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There is no doubt that the control of medicinal substances limits and complicates the free market distribution of medicines. Yet medicinal substances are not items of ordinary commerce. Whilst they can be life-saving and beneficial in many ways, they are also toxic and dangerous in their pharmacological action. Thalidomide is a good example. Today the development and testing of new medicinal substances has reached a high degree of sophistication and thalidomide types of drug epidemics are unlikely. The more likely threat today is far more insidious. It has to do with counterfeited medicines, medicines with undeclared substances, registration fraud, sale of illegal medicines, etc. The consequences could be catastrophic.

The control of veterinary drugs in South Africa originated in 1947 when the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No 36 of 1947) was promulgated. In terms of this Act the Department of Agriculture was given the responsibility of regulating the control of stock remedies. The intention of this Act was to ensure that farmers had access to products intended for use in farm animals (stock) and that these products conformed to basic safety, efficacy and quality standards. The necessary infrastructure was created to ensure that this could be achieved.

Products were evaluated and registered (licensed) for sale directly to farmers based on the principle that the farmer would be able to diagnose the disease condition that affected his stock and would therefore be able to choose the correct remedy for the condition. Strict conditions for the labelling and use of the remedies were put in place. The scope of control slowly increased as products intended for use in pets and companion animals were brought onto the market.

In 1965 the Medicines and Related Substances Control Act, 1965 (Act No. 101 of 1965) for the control of human medicines was promulgated. Veterinary medicines were not included in the Act. Between 1965 and 1977 the numbers and sophistication of veterinary medicines proliferated. They were not controlled by either Act as they were not intended to be sold to farmers or the public and therefore did not fall within the terms of reference of Act 36. They also did not fall within the responsibility of the Medicines Control Act. This led to an unacceptable situation and in 1977 the Department of Health added the definition of a veterinary medicine to Act 101.

However, it was not until 1979 that the definition of a medicine was amended to include a veterinary medicine that Act 101 was enabled to control veterinary medicines.

In 1983, all companies that could prove that they were selling a veterinary medicine by producing an invoice were allocated an application number (83/xxx). This application number entitled the applicant to continue to sell the veterinary medicine. In order to avoid a conflict between the Department of Health and the Department of Agriculture, the schedules to Act 101 were written to exempt any substance from the schedules when it was registered in terms of Act 36. Likewise Act 36 was amended to exclude all substances controlled in terms of Act 101.

It is important that medicine users understand and appreciate the reasons behind the need for control of medicines. Animal health care in South Africa covers a broad spectrum of requirements due to the diversity of:

- the vertebrate species, e.g. dogs, cats, horses, cattle, sheep, pigs, poultry, wildlife, fish, etc.;
- their purpose, e.g. production, aquaculture, companion animals, animals used in the entertainment industry, etc.; and
- the inter-relationship of human and animal health in a wide range of environments.

Besides promoting animal health, the provision of veterinary services covers aspects such as food production and security. The legislation also acknowledges the diversity of use of veterinary drugs, including the manipulation of animal behaviour and euthanasia of animals in the interest of their welfare.

To enable this function, the National Department of Agriculture has a responsibility to ensure that farmers have access to stock remedies for disease control and improved food production and to safeguard man by monitoring residues in products of food-producing animals, preventing zoonoses and controlling notifiable diseases. The Department of Health is responsible for controlling veterinary medicines in such a way as to ensure that they are produced, distributed and used without compromising human and animal health; and is also responsible for the international narcotic and psychotropic drug control in terms of international conventions.
Compliance to the Act and Regulations is mandatory and therefore knowledge of the requirements is essential for all practitioners, pharmacists and veterinarians. When veterinarians are discussed this must be understood to include all persons registered in terms of the Veterinary and Para-veterinary Professions Act, 1982 (Act No. 19 of 1982).

It is the objective of this booklet to inform all veterinarians and in particular veterinarians in clinical practice of the requirements for control and management of veterinary medicines.

In this respect the booklet will deal with medicines in general and veterinary drugs in particular. Veterinary drugs in this context consist of veterinary medicines as defined by the Medicines and Related Substances Control Act, 1965 (Act No. 101 of 1965) (Act 101) and stock remedies as defined in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No. 36 of 1947) (Act 36).

Since the booklet was first published the following major changes were introduced into South African legislation:

- The Medicines Act (101 of 1965) was amended to repeal the Medicines Control Council, and replaced the council with a regulatory agency named the South African Health Products Regulatory Authority.
- The Department of Health's attempt to bring a veterinary dispensing and/or compounding licence was deemed unfair by a Constitutional Court Decision.
- The regulations to the Medicines Act (Act 101 of 1965) were amended with impact on veterinary compounding, keeping of registers, the introduction of complementary medicines control processes, control processes for medical devices and *in vitro* diagnostics (IVDs).
- The Veterinary Profession was granted an exemption from the pricing regulations of Act 101/1965, on condition that differential pricing was not allowed.
- The rules to the Veterinary Act (Act 19 of 1982) were amended to bring in good dispensing practice for veterinary practices.
- The Veterinary Council (SAVC) began registering and monitoring the basic facilities in veterinary practices.
- The Stock Remedies Act (Act 36 of 1947) is in the process of amendment to bring in more control over certain drugs such as the antimicrobial agents.
- The Foodstuffs, Cosmetics and Disinfectants Act (Act 54 of 1972) was amended to reduce the default MRL (maximum residue level) from 0.05 mg/kg to 0.01 mg/kg.
- South Africa was granted observer status on the VICH, the international body looking at harmonising technical standards for the registration of veterinary medicines. Through this process, the country has agreed to follow VICH guidelines for the registration of veterinary medicines.
- The constitutional court ruled that marijuana may be used for personal use at a private residence only. The medicinal use of marijuana, related cannabinoids and oils thereof remain illegal for general sale and prescription.
A number of Acts of parliament are involved in the control of veterinary pharmaceuticals and remedies. Certain Acts are concerned with the control of the pharmaceutical or chemical substances that are used for therapy or control of disease conditions, infections and parasites.

Other Acts are concerned with the control of persons that would be entitled to use the substances.

There are further Acts that control the same substances that are controlled by the above Acts but that are used for purposes other than therapy or control of disease conditions. These Acts include those that control agricultural remedies, disinfectants, feedstuffs and foods.

**MEDICINES**

The scope of control of medicines in terms of the Medicines and Related Substances Control Act, 1965 (Act No. 101of 1965) (Act 101) as amended has been broadened.

The reasons that this has been done is to give medicines control improved capacity for effective control and thus ensure the confidence of the prescriber and protection of the patient.

The Act provides, amongst others, for:

- The registration of medicines for human and animal use;
- The establishment and constitution of the South African Health Products Regulatory Agency;
- The control of medicines, complementary medicines, scheduled substances, medical devices and in vitro diagnostics for human and veterinary use;
- The provision of prohibition of the sale of unregistered medicines;
- The import of unregistered medicines under special Section 21 permit;
- Labelling to be approved by the SAHPRA Board;
- Prohibition of bonusing and sampling;
- Licensing of persons to compound, dispense or manufacture medicines (with the exception of veterinarians following a constitutional court decision); and
- The establishment of a pricing committee (applicable only to human medicines), and
- The regulation of the purchase, and sale of medicines by manufacturers, wholesalers, pharmacists and persons licensed to dispense medicines.
- The regulation of advertising or promotion of human and veterinary medicines;
- Reporting of adverse drug events (ADEs) for human and veterinary medicines.

In terms of this Act the definition of a medicine includes a veterinary medicine.

