (13.84%) only partially fulfilled this requirement.

4.2.9.8 Precaution on contamination of water sources

Ninety-five (59.75%) package inserts, therefore the majority, lacked any information or precaution about not contaminating the environment. Only 41 (25.78%) package inserts adequately presented the precaution, while 23 (14.46%) partially complied.

4.2.10 Directions for use

In Figure 11, it is evident that there was a high rate of compliance with the requirement that directions for use should be presented. Directions for use were included in 158 (99.37%) package inserts. None of the package inserts had no directions for use, and only 1 did not comply in full. For the requirement that the words 'use only as directed' should appear in the directions for use, only 5 package inserts (3.13%) were non-compliant, with the majority (154; 96.87%) fully complying.

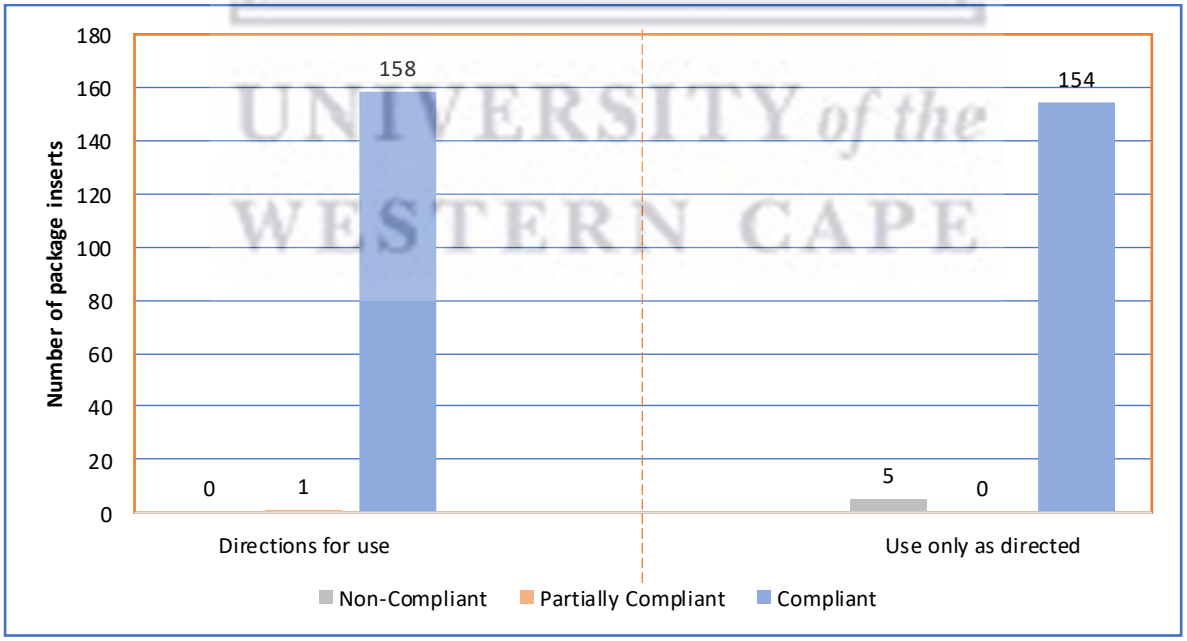

Figure 11: Compliance of package inserts (n = 159) in terms of inclusion of directions for use for the stock remedy

4.2.11 Anthelmintic efficacy

Figure 12 illustrates the results of the anthelmintic efficacy requirements. Of the 159 stock remedy package inserts evaluated, 62 were classified as anthelmintics, and therefore only these were evaluated for anthelmintic efficacy.

The required anthelmintic code was provided for 39 (62.90%) of the 62 anthelmintics. The remaining 23 package inserts (37.10%) did not indicate the anthelmintic coding. Of the 62 anthelmintic package inserts, 56 (90.32%) contained the anthelmintic efficacy tables as required, 1 (1.61%) partially fulfilled the requirement, and 5 (8.07%) did not comply. Only 16 of the package inserts stated that the list contains only the species tested for. The remaining 46 package inserts did not comply with this requirement.