A **veterinary medicine** means any substance or mixture of substances, other than a stock remedy or farm feed to be registered in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No. 36 of 1947) used or purporting to be suitable for use or manufactured or sold for use in connection with vertebrates, for the treatment, diagnosis, prevention or cure of any disease or unhealthy condition, for the maintenance or improvement of health, growth, production or working capacity, for the lasting capacity of carcasses, for curing, correcting or modifying behaviour or for the humane euthanasia, but does not include feedstuffs.

A **medical device** means any instrument, appliance, material, machine, apparatus, implant or diagnostic reagent used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification, monitoring or prevention of disease, abnormal physical or mental states or the symptoms thereof; or restoring, correcting or modifying any somatic or psychic or organic function; or the diagnosis or prevention of pregnancy and which does not achieve its purpose through chemical, pharmacological, immunological or metabolic means in or on the human body but which may be assisted in its function by such means; or declared by the Minister by notice in the Gazette to be a medical device, and includes any part or an accessory of a medical device;

A **complementary medicine** means any substance or mixture of substances that originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council, and is used or purporting to be suitable for use or manufactured or sold for use in maintaining, complementing, or assisting the innate healing power or physical or...
mental state, or to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state, of a human being or animal, and is used as a health supplement, or in accordance with those disciplines as determined by Council, or (d) is declared by the Minister, on recommendation by the Council, by notice in the Gazette to be a complementary medicine (At present although no veterinary complementary medicines are registered under Act 101/1965, they be registered as such in the future).

STOCK REMEDIES

The control of stock remedies is carried out in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No. 36 of 1947) (Act 36). This Act is in the process of amendment and the final draft has been published for comment.

The Act provides, amongst others, for:

- The appointment of a Registrar;
- The registration of stock remedies;
- The regulation or prohibition of the importation, sale, acquisition, disposal or use of stock remedies;
- The designation of technical advisors and analysts;
- The appointment of committees, and
- The appointment of assignees who are bodies or people delegated to perform certain functions outside the Department of Agriculture.
- The regulation of advertising or promotion of stock remedies.
- Reporting of adverse drug events (ADEs) for stock remedies.

A stock remedy means a substance intended or offered to be used in connection with domestic animals, livestock, poultry, fish or wild animals (including wild birds) for the diagnosis, treatment, prevention or cure of any disease, infection or other unhealthy condition, or for the maintenance or improvement of health, growth, production or working capacity, but excluding any substance in so far as it is controlled under the Medicines and Related Substances Control Act, 2002.

The products generally registered as stock remedies include (albeit not limited):

- Selected antimicrobials including antimastitic remedies and anticoccodial remedies;
- Growth promoters, including growth promoting antimicrobials;
- Anthelmintic and ectoparasitic drugs;
- Vitamins and mineral formulations for the treatment and prevention of disease;
- Probiotics, laxatives and similar;
- Vaccines.
- Selected complementary medicines

Note:

As evident from the definition, all substances that can have a medicinal effect is controlled by the SAHPRA unless registered as a stock remedy.

The major difference between the Medicines Act and the Stock Remedies Act is level of knowledge required for use. The use of veterinary medicines are restricted to veterinary prescription, while stock remedies are typically over-the-counter drugs.

VETERINARIANS

The control of the activities of veterinarians is carried out in terms of the Veterinary and Para-veterinary Professions Act. 1982 (Act No. 19 of 1982).

The Act provides, amongst others, for:

- The establishment, powers and functions of the South African Veterinary Council;
- The registration of persons practising veterinary professions and para-veterinary professions;
- The control over the practise of veterinary professions and para-veterinary professions;
- The control of veterinary practice standards including dispensing practice
- Matters connected therewith.

In terms of Section 34 of the Act a veterinarian may personally compound or dispense any medicine that is prescribed by himself or by any other person with whom he is in partnership of whom he is associated as a principal or an assistant or a locum tenens. This right is supported by Section 22A of Act 101. The veterinary act does limit the rights of the veterinarian:

- Veterinarians who does not register a practice or consultancy or work as a member of a registered practice may not use, sell of dispense medication.
- A veterinarian may not dispense drugs that are used for veterinary restricted procedures such as general anaesthesia.
- A veterinarian may not dispense any game capture (chemical immobilisation) drugs.


• A veterinarian may not run an open pharmacy
• A veterinarian is not allowed to treat people, as this is outside their scope of practice.

PHARMACISTS

Pharmacists and their activities are controlled in terms of the Pharmacy Act, 1974 (Act No. 53 of 1974).

The Act provides, amongst others, for:

• The establishment of a South African Pharmacy Council;
• The training and registration of pharmacists, pharmacist interns, pharmacy students, unqualified assistants, and pharmaceutical technicians;
• To provide for the control of the practice of the pharmaceutical profession.
• Registration of pharmaceutical places of practices

In this Act the acts specially pertaining to the profession of a pharmacist are;

• The manipulation, preparation or compounding of any medicine or medicinal or chemical substance for sale or supply as a medicine;
• The compounding or sale or supply of any medicine on the prescription of a medical practitioner, dentist or veterinarian;
• The manufacture or supervision of the manufacture of any medicine;
• The furnishing of advice to any person with regard to any medicine supplied to him.

FOODSTUFFS, COSMETICS AND DISINFECTANTS

Foodstuffs, cosmetics and disinfectants are controlled in terms of the Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972). This Act is intended to control the sale, manufacture and importation of these substances and to provide for incidental matters.

The importance for veterinarians is the fact that the Act controls certain food additives and disinfectants that may also fall under separate control in terms of the other Acts. The Act is also responsible for the establishment and publication of maximum limits for veterinary medicine and stock remedy residues that may be present in foodstuffs and for the approval of withdrawal periods.

BIOLOGICALS AND SUBSTANCES OF ANIMAL ORIGIN

The import and export of biologicals for use in animals and medicines and stock remedies that contain substances of animal origin are controlled in terms of the Animal Diseases Act, No 35 (Act No. 35 of 1984).

It is important to remember that all medicines whether for human or animal use that contain substances of animal origin and biologicals that are used in animals must have a permit from the Directorate Animal Health to import such medicines.

The Animal Diseases Act also has a list of controlled diseases, and through this list can restrict the treatment or preventative measures towards these controlled diseases e.g. vaccination of poultry against avian influenza is not allowed at present even though vaccines are available.

Note:

In addition to the main acts of control mentioned above, the use medicines of are also impacted upon by other legislation such as the Consumers Protection Act, The Meat Safety Act, Hazardous Substances Act, National Environmental Safety Acts and various municipal bylaws. The following booklet will not focus on these legislation.
APPLICATION FOR REGISTRATION

The application for registration of veterinary products is made either with Act 101/65 for veterinary medicines or Act 36/47 for stock remedies.

The requirements for registration are described in within these Acts, their regulations, as well as in guidelines.

Medicines (Act 101)

The Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) requires that an application for registration of medicines, including veterinary medicines must be submitted in a prescribed format.

The guidelines for veterinary medicines must be read in conjunction with the general guidelines for the application for registration of medicines.

The guidelines for veterinary medicines contain the following information:

- Functions and procedures of the Veterinary Clinical Committee
- Functions and procedures of the Veterinary Products Policy Committee
- Application and information requirements
- Pharmaceutical and analytical requirements
- Preclinical requirements
- Clinical efficacy requirements of veterinary pharmaceuticals
- Efficacy requirements of veterinary biologicals
- Safety of veterinary pharmaceuticals
- Safety of veterinary biologicals
- Bioavailability and bio-equivalence requirements
- Clinical Trials Application And Requirements
- Adverse Drugs Reactions
- Events Recalls
- Veterinary drug residue depletion studies

Stock remedies (Act 36)

Application must be made on the prescribed application form in triplicate. This must be accompanied by a covering letter in duplicate. Details of the application, that is new application, application for amendment, application for a “daughter” registration, etc., must be outlined briefly. Duplicates of all necessary letters of consent, that is permission for “daughter registration” or permission to use another company’s product name on the label, must accompany the covering letter.