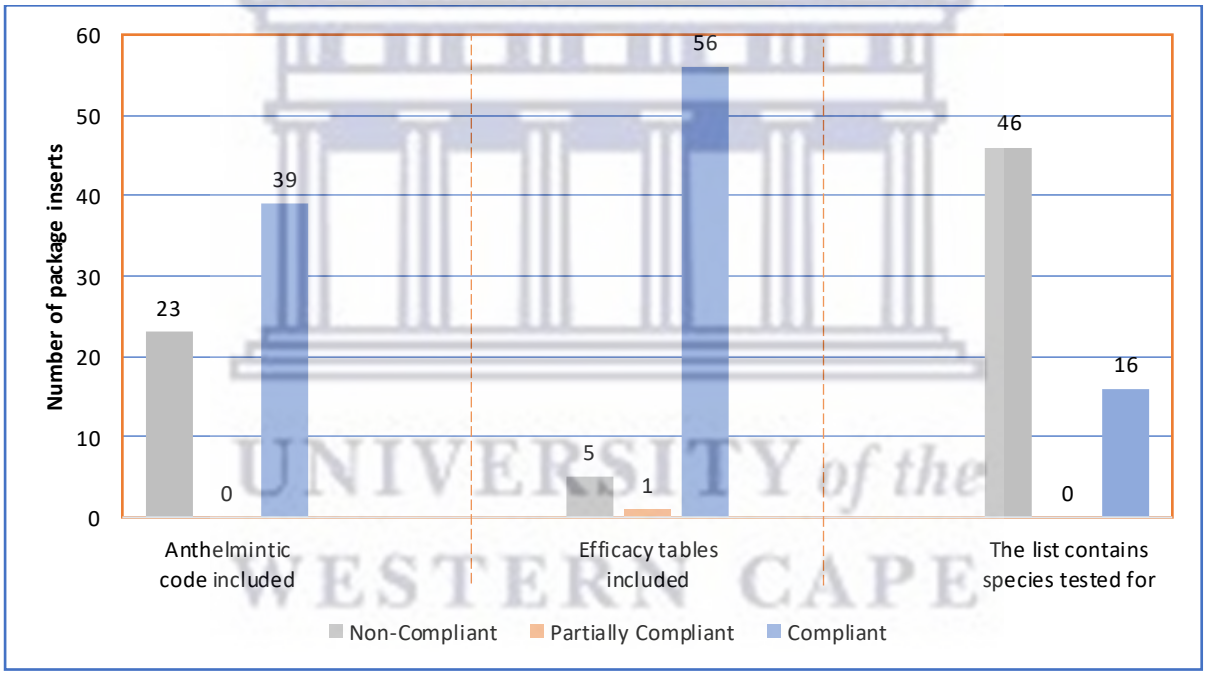

Figure 12: Compliance of package inserts (n = 159) in terms of inclusion of anthelmintic efficacy information for the stock remedy

4.2.12 Presentations

The requirement to include the presentations for the registered stock remedy was met by 146 (91.82%), while 13 package inserts (8.18%) did not meet this requirement (Figure 13).

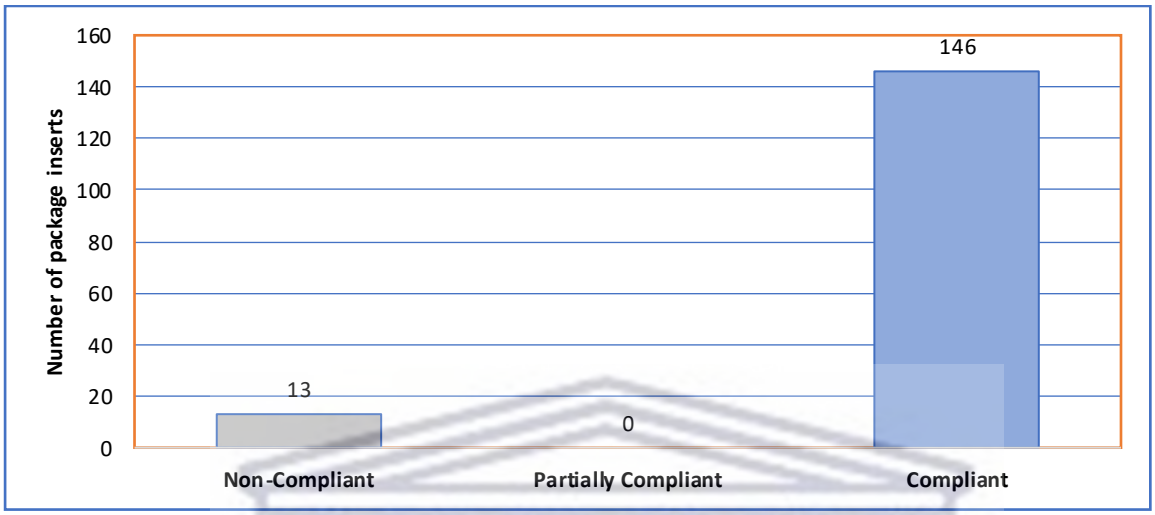

Figure 13: Compliance of package inserts (n = 159) in terms of inclusion presentations of the stock remedy

4.2.13 Registration holder

The requirement for the name and the address of the registration holder to appear on the package insert was fully complied with by 153 (96.22%) package inserts. The remaining 6 package inserts (3.77%) only partially complied (Figure 14).

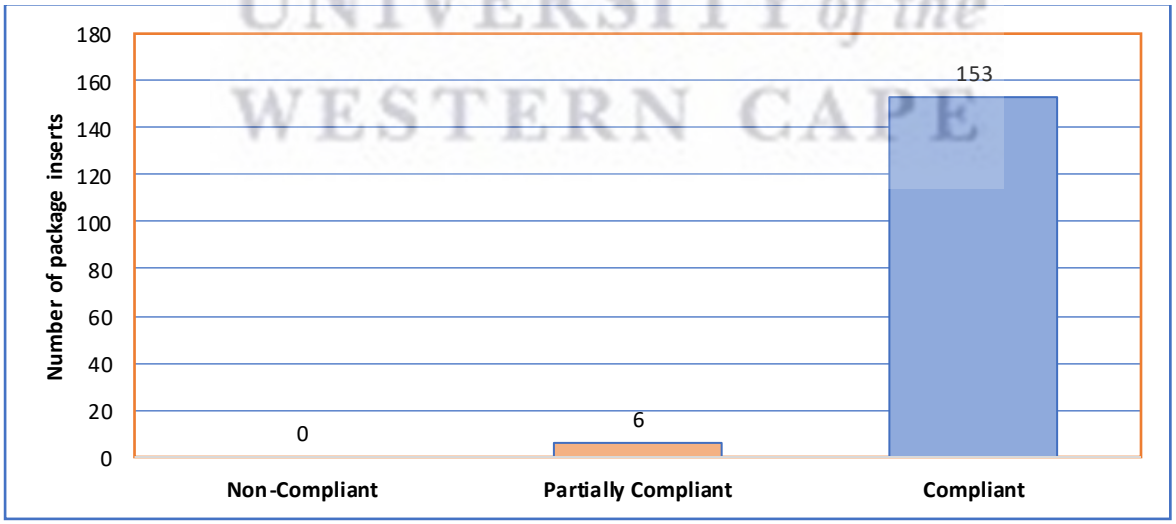

Figure 14: Compliance of package inserts (n = 159) in terms of inclusion of the registration holder of the stock remedy

CHAPTER 5: DISCUSSION

5.1 Introduction

The safe and rational use of veterinary medicines is an important aspect in the treatment of animals, and written information must be available to improve users' understanding and adherence during the treatment programme as many users rely on the written information in the package insert (Shrank and Avorn, 2007). In the current study, 159 package inserts of various registered stock remedies were evaluated to determine whether they contained the information prescribed by the regulatory authority under Act 36 of 1947. It was observed that, while certain aspects had a high compliance rate, many package inserts were inadequate in several aspects. Of particular concern was the insufficient or incomplete information under warnings and precautions, as well as the incomplete storage conditions.

The overall score of compliance of the 13 individual subsections of requirements evaluated, as displayed in Table 2, indicates that the trade name of the stock remedy, claims or indications, and the composition of the stock remedy were the only 3 sections that were 100% compliant. In contrast, the sections on precautions and warnings were the least compliant. The individual sections will be discussed below.

5.2 Discussion

Regulation (10)3 of Act 36 of 1947 stipulates that a stock remedy shall not be sold in a container or packaging which the registrar of Act 36 of 1947 did not approve of (Act 36, 1947). The purpose of this regulation is to ensure that registration holders comply with the guidelines and requirements in terms of the information that should be supplied with stock remedies. The findings of the presented compliance evaluation have shown that the package inserts were inadequate in many aspects. While there have been no studies conducted explicitly on veterinary package inserts, as discussed in the literature review, studies in India (Deep et al., 2016; Ramdas et al., 2013), Iran (Khamas et al., 2019) and the East African partner states of Kenya, Tanzania and Uganda (Sillo et al., 2018) found that package inserts for human

medicine, available in the respective markets, failed to adhere to the guidelines of the regulatory authorities. The current study's findings, therefore, resonate with earlier research, suggesting that the identified problem is not only prevalent in South Africa but also manifested in other countries. The following sections discuss the findings for the 13 compliance aspects reported in the previous chapters.

5.2.1 For (external) animal use only

The Act 36 of 1947 Labelling Guideline requires that the statement 'For (external) animal use only' should appear at the top of the package insert or label. While veterinarians and their staff usually dispense medication to patient owners themselves (McDowell et al., 2011), stock remedies in South Africa are available to the public from outlets without the consultation of or advice from a veterinarian or pharmacist. It is therefore important that the first statement on the package insert should clearly declare that the remedy the user is about to buy is for animal use only. In the case of remedies such as pour-ons and dips, it should be indicated that these remedies are for external animal use only, clearly indicating to the user, even before they read the rest of the labelling, that the product is not for oral dosing or injection.

The majority of the package inserts complied with this specific requirement, and a high compliance rate of 97.48% was observed in the results, indicating that registration holders are committed to this requirement. The high compliance rate may reduce the risk of humans accidentally taking the medicine themselves or administering external remedies as an oral remedy. Of the 159 evaluated package inserts, only 3 did not indicate that the stock remedy was for (external) animal use only. One package insert only partially fulfilled the requirement, in that the statement was available on the package insert but was not at the top of as the first statement.

5.2.2 The trade name of the stock remedy

The name of the remedy must correspond exactly with the registered name of the product as it appears on the registration certificate (Labelling Guideline, 2018). Brand names or trade names exist as a way for pharmaceutical companies to distinguish their products from those of other

pharmaceutical companies or competitors (Schuiling and Moss, 2004). Ideally, pharmaceutical companies would want their product trade name to be related to the product's intended use and relatively easy to remember so that consumers look for it by name.

All the package inserts evaluated displayed the stock remedy's trade name. As the trade name is an important identifier in the branding of the product, it is expected that the trade name will be one of the requirements that are highly unlikely not to be met. The 100% compliance rate confirms that companies take care and effort to brand and name their pharmaceutical products, as this distinguishes their product from competitors and indicates to customers tangible and intangible benefits such as the efficacy of the product but also trust in the brand name (Schuiling and Moss, 2004). The high compliance rate suggests that the incidence of accidental misidentification of stock remedies, and therefore the incorrect use, may be avoided. Hence, aiding in the safe and effective use of veterinary stock remedies.

5.2.3 The registration number of the stock remedy

As stipulated, the registration number of the stock remedy must always appear directly below the registered trade name and be followed by the words 'Act 36 of 1947'. When a regulatory authority approves a medicine, a registration number is awarded to the specific product. The registration number is therefore an indication that the regulatory authority found the product to be safe, effective and of quality. Not only does the registration number indicate that the product has been evaluated and found to have a positive risk–benefit ratio, but by including 'Act 36 of 1947', it also indicates the authority that has taken responsibility for the evaluation and registration of the product.

The registration number as allocated by Act 36 of 1947 appeared on 158 of the 159 package inserts. Only 1 package insert on one of the company's websites appeared without a registration number: the words 'registration number' appeared, but the space underneath it was left blank.

On another package insert, the words 'Act 36 of 1946' did appear beside the registration number, but there was an error in that it stated the wrong year of the Act. Technically, the wording did appear beside the registration number, but the fact that the year was incorrect made it only partially compliant. One hundred and fifty-six package inserts complied with the requirement that the registration numbers should appear directly below the tradename. It must be mentioned that the package inserts evaluated from the MIMS IDR, the registration number followed by 'Act 36 of 1947' appears at the bottom of the page, as this is the layout of the publication. Because this is the format of the MIMS IDR, the registration holders were not penalised and were scored as compliant.