REGISTRATION APPLICANT

Medicine (Act 101)

Any person residing and doing business in the Republic may make an application for the registration of a medicine.

The application shall include the particulars of the person who shall have appropriate knowledge of all aspects of the medicine and who shall be responsible for communication with the council.

Stock remedy (Act 36)

Only a locally registered company, a RSA citizen or a legal body that is registered in RSA may apply for the registration of stock remedies. The person that is legally responsible for and signs the application form must be identified and should act as the contact person. However, if a different person is responsible for being the contact with the regulatory office this contact person must have a signed letter of permission to act on the applicant’s behalf. The contact person must do all queries from a registration holder, particularly in the case of companies.

REGISTRATION EVALUATION PROCESS

Approval for registration of veterinary medicines and stock remedies is based on the evaluation of efficacy, safety and quality. Efficacy must be demonstrated in controlled dose finding and dose confirmatory studies. These studies must be performed according to scientifically acceptable procedures and in adequate numbers of animals.

Safety evaluation includes safety to the target animal, consumer and handler of the drug. For certain products, such as dips, information on environmental safety may also be required.

Preclinical safety studies in laboratory animals are performed to determine the acute, subacute and chronic toxicity, as well as the mutagenicity, carcinogenicity, embryotoxicity teratogenicity and immunotoxicity characteristics of the product. These studies are required.
for calculation of maximum residue limits (MRL’s) in animal food products and for designing residue depletion studies in the determination of withdrawal periods in food producing animals following administration.

Registration of generic compounds based on bio-equivalence is accepted. Guidelines for bio-equivalence evaluation of generic compounds and new formulations are available to applicants and are the same for both regulatory authorities.

Efficacy and safety data not generated in South Africa are accepted for most products, except for anthelmintics and acaracides registered as stock remedies or any veterinary medicine deemed necessary by the Veterinary Clinical Committee (VCC) of the SAHPRA. Local studies based on the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines are accepted by Act 36/1947. According to this guideline, these studies may use indicator worms which are those worms most resistant to the anthelmintic so that not all the worms claimed for have to be included in these studies.

In the case of veterinary medicines the safety and efficacy are evaluated by the VCC and quality by the Pharmaceutical & Analytical Committee of the SAHPRA. All veterinary medicines are approved by the SAHPRA on the recommendation of the VCC. The Registrar and Secretariat of Act 101/65 administer the decisions made by the SAHPRA.

The efficacy, safety and quality of stock remedies are evaluated by Technical Advisors appointed by the Minister of Agriculture within the Department of Agriculture. These advisors are responsible for making final recommendations to the Registrar. These advisors are supported by external Technical Advisors appointed by the Minister for their technical expertise. In addition, the Registrar has the power to appoint consultants as Technical Experts. These consultants also advise the internal Technical Advisors in the Department.

**CONDUCT OF CLINICAL TRIALS**

**Medicine (Act 101)**

The conduct of clinical trials with any unregistered drug in South Africa is under the control of Act 101/65. The Medicines Control Council has issued a guideline that specifies the following:

- Scope of the guideline
- Responsibilities
- Guideline for the conduct of clinical trials
- Data handling
- Statistics
- Data verification

**Stock Remedies (Act 36)**

Products or active ingredients already registered as stock remedies or veterinary vaccines are under the control of the Registrar Act 36. For these products, the technical managers appointed under Act 36/47 approve clinical trials. Application for approval of such trials must be made prior to the start of the trial.

Approval of all trials of products for use in food producing animals must also be obtained from the Directorate of Animal Health in terms of Act 35.
Medicines are substances that require professional knowledge to ensure their effective and safe use. It is for this reason that the Act controlling medicines are written to control the distribution and use of the substances.

It is also important that the control is vested with authorities that have the resources and the will to enforce the correct supply and use.

GUIDELINE FOR THE CATEGORISATION OF MEDICINES IN THE SCHEDULES

The Medicines and Related Substances Control Act, 1965 (Act No. 101 of 1965) describes various levels of control, which is intended to ensure the safe supply of medicines to the public but also to restrict the supply of substances, or drugs, which are dangerous or harmful. All applications for registration of medicines are subject to the scheduling process. Substances may also be considered for rescheduling to higher schedules when it is found to be less safe than originally believed or when reports of abuse are received.

Rescheduling to a lower schedule can be considered when additional safety data are submitted or if it is in the interest of the public. The Scheduling Committee uses both the general and specific guidelines for the categorization in the schedules when allocating a schedule. The general guideline focuses on the nature of the product, its intended use and public health consequences whereas the specific guideline focuses on the conditions for sale to the public and the level of professional supervision required in terms of Section 22 A of the Act.

GENERAL GUIDELINES FOR CATEGORIZATION IN THE SCHEDULES

A. Safety

• Inherent safety characteristics of a medicine/substance. In general, the more toxic the compound, the higher the schedule becomes. Also substances with a small therapeutic index.
• The nature and severity of side effects that may require close monitoring or further investigation.
• The number and severity of contraindications in certain conditions and interactions with other drugs.

• The existing scheduling status of a compound that is contained in a medicine already registered under the same or different pharmacological classification.
• Long-term safety.

B. Professional Advice / Supervision

• The complexity or severity of the condition for which the medicine is indicated.
• Medicines used for complex disease and/or severe life threatening conditions require advanced clinical therapeutic knowledge. Access is restricted through prescription or use by the appropriate health professions and the duration of therapy limited to permit re-evaluation.
• Necessity for an accurate diagnosis. The access of medicines used for the treatment of disease conditions that require an accurate diagnosis are restricted through prescription or use by the appropriate health professions.
• Requirement for maintenance of treatment. Specific accessibility and availability of medicines or substances used chronically.
• Dosage form and complexity of route of administration. The use of formulations or dosage forms of medicines which require specialized knowledge or skill are restricted to appropriate health professions. Parenterally administered drugs are usually scheduled.
• The effect of overuse or indiscriminate use due to the absence of professional advice/monitoring (OTC).
• The need for the availability of professional advice when the products are supplied. (OTC)

C. Control

• Requirements in terms of international psychotic and narcotic drug conventions. Substances with an abuse or habit forming potential are placed in higher schedules (5 to 8).
• The possibility of abuse or misuse of the substance.

D. Public Health Considerations

• The availability of certain drugs for use during emergencies may be excluded from higher schedules under specific conditions.
• Essential needs of society. The need for availability
of essential medicines by society will necessitate the categorization into lower schedules.

• Socio-economic factors may be considered for example the need for drugs to be available for professions practicing primary health care.
• Demographic and epidemiological factors may be taken into account. (e.g. travelling of people to malaria areas)
• Education /public perceptions that may lead to incorrect/ correct use.

E. Usage

• Safety to the handler of the medicine. Reduced accessibility or increased control measures will be afforded to substances with increased risk to the handler of the substance.
• Safety for the consumer of animal products viz. withdrawal periods. Veterinary medicines with an extended withdrawal period and in conflict with standard management practices will require increased control measures to ensure compliance and safety to the consumer.
• Environmental safety. Substances that are potentially hazardous to the environment will be placed into a higher schedule category.
• Special storage procedures. Specialized storage conditions (e.g. extreme temperatures) may necessitate control by certain professions.
• Packaging and labelling that may have safety implications. (OTC)

F. International Drug Regulation

• Scheduling status in other countries, including international conventions such as the Single Convention on Narcotic Drugs.

SPECIFIC GUIDELINES FOR THE CATEGORISATION IN THE SCHEDULES

This is a summary of the conditions under which medicines and scheduled substances may be sold and also serves as a guide to understanding the schedules to the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965), as amended.