5.2.4 Claims or indications

Act 36 of 1947 requires that the claims for the remedy correspond exactly with the claims submitted in the registration application dossier. During the registration process of bringing a stock remedy to market, the claims or indications on the package insert must be referenced to the dossier and should correspond exactly with the relevant data in the dossier that substantiate the claims. Referencing and linking each claim on the package insert to the dossier ensures that each claim or indication is based on scientific evidence and approved by the regulatory authority (Sykes et al., 2019).

Evidence shows that information about a medicine's indications is among the information that patients require (Jeetu and Girish, 2010) and that this information is critically utilised to determine the appropriate use of medicines (Salmasian et al., 2015). Moreover, the claim or indication of a product may be the biggest selling point of the product, as it provides information on the use of the product and assists users in their decision-making regarding a treatment option. Therefore, it is not surprising that all 159 package inserts included claims or indications.

5.2.5 Toxicity statement

The toxicity group applicable to the stock remedy should appear on the labelling, as stipulated by Regulation 8(2) of Act 36 of 1947. The toxicity or potential hazard of the stock remedy is

based on the determination of the LD_{50} value. Based on the established LD_{50} value, the toxicity indication is placed into one of the following four groups (Labelling Guideline, 2018), which should be clearly visible on the product label:

Group I – Poisonous or Extremely Toxic

Group II – Poisonous

Group III – Caution

Group IV – No poison group indication

Two of 159 package inserts partially complied in that they reflected the toxicity statement under the heading of 'Precautions'. Therefore, while it was stated in the information, it did not comply with the required format to have the toxicity statement as a separate heading. Of the 159 package inserts, 72 (45.28%) included no toxicity statement or indication, while 85 (53.46%) fully complied with the requirements. Of the 72 package inserts that had no toxicity indication, according to the researcher, 40 were lacking the statement, as proven by identifying other products with similar active ingredients and concentrations that did have a toxicity statement. For the remaining 32, it is not clear whether the stock remedies lacked the toxicity statement or whether they may belong to Group IV, for which no poison indication is necessary. The toxicity statement is important to advise users to take proper precautions while handling the stock remedy, according to its risk classification (Sykes et al., 2019).

5.2.6 Storage instructions

According to the Labelling Guideline (2018), stock remedy labels and package inserts are required to display the relevant temperature ranges for the storage of the product, and not only general statements such as 'store in a cool place' or 'store at room temperature'. Environmental factors may affect the physical and chemical stability of a medicinal product. (Bott and Oliveira, 2008). Such changes in the stability of a product may result in a loss of potency, or the active ingredient may break down into toxic degradation products. When the stability is affected, the quality, safety and efficacy may be affected as well.

As storage conditions are based on the stability tests conducted during the development of the stock remedy, the storage conditions are those determined as the optimal temperature ranges and conditions under which the product should be stored in order to retain its stability throughout its shelf-life.

Fifteen of the package inserts did not mention any information relevant to the storage of the products. Seventy-three package inserts stated only general storage conditions, such as 'store at room temperature' or 'store away from food and feed', but there was no indication of temperature ranges. Only 71 package inserts stipulated the exact temperature ranges.

As the storage conditions of medicines and stock remedies are crucial to maintain the quality, safety and efficacy of the finished product, proper storage instructions are imperative to prescribe the optimal storage conditions to users. In general, the storage indications of the evaluated package inserts were insufficient to provide users with thorough instruction on the optimal storage of veterinary stock remedies.

Given that less than half of the evaluated package inserts contained specific storage temperatures, it can be said that the storage instructions on package inserts are not adequately addressed and are insufficient to provide users with instruction on optimal storage for stock remedies to retain its stability for the duration of the shelf-life.

5.2.7 Composition of the stock remedy

Act 36 of 1947 requires that the active ingredient of the stock remedy should be stated. In this instance, all of the 159 package inserts complied with the requirement. The observation of a 100% compliance rate for the active ingredient being visible on the package insert or label is welcomed, as it is important for users to know the active ingredient in the stock remedy for the following reasons. First, many companies may market the same active ingredient under different brand names, and the brand names are not necessarily indicative of the active ingredient. When the active ingredient is displayed on the product information, it assists users

in distinguishing different products that contain the same active ingredient. Secondly, it is essential for users or consumers to know the active ingredient when there is a possibility that the user or the animal has an allergy or sensitivity to this active ingredient. Finally, it may aid in the prevention or delay of active ingredient resistance development. Users should be made aware of the emerging problem of antimicrobial, anthelmintic and pesticide resistance, and, when they suspect resistance to a particular active ingredient, they should switch to a product with a different ingredient to ensure that the animals are treated optimally and to reduce the emergence of stock remedy resistance (Shalaby, 2013).

5.2.8 Warnings

Stock remedy warnings to consumers can decrease the incidence and severity of adverse reactions by allowing early recognition of possible adverse reactions or possible interactions. With regard to warnings, the Labelling Guideline has the following specific requirements.

5.2.8.1 Warnings must be included

Only 3 of the 159 package inserts did not display any warnings for the user or administrator of the product. The remaining 156 package inserts included warnings for the user to read. However, the high compliance rate with the inclusion of warnings is not an indication of the quantity or quality of the information provided in the warning section. While the majority of the package inserts did include a section on warnings, the completeness varied, as discussed for each individual section below.