This section also lists specific criteria according to which substances are assessed before being placed in the schedules.

The Schedules should be read together with the Act (Act 101 of 1965) and its supporting regulations.

SCHEDULED MEDICINES

Schedule 1 to 6 medicines may be sold only by members of the pharmaceutical, medical, dental and veterinary professions. The pharmaceutical profession may sell by retail to the public on certain conditions or by wholesale to other pharmaceutical dealers, general practitioners, dentists and veterinarians. General practitioners, dentists and veterinarians may sell schedule 1 to 6 substances to a patient or in the case of a veterinarian, to the owner of an animal under their care (For the veterinarians there are restrictions enforced by the rules to the Veterinary Act). Sale by any other profession may only take place if that professional is the holder of a Section 22C licence and as permitted in terms of the provisions of the Act. The sale of scheduled medicines by any of the professions listed may only be for purposes for which the person is qualified. Section 22A (16) (b) reads “any medicine or scheduled substance may be possessed by a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act, 1974, or under the Veterinary and Para-Veterinary Professions Act, 1982, for the purposes of administering it in accordance with his or her scope of practice;”

The sale of a medicine may only take place from a practice registered with the SA Pharmacy Council, the Health Professions Council or the SA Veterinary Council.

Section 22A of the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965), as amended describe in detail the conditions for the sale and possession of all scheduled substances. However, in the discussion of the schedules that follows, only those conditions that are specifically examined during the allocation of a schedule to a substance are considered. These focus on prescription requirements and records.

Prescription requirements indicate the level of professional interaction required and records indicate the level of control required.

SCHEDULE 0

WIDELY AVAILABLE OTC MEDICINES (Open shop)

Description

These medicines or substances are known to be substantially safe in use and for which advice or counselling by a pharmacist is not required. The products are indicated for minor, self-limiting disease or symptoms which can be easily recognised by the patient and which does not require medical diagnoses or monitoring.
Conditions of Sale
Schedule 0 medicines may be sold in an open shop (e.g. supermarkets) as well as by a medical practitioner, dentist, pharmacist or veterinarian.

Examples
Analgesics, e.g. aspirin and paracetamol (in limited pack sizes); antacids; anthelmintics (some of them); antiseptics; caffeine; laxatives; trace elements; vitamins (within limits).

Conditions of Advertising
Schedule 0 medicines may be advertised to the public.

SCHEDULE 1
PHARMACY OTC MEDICINES

Description
Schedule 1 medicines or substances are known to be substantially safe in use, but advice or counselling by a pharmacist may be required. The products are indicated for minor self-limiting disease or symptoms which can be easily recognised by the patient and which does not require medical diagnoses or monitoring.

Purpose
To allow effective medicines to be available to the public without a prescription from a pharmacy where professional advice or counselling may be supplied if required by the consumer.

Conditions of Sale
The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965). For ease of reference, these are tabulated and described in the Annexure at the end of this section. The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [001], [002], [003], [004], [013], [015], [017], [018], [023]

Conditions of Advertising
The advertising of Schedule 1 medicines to the public is permitted by Regulations

Assessment Criteria
• A wide therapeutic index.
• Extremely low abuse potential.
• Low potential for harm from inappropriate use.
• Low or well characterised incidence of adverse effects and contra-indications for which advice or counselling is available.
• Only minor or well-characterised interactions with commonly used substances or food for which advice or counselling is available.
• Low risk of masking a serious disease.
• Low risk of compromising medical management of a disease.
• Generally used for self-treatment of minor ailments or symptoms which:
  o May easily be recognised by the patient.
  o May easily be monitored and self-managed by the patient with counselling if necessary
• Does not require close medical diagnoses or management.
• Requires short term treatment
• Restricted storage, handling required.
• Restricted supply required (not to minors).
• Public health factors listed under general must also be considered.
• Favourable post marketing experience.

SCHEDULE 2
PHARMACIST PRESCRIPTION MEDICINES

Description
Schedule 2 medicines or substances are known to be substantially safe in use but advice, counselling and management or monitoring by a pharmacist is required.

The products are indicated for minor disease or symptoms which can be recognised by the patient and verified by a pharmacist and which do not require initial medical diagnoses or medical management.

Purpose
To allow effective medicines requiring professional advice on use, to be made available to the public from a pharmacist without a medical of veterinary prescription.

Conditions of Sale
The conditions under which scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965). For ease of reference, these are tabulated and described in the Annexure at the end of this section.

The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [001], [002], [003], [004], [005], [007], [008], [010], [013], [014], [015], [017], [018], [023]
Conditions of Advertising
The advertising of Schedule 2 products to the public is not permitted by Regulations.

Assessment Criteria
- A medium to wide therapeutic index.
- Low abuse potential.
- Low potential for harm from inappropriate use.
- Low incidence of severe adverse effects or side effects that are likely to require medical intervention.
- Only interactions with commonly used medicines or food, which can be managed by a pharmacist.
- Only contra-indications that can be dealt with by a pharmacist.
- May be used safely after counselling by pharmacist
- Generally indicated for treatment of ailments or symptoms which:
  - May easily be recognised by the patient with the assistance from a pharmacist.
  - May easily be monitored by the patient with assistance from a pharmacist.
- Does not require close medical diagnoses or management.
- Low risk of masking a serious disease.
- Low risk of compromising medical management of a disease.
- Restricted storage, handling required.
- Restricted supply required (not to minors).
- Public health factors listed under general must also be considered.
- Post-marketing experience may be taken into account.

SCHEDULE 3
PRESCRIPTION ONLY MEDICINE

Description
Schedule 3 medicines are indicated for use in disease or conditions that require professional medical, dental or veterinary diagnoses and management but do not require close medical monitoring after treatment has been initiated.

The substances are often indicated for chronic use and the long-term safety and efficacy of the substances are well established. Supply should be on prescription only, but may be repeated at the discretion of a pharmacist on a non-recurring basis.

Purpose
To make available medicines or substances which should be used, supplied or prescribed by medical practitioners, dentists and veterinarians or when supplied by a pharmacist, should be on prescription.

Conditions of Sale
The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965). For ease of reference, these are tabulated and described in the Annexure at the end of this section. The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [003], [004], [005], [007], [008], [010], [013], [014], [015], [017], [018], [023].

Conditions of Advertising
Schedule 3 medicines may only be advertised to the professions.

Assessment Criteria
- Disease or symptoms require professional medical, dental or veterinary diagnosis or management (stabilisation of a condition).
- Substances are usually for chronic use (Hypertension, diabetes, epilepsy) and there is a necessity to maintain continuous treatment.
- Routine medical monitoring is required. Continuation of treatment can be managed by a pharmacist.
- Long-term safety data established.
- Moderate therapeutic index.

SCHEDULE 4
PRESCRIPTION ONLY MEDICINE

Description
Schedule 4 medicines are indicated for use in disease or conditions that require professional medical, dental or veterinary diagnoses, management and monitoring. The safety and efficacy of the substances may require further evaluation.

Purpose
To make available medicines or substances which should be used, supplied or prescribed by medical practitioners, dentists and veterinarians or when supplied by a pharmacist, should be on prescription.

Conditions of Sale
The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965). For ease of reference, these are tabulated and described in
the Annexure at the end of this section. The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [003], [004], [005], [007], [010], [012], [013], [014], [015], [017], [018], [023]

Conditions of Advertising
Schedule 4 medicines may only be advertised to the professions.

Assessment Criteria
• Disease or symptoms require professional medical, dental or veterinary diagnosis, management or monitoring
• Relatively narrow therapeutic index.
• Specialized route of administration.
• Serious side effects that require further evaluation.
• Serious contra indications.

SCHEDULE 5
POTENTIALLY HABIT FORMING DRUGS

Description
Schedule 5 substances may have a low to moderate potential for abuse or producing dependence, which necessitates medical management and supervision and control of supply.

Purpose
To control medicines or substances which have a potential for abuse and dependency, and to allow the use, supply and prescription thereof only by medical practitioners, dentists and veterinarians or supply by a pharmacist only on prescription.

A few of the substances, mainly the diazepenes, are further restricted due to their control by the Single Convention on Narcotic Trade and are referred to in the Act as Specified Schedule 5 substances.

Conditions of Sale
The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965).

For ease of reference, these are tabulated and described in the Annexure at the end of this section.

The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [003], [004], [006], [007], [009], [013], [015], [016], [017], [018], [019], [020], [021], [023]

Conditions of Advertising
Schedule 5 medicines may only be advertised to the professions.

Assessment Criteria
• Low to moderate abuse potential or dependency producing.
• Psychoactive properties: central nervous system stimulation or depression resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood
• If there is sufficient evidence that the substance is being or is likely to be abused or misused as to constitute a public health and social problem warranting specific control
• Substances listed in schedule IV of the 1971 Convention on Psychotropic substances.

SCHEDULE 6
HABIT FORMING DRUGS AND POTENTIALLY HABIT FORMING DRUGS WHICH REQUIRE ADDITIONAL CONTROL OVER SUPPLY

Description
Schedule 6 substances may have a moderate to high potential for abuse or producing dependence, which necessitates close medical management and supervision and strict control over supply.

Purpose
To strictly control medicines or substances which have a moderate to high potential for abuse or dependency, and to allow the use, supply and prescription thereof only under close supervision by medical practitioners, dentists and veterinarians or supply by a pharmacist only on prescription.

Conditions of Sale
The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965).

For ease of reference, these are tabulated and described in the Annexure at the end of this section.

The following conditions, cross-referenced from the Annexure and identified by codes in parentheses, apply to this schedule: [003], [004], [006], [007], [011], [012], [013], [015], [016], [017], [018], [019], [020], [021], [023]

Conditions of Advertising
Schedule 6 medicines may only be advertised to the professions.
**Assessment Criteria**

- Substance has the capacity to produce a state of dependence and/or central nervous system stimulation or depression resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood.
- If there is sufficient evidence that the substance is being or is likely to be abused as to constitute a public health and social problem warranting specific control.
- If a substance is liable to similar abuse or can produce similar ill effects as drugs already listed in Schedule 6 or is easily converted to a drug listed in Schedule 6.
- Substances listed in Schedule II or III of the 1971 Convention on Psychotropic substances.
- Narcotic drugs listed in Schedules of the 1961 Convention on Narcotic Drugs, except those listed in Schedule III.

**SCHEDULE 7**

**BANNED SUBSTANCES**

**Description**

Schedule 7 substances are not recognised for medical use and have a extremely high potential for abuse or producing dependency which renders their possession unnecessary and undesirable, except for limited scientific purposes.

**Purpose**

To prevent the medical use of substances that have an extremely high potential for abuse or dependency and limited or no recognised medical uses, and to limit their availability for approved scientific purposes only.

**Conditions of Sale**

The conditions under which Scheduled medicines and substances may be sold or supplied are described in detail in Section 22 A of the Act (Act 101 of 1965).

For ease of reference, these are tabulated and described in Annexure 1 at the end of this section. The following conditions, cross-referenced from Annexure 1 and identified by codes in parentheses, apply to this schedule:

- [019], [021]

**Advertising Restrictions**

The advertising of Schedule 7 substances is strictly prohibited.

**Assessment Criteria**

- Substances with no recognised medicinal use and which are liable to abuse or which have the capacity to produce a state of dependence and/or central nervous system stimulation or depression resulting in hallucinations or disturbances in motor function, cognition, behaviour, perception or mood. (No recognised medicinal use and also includes substances of which the risks involved in their use, are outweighed by the availability of safer drugs)
- If there is sufficient evidence that the substance is being or is likely to be abused as to constitute a public health and social problem warranting specific control
- If a substance is liable to similar abuse or can produce similar ill effects as drugs already listed in Schedule 7 or is easily converted to a drug listed in Schedule 7.
- Evidence of illicit trafficking.

**SCHEDULE 8**

**UNDESIRABLE HABIT FORMING DRUGS - LIMITED USE**

**Description**

Undesirable habit-forming substances with limited medical use.

**Purpose**

To limit the medical use and prescription of substances which have an extremely high potential for abuse or dependency and limited recognised medical uses, to medical practitioners and veterinarians who have obtained special permission from the medicines Control Council for such use and prescription and to limit the availability and supply thereof to the Director-General only.

**Conditions of Sale**

The Schedule 8 substances may only be obtained by the Director-General, for supply to medical practitioners and veterinarians who have been granted permission from the Medicines Control Council, subject to conditions as determined by the Director-General, to treat specific medical conditions.

The following conditions, cross-referenced from Annexure 1 and identified by codes in parentheses, apply to this schedule:

- [021], [022]

**Advertising Restrictions**

Advertising of Schedule 8 substances is strictly prohibited.
**Assessment Criteria**
- The criteria for Schedule 7 apply, and
- Only specific indications allowed: narcolepsy, hyperkinesias in children, and in exceptional cases, depression.
  Specialist and laboratory reports must accompany all such applications by medical practitioners.

**Specific Substances**
- Amphetamine
- Dexamphetamine
- Nabilone

**ANNEXURE 1: SECTION 22A CONTROL PROCEDURES**

<table>
<thead>
<tr>
<th>CODE</th>
<th>DESCRIPTION OF CONTROL PROCEDURES</th>
<th>SECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>Schedules 1 and 2 may be sold under the personal supervision of the pharmacist, without a prescription</td>
<td>22A(4) and (5)(a)</td>
</tr>
<tr>
<td>002</td>
<td>Schedules 1 and 2 may be sold only to persons over the age of fourteen, except when issued on prescription, or on a written order, as indicated.</td>
<td>22A(4)(b) and (6)(e)</td>
</tr>
<tr>
<td>003</td>
<td>Schedules 1, 2, 3, 4, 5 and 6 may be sold by manufacturers, wholesalers and professions as indicated in the Act and subject to the conditions listed in the Act.</td>
<td>22A(4) and (5)</td>
</tr>
<tr>
<td>004</td>
<td>Schedules 1, 2, 3, 4, 5 and 6 may be sold by a pharmacist, on a written or verbal prescription from a medical practitioner, dentist or veterinarian or professions as indicated in the Act and subject to the conditions listed in the Act. Dispensing by professions other than pharmacists and veterinarians, only allowed to license holders.</td>
<td>22A(5)</td>
</tr>
<tr>
<td>005</td>
<td>Schedules 2, 3 and 4 - Verbal prescriptions may be issued for 7 days only and must be followed up with a written prescription within 7 days.</td>
<td>22A(6)(b) and (c)</td>
</tr>
<tr>
<td>006</td>
<td>Schedules 5 and 6 may be sold in an emergency by a pharmacist, on a verbal prescription from a medical practitioner, dentist or veterinarian or professions as indicated in the Act and subject to the conditions listed in the Act. Only 48 hour supply, written follow-up in 72 hours.</td>
<td>22A(6)(k)</td>
</tr>
<tr>
<td>007</td>
<td>Schedules 2, 3, 4, 5, and 6 - Prescriptions must be presented within 30 days for dispensing.</td>
<td>22A(6)(d)</td>
</tr>
<tr>
<td>008</td>
<td>Schedules 2, 3, and 4 - Prescription may be repeated if the prescriber has indicated the number of repeats (not longer than six months).</td>
<td>22A(6)(f)</td>
</tr>
<tr>
<td>009</td>
<td>Schedule 5 - Prescription may be repeated, provided that the prescriber indicates the number of times and intervals it may be repeated on the prescription (not longer than six months). Anxiolytic, antidepressant and tranquillising medication, require a second professional opinion after six months.</td>
<td>22A(6)(g) and (h)</td>
</tr>
<tr>
<td>010</td>
<td>Schedules 2, 3 and 4 – In an emergency, a pharmacist may repeat the treatment on a non-recurring basis to ensure continuation of therapy.</td>
<td>22A(6)(l)</td>
</tr>
<tr>
<td>011</td>
<td>Schedule 6 - Only 30 days supply and prescription not repeatable.</td>
<td>22A(6)(o)</td>
</tr>
<tr>
<td>012</td>
<td>Schedule 6 - wholesale supply only on a written order except in emergencies (48hr supply)</td>
<td>22A(6)(j)</td>
</tr>
<tr>
<td>013</td>
<td>Schedules 1, 2, 3, 4, 5 and 6 - Prescriptions must be endorsed with date of sale and quantity issued and retained by the supplier for five years.</td>
<td>22A(6)(q)</td>
</tr>
<tr>
<td>014</td>
<td>Schedules 1, 2, 3 and 4 – A Pharmacist may supply 25% more or less than quantity on prescription according to therapeutic pack.</td>
<td>22A(6)(m)</td>
</tr>
</tbody>
</table>
PERSONS ENTITLED TO USE VETERINARY PRODUCTS