5.2.8.2 Warnings must be bulleted

According to Tong et al. (2014), the design of package inserts using headings and bullet points can improve the experience of the reader as it highlights important information. Of 159 package inserts, 133 (83.65%) had the warning sections presented as bullets. Only 26 of the 159 package inserts (16.35%) did not have the warnings presented in a bulleted manner. As 3 package inserts that did not state any warnings at all, a total of 23 package inserts had warnings that were not bulleted.

5.2.8.3 The withdrawal period as the first bulleted warning

Listing the withdrawal period of the stock remedy as the first bulleted warning was complied with by 110 of the 159 package inserts. For 34 of the package inserts, the withdrawal period was mentioned but not in the prescribed position. Fifteen package inserts did not indicate any withdrawal period. Considering that 144 (90.57%) of the package inserts did state the withdrawal period, the majority of package inserts complied. It was not within the scope of the study to determine whether the correct and approved registration information was supplied on the product information, and therefore it may be that the package inserts that did not state any withdrawal period actually did not have a withdrawal period.

As residues of veterinary medicines could be a likely food safety and public health concern, it is imperative that the withdrawal period of animal products is reflected on the package insert (Smith, 2013). The inclusion of the withdrawal period as the first bulleted warning ensures visibility to the user and encourages compliance.

5.2.8.4 Do not mix with other products

Only 14 (8.80%) of the package inserts complied with the required statement that the medication should not be mixed with any other product. One reason for the low level of compliance in the case of an antibiotic preparation may be that it is sometimes used together with an anti-inflammatory. In many cases, it may therefore be possible to use more than one product simultaneously. Hence, it may be impractical to have this exact standard statement for all types of stock remedies. However, in the case of insecticides, the simultaneous use of different active ingredients may increase the insecticidal efficacy but also the toxicity (Anadón et al., 2009).

Fifty of the package inserts (31.45%) were found partially compliant in that they made mention of specific products that the stock remedy may or may not be used with.

5.2.8.5 Information on human exposure

The package insert should include the symptoms of human poisoning, recommended first aid treatment and a note to the medical practitioner or veterinarian. The warning section should

provide safety information to the user not only about how to avoid exposure to the medicinal product but also about what to do in the case of exposure.

In the overall warning section, this warning statement had the worst compliance. Only 5.03% (8) of the package inserts provided sufficient information. Fifty-five package inserts were partially compliant and were found lacking in that they mention symptoms of human poisoning or first aid treatment or a note to a medical professional, but not all three. Considering the importance of safety information to the person handling the veterinary medicines and risking coming into contact with it, the information about human exposure on the evaluated package inserts were not appropriately addressed.

5.2.8.6 Information on allergic reactions

The package insert should include symptoms of allergic reactions or anaphylaxis, recommended first aid treatment and a note to the medical practitioner or veterinarian. Information about allergic reactions was the second-worst performing section in the overall warning section. Only 6 package inserts (3.77%) provided sufficient warnings about allergic reactions. A total of 104 package inserts (65.41%) completely lacked information, while the remaining 45 (28.30%) contained some information, although this was not sufficient.

As with humans and human medicines, there are also instances where animals are allergic to antibiotics (Omidi, 2009) or where they show allergic reactions to pesticides (Anadón et al., 2009). With the handling, administration or receiving of the stock remedy dose, humans or animals may present with allergic reactions or, even worse, anaphylaxis. Most drug allergies are not life-threatening and will resolve once treatment with the causative medicine is brought to an end. In these cases, treatment is largely symptomatic (Voie et al., 2012). Anaphylaxis, however, is a severe, potentially life-threatening allergic reaction. It is concerning that so few package inserts sufficiently provided information on allergic reactions. It is therefore important for package inserts to warn users about how these symptoms present and what to do in the case of an event.

5.2.8.7 Keep out of reach of children, uninformed persons and animals

The majority (93.71%) of the package inserts were compliant, with only 6 not complying. The statement to keep the stock remedy out of reach of children, uninformed persons and animals is included with the intention to prevent accidental ingestion of or exposure to the stock remedy. Four of the package inserts were partially compliant, in that 2 did not include the words 'children, uninformed persons and animals', 1 had the statement positioned under 'storage instructions' and 1 included it under 'precautions'. While there is a high compliance rate with this warning statement, it does not guarantee that consumers read or obey the warning, but the positioning of text may increase the likelihood.

5.2.8.8 Reporting of suspected failure

The inclusion of the statement that failure of efficacy should be reported was the second-most frequently included warning in the warning section. It appeared on 155 package inserts, giving a compliance rate of 97.48%. The remaining 4 package inserts (2.52%) failed to include the statement. It should be noted that, while the reporting of suspected lack of efficacy plays a vital role in the pharmacovigilance of veterinary medicines, adverse reactions and adverse events, especially the examples of human exposure and allergic reactions discussed above, should also be reported to pharmaceutical companies and the regulatory authority. The safety and efficacy of stock remedies should be continuously monitored. The responsibility of applicants does not stop once the product is registered. To monitor any trends or changes in the quality, safety and efficacy of a product, consumers should report any suspicions to the registration holder.

5.2.9 Precautions

The package insert should contain precautions that explain how to use the stock remedy safely.

5.2.9.1 Precautions must be included and appear under warnings

The requirement to include precautions on the package insert, listed under warnings, was the most compliant section of the precaution requirements, although only 67.92% (108) of the package inserts complied. Three package inserts were considered to be partially compliant for the reason that, while all 3 contained precautionary information under the heading for

precautions, it appeared further below in the text and not directly under the warnings section. No precautions were presented in 48 of the package inserts.

5.2.9.2 Precautions must be bulleted

The requirement that precautions should be bulleted was adhered to by 92 (57.86%) package inserts. Considering that only 108 package inserts had precautions, and only 92 of these were bulleted, the remaining 16 package inserts that had precautions did not bullet them.

5.2.9.3 Advice on protective clothing

Precautions should include the statement that users should wear protective clothing, masks, gloves, boots, and so on, according to hazard standards.

A high number, 132 of 159 package inserts (83.02%), provided no advice on the wearing of protective gear. This advice was supplied for only 23 package inserts. While there is no direct correlation between the toxicity statement of the stock remedy and the wearing of protective gear, it can be assumed that stock remedies with a toxicity statement should provide advice on protective gear. Only 10 package inserts that had toxicity statements ('caution', 'poisonous', 'harmful', 'toxic') had corresponding advice on protective gear. Four of the package inserts were partially compliant because advice on protective gear was included in the text but not under precautions.

The use of PPE is important, especially during the mixing and application phase when users are in contact with the concentrate (MacFarlane et al., 2013). The PPE ultimately used includes masks, goggles, gloves, boots, overalls and gloves and is ultimately selected based on the type of pesticide, the circumstances under which it is used, and the type of application involved. While advising the use of PPE is not always a guarantee for effective use and protection, PPE considerably limits exposure.

5.2.9.4 Avoid contact with the stock remedy

It is required that users are advised to avoid contact with the product with the skin, eyes and mouth. The results indicate that the precaution to avoid contact with the stock remedy is not adequately addressed by registration holders, as the majority of the package inserts (64.15%) did not contain this precaution, posing a risk to consumers of unsafe use of the stock remedy.

5.2.9.5 Do not eat, drink or smoke while handling

The Labelling Guideline (2018) requires the package insert to caution users that they should not eat, drink or smoke while handling the product. This requirement was adhered to by only 25.79% of the evaluated package inserts, which is not adequate in terms of safety information provided to the user. The inadequate level of compliance may result in the ingestion of harmful product when users eat, drink or smoke during the handling of the stock remedy. Moreover, flammable stock remedies should be kept away from any open flames or sources of ignition. While users are discouraged from smoking to prevent the transfer of product between their hands and faces, smoking is also advised against due to the flammable hazard.

5.2.9.6 Disposal instructions

The requirement to fulfil in terms of disposal conditions is that the package insert should provide caution to users to dispose of empty containers in accordance with the National Environmental Management Waste Act regulations (Act 59, 2008). The objective of Act 59 of 2008, and therefore of the inclusion of the precaution, is to protect the environment by minimising its contamination.

Only one of the package inserts contained the exact wording as required by Act 36 of 1947, in that it made mention of the specific Act, Act 59 of 2008. The reason for this extremely low compliance may be because this requirement only came into effect in November 2018, when the Labelling Guideline was published. Prior to that, it was sufficient to state safe disposal information without referring to the specific Act. It may therefore be possible that most applicants have not yet revised their product information in the marketplace with the updated statement. Another reason for the failure to mention the specific Act may be that many stock

remedies sold in South Africa are also exported to the African market, and registration holders may prefer to state that disposal should take place according to local regulatory requirements, instead of referencing the applicable South African Act.

While 54.72% did contain safe disposal instructions without mentioning the Act, it is the 44.65% of package inserts that included no instructions at all that create a bigger concern. Without instructions on how to safely dispose of empty stock remedy containers or unused stock remedies, there is a risk that the environment may be contaminated.

5.2.9.7 Precaution on future use of empty containers

A precautionary measure should be included that empty containers should not be stored for future use or should not be reused for any other purpose (Act 36 of 1947). The majority of package inserts (54.08%) did not contain this precaution. The level of compliance is not adequate when considering the safety and health implications; for instance when empty pesticide containers are used for drinking water. In many countries, including South Africa, a practice exists to reuse empty pesticide containers for household purposes; for example, to store water or food (Rother and Jacobs, n.d.; Huici et al., 2017). As empty containers may contain residues of pesticides, there is a risk that when these containers are reused for any other purpose, it may cause serious health risks to consumers.

5.2.9.8 Precaution on contamination of water sources

Act 36 of 1947 instructs registration holders to include the precaution that warns against the contamination of rivers, dams or water sources with either containers or the product itself. The majority of the package inserts (59.75%) did not provide any precaution to users to avoid contamination of the environment, adding to the lack of safety information of package inserts.

5.2.10 Directions for use

For each stock remedy, directions for use should be included, together with the statement that the product should be used only as directed. As stipulated by the requirements, 158 (99.37%)

of the package inserts did include directions for use, and 154 (96.86%) fulfilled the additional requirement to state that the stock remedy should be used only as directed. In 1 package insert (0.63%), while it did contain directions for use, it was not clear what the route of administration should be. Only 5 package inserts (3.14%) did not state that it should be used only as directed. While there was a very high level of compliance in that the package insert provided directions for use, differences in the quality between package inserts were observed, as some contained a lot of detailed information while others provided very little.

5.2.11 Efficacy in the case of anthelmintics

For anthelmintic stock remedies, Act 36 of 1947 expects registration holders to include the anthelmintic code and the efficacy tables of the endoparasite species that it is effective against, as well as the following statement: 'The list contains the parasite species tested. This remedy may also be effective against other species. For more information, consult your veterinarian.'

As with antimicrobials and external pesticides, anthelmintic resistance is a problem in the use of veterinary medicines. In an attempt to overcome this issue, anthelmintic codes are included on anthelmintic stock remedies. The reasoning is that when a user has been using the active ingredients of a specific group, and the remedies are no longer effective, they should switch to another group (Shalaby, 2013). Examples of the different groups and classes of anthelmintic stock remedies are listed in Table 3 below.