A medical practitioner, veterinarian, pharmacist, dentist and nurse are the only persons entitled in terms of Act 101/65 to use scheduled medicines. It specifies inter alia that only these professions in the course of lawfully carrying on their professional activities may use scheduled substances. In terms thereof a medical practitioner, dentist, practitioner and nurse (excluding a veterinary nurse) are not permitted to use any scheduled substance in animals.

Medical Practitioners, according to an ethical rule of the Medical and Dental Council, may not use a Veterinary Medicine in humans.

Pharmacists may supply any medicine up to Schedule 2 and as well as any other medicine as authorised in the regulations directly to clients for use in animals without a veterinary prescription. A veterinary prescription is required for all other scheduled substances for which the pharmacist is not authorised.

A veterinary nurse or nursing assistant in the employment of a veterinarian may handle, use and sell veterinary medicines up to and including Schedule 4 substances on the instructions (oral or written) of the veterinarian as contemplated in the Veterinary and Para-Veterinary Professions Act, 1982. However, the veterinarian is in control of all medicines in his practice and must take full responsibility therefore. The use of Schedule 5 and 6 medicines by a qualified veterinary nurse may only occur under the specific instructions of a veterinarian for use in individual animals. For this purpose the veterinarian may supply the veterinary nurse with an adequate quantity of these substances.

Persons, other than those entitled in the Act may obtain special authorisation to acquire, from the Director General of the Department of Health. The Director-General, on the recommendation of the Medicines Control Council will issue a permit to that specific person to obtain, store and use the product. The permit is issued for a period of one year and is subject to certain prescribed conditions. The expertise, training and responsibilities of the person need to be stipulated e.g. Animal Welfare Officers.

DISPENSING OF VETERINARY PRODUCTS

Schedule 0 medicines and stock remedies are over-the-counter (OTC) products and can be supplied in an open shop. They are legally available directly to the public from any retail outlet that complies with the requirements of either
Act, or their respective regulations. These products can therefore be freely recommended and supplied by Animal Scientists.

As general policy the dispensing of Schedule 1 to 6 medicines is the function of a pharmacist and not the primary function of a veterinarian, medical practitioner, dentist, practitioner or nurse. However, according to Act 101 and Section 34 of the Veterinary Act a veterinarian is entitled to dispense any Scheduled substance in the course of his normal professional activities.

A Schedule 1, Schedule 2, Schedule 3 and Schedule 4 substance for the treatment of an animal may be supplied by any person practicing a para-veterinary profession within the meaning of the Veterinary and Para-veterinary Professions Act 1982 (Act 19 of 1982) upon a written prescription or on the verbal instruction of a veterinarian.

All requirements in terms of record keeping, registers, storage of medicines, labelling and advice associated with the dispensing of medicines must be maintained and are subject to inspection by the Medicines Control Inspectorate or an inspector in terms of Act 36/47 in the case of stock remedies. A veterinarian or any other person cannot keep or dispense any unregistered medicine, unless otherwise authorized by the MCC.

**HANDLING OF EXPIRED PRODUCTS**

It is illegal for any person to use an expired product for treatment under any conditions e.g. even for welfare cases. The use of expired stock can incur a penalty and possible jail time, as it is seen in the same light as using an unregistered/illicit substance. Expired stocks must be handled correctly. SAHPRA has considered this aspect and all expired stock must be kept separate from normal stocks. Schedules 5 and 6 expired drugs must still be double-locked. It may be in the same schedule cupboard, but must be physically separated and clearly marked as ‘expired’.

**DESTRUCTION OF MEDICINES (INCLUDING EXPIRED STOCK)**

A medicine or scheduled substance shall only be destroyed by:

- A waste treatment facility authorised to destroy medicines or pharmaceutical waste in terms of the National Environmental Management: Waste Act, 2008 (Act No. 59 of 2008).
- When destroyed the medicinal substances must be undertaken in a manner that ensures that the medicines or scheduled substances cannot be salvaged and that it is denatured.

- The waste treatment facility shall issue a certificate which shall contain the following information: (a) the name of the medicine or scheduled substance if known or the schedule of the medicine or scheduled substance concerned; (b) the quantity destroyed; (c) the date of destruction of the medicine or scheduled substance; (d) the name and designation of the person in whose presence such destruction took place; and (e) any other information as determined by the Authority.

No medicines or scheduled substances shall be disposed of into municipal sewerage systems.

This is also generally supported by municipal regulations.

While schedule 0 to 4 substances or medicines must be destroyed directly by the registered waster disposal company, Schedule 5 or 6 substances must be destroyed in the presence of an inspector, a pharmacist; or a person authorised by the Chief Executive Officer of SAHPRA.

**SALE OF MEDICINE OR SCHEDULED SUBSTANCES**

The sale of a medicine by wholesale or retail includes import, offer, advertise, keep, transmit, consign, convey, or deliver for sale or authorize, direct or allow a sale or prepare or possess for purposes of sale, or exchange or supply or dispose of to any person whether for a consideration or otherwise: “sale”, “sell” and “sold” have corresponding meanings.

This definition is extremely broad and all veterinarians are well advised to remember that every aspect of the handling of medicines is covered by the Act in terms of this definition.

**PRESCRIPTION FOR A MEDICINE OR SCHEDULED SUBSTANCE**

An authorised prescriber means any medical practitioner, dentist or veterinarian and in certain specified categories a practitioner, nurse of person registered under the Health Professions Act, 1974.

The requirements for a veterinary prescription are specified in Regulation 28. **According to this regulation every prescription shall be personally signed** by an authorized prescriber and shall state:
• Name, address, qualification and licencing number of the veterinarian
• Name and address of the person to whom the prescription is supplied
• Name of the medicine of each active ingredient or constituent
• Dosage form and the strength of the dosage form
• The quantity of the medicine or Scheduled substance to be supplied
• Date of issue of the prescription
• Species, age and sex of the patient
• Direction for use including dose and interval of use
• If applicable the warning regarding the withdrawal period
• The number of times the prescription may be repeated

A telefax prescription, as well as a prescription sent by other electronic means is acceptable.

In such cases the pharmacist is required to verify the origin of the prescription and must make a hard copy for record purposes.