Table 3: Ruminant anthelmintic coding in South Africa (Anipedia, n.d)

Group Code	Class	Examples
1	Macrocyclic lactones	Ivermectin, abamectin, moxidectin
2	Benzimidazoles and Probenzimidazoles	Fenbendazole, albendazole, oxfendazole, triclabendazole
3	Imidazoles	Levamisole
4	Halogenated salicylanilides	Closantel, niclosamide, rafoxanide
5	Nitrophenols	Nitroxinyl
6	Sulphonamides	Clorsulon
7	Organophosphates	Trichlorfon, dichlorvos
8	Isoquinoline	Praziquantel
9	Miscellaneous	Piperazines, bunamidine, epsiprantel

The anthelmintic coding was provided in only 62.90% of the package inserts, which may not be considered sufficient in the attempt to avoid resistance.

5.2.12 Presentations

Registered pack sizes should correspond to the application for registration. A high compliance rate of 91.82% among the package inserts was observed. The inclusion of the available presentations, however, is not relevant to the safety and efficacy information. It is also not possible to confirm whether the presentations listed correspond to the registration holder's registered pack sizes or whether all the listed pack sizes are indeed marketed.

5.2.13 Name and address of the registration holder

The name and address of the registration holder should appear on the package insert. While this information may seem administrative, it does play an important part in the safe and

effective use of medicines as any suspected lack of efficacy or adverse events should be reported to the registration holder. The requirement was fully complied with by 153 (96.22%), the remaining 6 package inserts (3.77%) only partially complied, but there were no package inserts completely lacking the information. Of the 6 partially compliant package inserts, 3 contained the name at the top of the package insert but did not indicate that it was the registration holder. They did include the name and address, though. The other 3 package inserts were found on the company website, and the name of the company but not the address is on the package insert. In these cases, as the address was available on the particular website, they were considered partially compliant.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Introduction

The rational use of stock remedies has various benefits, such as increased efficacy, decreased potential for adverse events, reduced residue exposure and reduced active ingredient resistance. While veterinary stock remedies play an imperative role in the safekeeping of animals and in ensuring food security, the incorrect or indiscriminate use of these medicines can be disastrous for the animals, users, consumers and the environment. Veterinary stock remedies are not ordinary consumer products, and it cannot be assumed that most consumers are able to make decisions about the safe and effective use of these products if they are not adequately advised. When these stock remedies are obtained without the supervision of a veterinarian, the information available to the user should be of such quality and usefulness that they are able to make an active, informed decision in treatment programmes. The current study was undertaken to evaluate the compliance of veterinary stock remedy package inserts with the prescribed regulatory authority guidelines.

6.2 Conclusion

The following conclusions were drawn from the study. While the analysed package inserts were deficient in numerous aspects, of particular concern was deficient information relating to the safe and effective use of the veterinary stock remedies, including unclear storage indications and lack of warnings and precautions. The conclusion that the safe and appropriate use of medication was compromised due to the lack of adequate information concurs with that of Al-Aqeel (2012), who found that the information relevant for the safe and appropriate use of medication was not uniformly provided in the package inserts. The majority of the package inserts in the representative sample were compliant with the required headings. Deficiencies were, however, notable in the quantity and quality of the information presented under the stipulated headings. Thus, animals, users, consumers and the environment are being exposed to the risks associated with the poorly informed or uninformed use of veterinary stock remedies.

6.3 Limitations

This study has four main limitations that should be considered when interpreting the results. First, the study did not evaluate whether the information presented on the package insert is comprehensible and understandable to the user. Secondly, when considering the vast number of stock remedies, only a small number of package inserts were analysed as many categories like vaccines, hormones, supplements and companion animal products were excluded. As a result, it may be possible that including the other medicine categories could lead to different findings. A further limitation was the absence of previous studies on the package insert information of veterinary drugs. While it was difficult to make comparisons, this study is attempting to indicate the presence of incomplete package insert information. Lastly, it was only later realised that the IDR is only available to veterinarians and not to the public. The study thus makes the assumption that the information in the IDR available to veterinarians corresponds to the product information accompanying the product that is available to the customer.

Despite these limitations, this study represents the first attempt to evaluate package insert compliance with regulatory guidelines in South Africa. The results presented in this study demonstrate the necessity to improve the written information contained in package inserts that are provided to users. While the findings of this study do not mean that the shortcomings will be fully resolved, it is hoped that they will stimulate further research on the effects of content on package inserts on medicine usage and safety.

6.4 Recommendations

Medicinal information on labels and package inserts is a major source of knowledge for consumers as they attempt to balance the risks and benefits of drugs and administer them safely.

The findings from this study indicate that more should be done to promote the safe and effective use of stock remedies through the information provided with the product. Pharmaceutical companies (or the registration holder) and regulators have an obligation to sufficiently inform users, not only for the safety of the animals but also the users and the global population.

Pharmaceutical companies are advised to follow the requirements and formats stipulated by regulatory authorities. To avoid medication errors due to deficient instructions, it is recommended that existing package inserts be improved according to best practices for information and content design. Users should be encouraged to read package inserts, and this is easier when the content and layout is user-friendly. Making use of standard templates and consistent layouts will combat the difficulty that users have in readily finding information.

It is recommended that registration holders make use of the specified layout and that warnings and precautions appear at the top. This will ensure that users will find the warnings and precautions on medications and read them before use. Van Dijk et al. (2014) agreed that improvements to package inserts, such as a generic structure with transparent and concise headings, enhanced their visibility and use by users. By making use of the generic template, users will become accustomed to the layout and know where to search for information.

As commonly used antibiotics in livestock in the food production industry contribute to the development of antimicrobial resistance in animals as well as humans (Falowo and Akimoladun, 2019; Founou et al., 2016), users should be made aware of the consequences, and a statement to that effect should be added to the package insert. Such a proposed statement should typically state that antimicrobial resistance may develop to antimicrobial preparations, especially when such products are used outside of their prescribed instructions. In the event that antimicrobial resistance is suspected, veterinary expertise should be sought.

Resistance is a problem not only with the widespread use and overuse of antimicrobials but also with anthelmintics (Beyene, 2015). As with antimicrobials, the growing problem of anthelmintic resistance results from unnecessary use of anthelmintics, inappropriate dose and inadequate duration of therapy. Pharmaceutical companies should oblige with the regulatory requirements to include the anthelmintic coding on the packaging. Furthermore, awareness should be created for users to encourage them to make use of the anthelmintic coding to reduce the emergence of anthelmintic resistance.

For storage conditions, registration holders are urged to update their storage instructions to include specific temperature ranges, and special instructions where applicable, under which medicines should be stored.

Furthermore, it is recommended that registration holders include clear toxicity statements for stock remedies, together with the appropriate protective measures to take in such cases. While more can be done in general to advise users on personal protective equipment, it is especially important where the product is classified as a potential hazard.

The disposal instructions on stock remedies should be updated to include well-defined and detailed directions on how to discard of empty containers and excess product in such a manner that there is no harm to the user or the environment.

Finally, and importantly, registration holders should improve the quantity and quality of information supplied to users pertaining to the risk of human exposure to stock remedies, as well as the information on allergic reactions. Information that should be communicated should include typical signs and symptoms that can be expected in the event of accidental exposure or allergic reaction, as well as the measures to take in such an occurrence. Users should be advised when veterinary or medical attention should be sought, and it will be beneficial to include any specific measures that should be taken by a medical professional.

6.5 Recommendations for future research

Further recommended research relating to this study should include the assessment of:

- Users' knowledge on the proper usage, storage and disposal of veterinary stock remedies.
- The veterinary stock remedy package insert compliance of other medicines, including steroids and vaccines.
- The veterinary stock remedy package insert compliance of imported medicines.

These studies will provide further information that will improve the knowledge about veterinary stock remedy package insert compliance, animal and user safety and recommendations for improvement.

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ANNEXURES

Annexure A: Data collection tool

Product Number			
Source			
Generic Name			
Dosage Form			
Strength			
Product Category	**Endectocide** ☐	**Endoparasiticide** ☐	**Ectoparasiticide** ☐
	Antimicrobial ☐		
Target Species	**Cattle** ☐	**Sheep** ☐	**Goats** ☐
	Poultry ☐	**Pigs** ☐	**Game** ☐
	Horses ☐	**Other** ☐	

	Regulatory Requirements	**Non-Compliant 0**	**Partially compliant (0,5)**	**Compliant (1)**	**Not Applicable**
1.	**For (external) animal use only**				
	The words "For (external) animal use only" must appear at the top of the package insert				
2.	**Trade name**				
	The trade name or name of the remedy should appear on the package insert				
3.	**Registration number**				
	The registration number should be stated on the package insert				
	Registration number should be followed by the words (Act 36/1947)				
	The registration number should appear directly below the trade name				
4.	**Claims or indications**				
	Claims or indications for the product				
5.	**Toxicity Statement**				
	Toxicity indication according to poison classification				
6.	**Storage instructions**				
	Storage instructions should include specific storage requirements (i.e. and should between 2 °C and 8 °C or store at or below 25 °C). The use of terms like "ambient temperatures" or "room temperature" is not acceptable.				
7.	**Composition**				
	Only the active ingredient need to be stated. The quantity of the active ingredient shall be stated as g/kg or ml/l				
8.	**Warnings**				

	Warnings are included				
	Warnings should be bulleted				
	The withdrawal period(s) should be clearly indicated and should appear as the first warning statement				
	Do not mix product with other medications				
	Symptoms of human poisoning or accidental exposure, first aid treatment and note to the physician				
	Symptoms of allergic reactions/anaphylaxis				
	Keep out of reach of children, uninformed persons and animals				
	Although this remedy has been extensively tested under a large variety of conditions, failure thereof may ensue as a result of a wide range of reasons. If this is suspected, seek veterinary advice and notify the Registrar				
9.	**Precautions**				
	Precautions are included and should appear below warnings				
	Precautions should be bulleted				
	Wear protective clothing, masks, gloves, boots, etc. according to hazard standards				
	Avoid contact of the product with skin, eyes and mouth				
	Do not eat, drink or smoke whilst handling the product				
	Dispose of any containers, disposable equipment and any other waste after use in accordance with National Environmental Management: Waste Act, 2008 (Act No. 59 of 2008)				
	Do not store unused containers for future use				
	Do not contaminate rivers, dams or any water sources with containers or waste				
10.	**Directions for use**				
	The words "Use only as directed" must be stated				
	Directions for use should be available and where applicable should be specific for the				
11.	**Efficacy in the case of anthelmintics**				
	Anthelmintic code				
	Efficacy tables				
	The words “The list contains the parasite species tested. This remedy may also be effective against other species. For more information consult your veterinarian”				

12.	**Presentations**				
	Available pack sizes are listed				
13.	**Registration holder**				
	Name and address of the registration holder				
	Total:				