A telefax prescription must be transmitted from the address of the authorized prescriber. The faxed, e-mailed, telephone or other electronic transmitted prescription or order should be followed by the original prescription or order within 7 working days.

PRESCRIPTION BOOK (WRITTEN RECORD)

The requirements for a veterinary prescription are specified in Regulation 11(1) of Act 101. According to this regulation a prescription book or other permanent record (such as a patient card) in respect of Schedule 2, 3, 4, 5 and 6 medicines or substances shall be kept on all premises where prescribed medicines are dispensed or sold and shall contain the following details:
• the name of the medicine or scheduled substance;
• the date on which the prescription was dispensed;
• the dosage form and quantity of the medicine or scheduled substance;
• the name and address of the person to whom the medicine or scheduled substance was sold;
• the species of animal for which the medicine was intended;
• where applicable the name of the authorised person who issued the prescription; and
• prescription reference number.

In the case of Schedule 1 medicine sold without a prescription in terms of section 22A(4) of the Act, the following shall be recorded:
• the name of the person to it was sold;
• its name and quantity; and
• the name of the veterinarian or duly authorised para-veterinary person who sold it.

A prescription record shall be retained at the business address of the seller for a period of at least five years after the date of the last entry made therein.

SPECIFIED SCHEDULE 5 & SCHEDULE 6 SUBSTANCE REGISTER

The need and requirements for a register of Specified schedule 5 & Schedule 6 substances are contained in Regulation 30 of Act 101 and include:

A person importing, exporting, manufacturing or selling specified Schedule 5 & 6 medicines or substances shall keep a register of such medicines or substances.

The register must indicate the quantity of every such medicine or substance remaining in stock on the last day of March, June, September and December of each year and must also contain the following information:
• the date on which the medicine or substance was received or supplied;
• the name, business address of the person from whom the medicine or substance was received.

HIMALAYAN VETERINARY CLINIC
759 Elevated Heights, Montana Top 9870
Tel: (000) 3019 6634  Fax: (000) 3019 665
E Hillary [BSc, MMedVet (Poultry)] T Norgay [BVSc]

Date 21/04/07  Ref No. 03: 1001
Owner Name: Miss E Sykes  Animal Name: Poultry house 1
Address: 374 Diamond Street, Old Mines Down, Maritzburg. 0110
Species: Poultry  Breed: Broilers  Age: 4 weeks

Drug Details:
Amoxicillin: Mix 1kg of Amoxicillin into 1 tonne of feed. Keep birds on medicated food for 7 days.

Special Instructions: Do not slaughter animals within 4 days of withdraving the medicated feed.
Do not repeat. No generic substitution.

DR E Hillary
or sent and in the case of imported medicine or substance, the import permit number;

• the name and address of the person who purchased the medicine or substance;

• the quantity, in words and figures, of such medicine or substance indicated per dosage unit, mass or volume;

• in the case of the supply of the medicine or substance on prescription, the name and address of the authorised prescriber unless such prescription was issued at a hospital in which case the name of the authorised prescriber shall be recorded;

• the quantity of the medicine or substance manufactured or used during the manufacturing process; and

• any other information as the Council may determine.

The register must be kept for a period of five years after the date of the last entry made therein. In a case where the register is kept by computer, a computer print out must be made monthly, dated, signed and filed. Records must be stored in an orderly manner so that they can be accessed easily.

LABELLING REQUIREMENTS

Label requirements of veterinary medicines by veterinarians are specified in regulation 48(2). Any medicine sold by a veterinarian must labelled according to the requirements of Regulation 48(2) and must containing the following information:

(i) the proprietary name, approved name, or the name of each active ingredient of the medicine, where applicable, or constituent medicine;

(ii) the name of the person to whom the medicine was sold and a description, as accurately as possible of the animal/s for which the medicine/s are intended;

(iii) the directions in regard to the manner in which such medicine should be used;

(iv) the name and business address of the veterinarian or person authorised to sell such a medicine;

(v) the reference number allocated to the sale of the medicine as referred to in regulation 11(1) (f); and where applicable, the warning regarding the withdrawal period of such medicine; and

(vi) date of dispensing;

For animal use only

PERMITS

A veterinarian desiring to be provided with a Schedule 7 or Schedule 8 substance or medicine for the treatment or prevention of a medical condition in a particular patient shall apply to the Director-General for a permit to use such substance.

An application shall contain at least the following information:

• name and address (both physical and postal) of applicant;

• identification number of the applicant;

• registration number of the applicant with statutory council;

• qualifications of the applicant;

• telephone and facsimile numbers of applicant;

• purpose for which the application is made;

• in the case of a veterinarian, the name and address of the owner, diagnosis, dosage and period of treatment in the case of a particular animal or a group of animals.

IMPORT AND EXPORT OF VETERINARY MEDICINES

The import of veterinary medicines is controlled and any person wishing to import needs to apply for a permit to do so. This shall apply to Schedules 5 to Schedule 8. If such a permit is issued the holder of the permit is required to furnish the registrar with such information that is prescribed.

The quantities that may be imported will be set and must be adhered to unless they are less than that permitted.
REQUIREMENTS FOR USE OF STOCK REMEDIES

Unlike medicines, stock remedies are not classed by schedule and neither does the Act allow for scripting. At present they are over-the-counter and freely available for sale to any person or veterinary restricted in that a veterinary consultation is required. A third category of paraveterinary restricted is in the process of being considered. As mentioned above, the Animal Diseases Act may also limit the use of certain stock remedies.

The control of stock remedies is specified in Act 36 of 1947. The Registrar of Act 36 of 1947 may apply any restrictions or conditions in terms of the control and supply of a particular stock remedy. The restrictions are specified on the approved label. Act 36 products are recognisable by their G registration number on the packaging.

In terms of Article 7(2) the user of a stock remedy may not deviate from the requirements and instructions as indicated of the label. In terms of Article 7 (2) (a) of the Act the veterinarian, however, is excluded from this requirement and may use a stock remedy for other purposes as registered.

In general a stock remedy may only be sold in its original pack. Veterinarians are however exempted from this restriction as long as properly packaged and labelled. While no regulations are present for the latter, the conditions stipulated for medicines can apply.

USE OF UNREGISTERED DRUGS IN ANIMALS

Extra label use of medicines

Only a veterinarian may use a veterinary medicine for unregistered indications, animal species, or at different doses. Similarly a veterinarian is also entitled to use a human medicine for veterinary purposes.

The use of drugs under such circumstances must be done after adequate consideration of the risk-benefit and with the necessary precautions, particularly in food producing animals.

A veterinarian accepts full responsibility and liability for the extra-label use of drugs. Extra-label drug use should only be done if no suitable alternative is available and the use is justified scientifically. An adequate withdrawal period must be advised in such cases were products are used in food producing animals.

Compounding of Veterinary Medicines

When a particular medicine already listed in the schedules of the Medicines Act is unavailable for use or is in an unusable dosage form, a veterinarian may compound (mix or make) a product for use by the patient or request a pharmacist to prepare the medicine.

When using the a compounded medicine, the conditions set by the rules of the Veterinary Act need to be complied with viz.

A veterinarian may only use compounded veterinary medicine for a food producing animal(s), including wildlife intended for human consumption, subject to the following:

a) The use of the compounded medicine is limited to the emergency management of a new disease/condition or the management of a disease/condition to which no local registered product exists, or is not readily accessible at the time, as restricted by the conditions in Rule 10(5) (a) to 10(5)(g) above;

b) The reason for compounding is not an attempt to enhance growth promotion in any food producing species in the absence of disease;

c) The withdrawal period associated with its use as prescribed by the veterinarian must be approved in writing by the Food Safety and Security Committee of the Council or the Veterinary Clinical Committee of SAHPR, as the case may be, in accordance of the requirements of the Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972 or hundred and twenty (120) days, or otherwise ten times the half-life of the medicine, unless another withdrawal period is set by one of the two Committees;

d) The food produced by said animal is unsuitable for human consumption until such time that the withdrawal time is approved by either or both of the Committees listed in Rule 10(6)(c), unless any one of the conditions in Rule 10(6)(c) is met;

e) Medicines prohibited for use in food producing species as set out in Rule 10(11) may not be used in compounded medicines; and (f) It is not intended for continued, sustained and/ or frequent use on any one farm, by any one farm owner, by any one farm manager, by any one veterinarian or by any one person as this constitutes manufacturing, unless the use of the compounded medicine is reasonably justifiable and substantiated by facts.

f) A veterinarian is not allowed to mark up the price on a compounded medicine to make a profit.
The following restrictions also apply in terms of the Medicines Act:

- Compounding is patient specific and this needs to be compounded after a patient has been seen i.e. compounding is not to be used for open sale.
- When a product is compounded for a patient, it shall be limited to 30 days worth of use and must state “Use within 30 days” are clearly indicated on the label.
- A compounded medicine cannot be advertised or displayed for sale.
- Compounding for growth promotion or performance enhancement is not allowed.
- Requires an adequate withdrawal period to be set when used in a production animal.
- Cannot be used in a patient that is not under the professional care of an authorised prescriber.
- Are not allowed to be exported, which will include taking drugs to neighbouring SADC countries.
- The compounding of S5 and S6 requires further permission from the SAHPRA for their compounding.

### USE OF UNREGISTERED MEDICINES OR SCHEDULED SUBSTANCES

A veterinarian or any other persons entitled may not use any unregistered medicine, stock remedy or scheduled substance without permission (excluding products falling under the compounded class above). Permission to use unregistered medicines can only be given by SAHPRA in terms of Section 21 of Act 101.

Applications or such permission must be made to SAHPRA on the prescribed form giving the reasons for the application, the patient details and the amount needed. At the end of treatment a report of the outcome of the treatment must be submitted.

### COUNTERFEIT MEDICINES

Counterfeit medicines are pharmaceutical products that are accompanied by false information about the ingredients and/or manufacturer.

This implies that they may contain ingredients that are substandard and ineffective (including the active and excipients) and toxic to the patient, the veterinarian and the consumer (in the case of a food producing animal). A large number of counterfeit medicines occur in the market. In the case of counterfeit medicine, these products are manufactured by an unauthorised company and are packed in the identical format to a product that exists on the market.

Normally the target is the larger volume products and they are introduced into the market at lower prices. The product looks identical to the established product. Counterfeit medicines could represent up to 20% of the volume of sales of a particular product.

Veterinarians must be alert to the presence of such products, particularly in the case of brand name products that are supplied directly to the veterinarian at special prices.
The administration, intake or exposure of animals to drugs may result in the presence and accumulation of drug residues in various body tissues, body fluids and animal products. Drug absorption and distribution will determine the extent or amount of residues in the body, respectively, whereas drug metabolism and excretion will influence its duration.

The blood drug concentration versus time profile represents the time frame of a drug within the body. It is assumed that changes in blood drug concentrations over time are proportional to changes that occur in tissues.

Physicochemical characteristics of the drug such as lipid solubility, molecular size and dissociation constant and physiological processes including tissue perfusion, pH, motility, macromolecular binding and membrane permeability will determine the amount and distribution of residues in the body.

Differences in blood flow, body pH, tissue affinity and active transport mechanisms are some of the factors responsible for differences in drug residues in various tissues.

Drug metabolism also affects the type of residue. Some drugs are excreted unchanged while others undergo extensive biotransformation with the formation of one or more metabolites. Metabolites may either be pharmacologically or toxicologically more active, have similar activity or be inactive.

Both the parent molecule and metabolite may therefore contribute to the presence of residues.

Human health risk

Drug residues may result in direct systemic or microbial effects in man.

Systemic effects include general pharmacological effects and signs of toxicity, as well as potential mutagenic, carcinogenic, teratogenic and embryotoxic effects. These effects are commonly evaluated in preclinical trials in laboratory animals and are extrapolated to humans. More recently the immunotoxicity of residues regarding the sensitising nature of the drug residue and the potential to trigger a hypersensitivity reaction in a consumer previously sensitised to the drug is also considered. Suppression of the immune system in the consumer by the presence of a drug residue is more difficult to predict. Currently there is no validated method for evaluating this particular effect.

Antimicrobial drug residues may pose a direct systemic effect as described but may also result in a microbial human health risk. Microbial risk is divided into two types: due to contamination of the consumer by resistant bacteria occurring in food produced by animals after veterinary therapy; and due to antimicrobial residues in food resulting in the selection of resistant bacteria in human intestinal flora.

Antimicrobial residues resulting in the selection of resistant bacteria in human intestinal flora is more significant and is currently receiving much more attention. In this case the residue has been shown to disturb gut flora, often at very low levels, resulting in the development of already present resistant bacteria in the gastrointestinal tract caused by a gap created in the flora.

Procedures for control of residues

The approach to residue control in animal products have been based on either the requirement that food must be free from residues or based on a maximum residue tolerance limit.

A more acceptable and scientific approach is to derive a maximum residue tolerance level (MRL) for each foodstuff. This is achieved by establishing an acceptable daily intake (ADI) for the drug based on toxicological examination of the compound and determination of its no observable effect level (NOEL) expressed in mg/kg/d. This ADI represents the sum total of the residue of the particular ingredient, whether active or inactive, in the daily food intake for an individual. Residue tolerance (MRL) is calculated using an average body weight of 60kg for humans and the amount of food consumed. In order to take differences of ethnic origin, religion and climate into account, which may influence food intake of various sections of a population, intake data representing the upper limit of the range for individual edible tissue and animal products have been accepted.

The following intake values are used: 300g of meat (as muscle tissue); 100 g of liver; 50 g of kidney; 50 g of tissue fat; 100 g of egg; and 1.5 l of milk.
The NOEL is the drug level at which no adverse effects are observed in the most susceptible species. An ADI, expressed in the same unit as the NOEL, is derived by using a safety factor that usually lies between 100 and 1000.

A safety factor of 100 is most commonly used representing a factor of 10X, to take into account discrepancies in extrapolation of toxicity results between animal and man and a factor of 10X to provide for differences in susceptibility between humans.

Apart from establishing the MRL on the basis of toxicological examination it may also be determined on the basis of good husbandry (or veterinary) practice. A withdrawal period based on normal husbandry practices e.g. the use of anabolic steroids in feedlot cattle can be extended and therefore a lower MRL can be set. This approach, however, may discourage the pharmaceutical industry to find safer compounds since the marketing advantage i.r.o. a shorter withdrawal period will be removed. MRL values are set locally by the Department of Health under the provisions of Act 54 of 1972 from data submitted by the sponsor of the drug, or more commonly according to levels published by the international residue agencies, JEFCA (FAO/WHO Joint Expert Committee on Food Additives), Codex Alimentarius Commission and European Communities.

The withdrawal period of a drug used in a food-producing animal will be finally determined by the pharmacokinetic characteristics of the compound. This is the interval required following administration of a drug and the stage at which residue levels drop below the MRL.

Tissue residue studies to establish the withdrawal period are performed for all food-producing animals for which a drug is indicated and for each formulation. A marker residue substance, being the whole residue (microbial method), parent compound, predominant metabolite or toxic metabolite, is established for every product.

**Drug residue monitoring**

An effective residue-monitoring programme is essential to the control of residues in animal foodstuffs. Conditions for setting up of such a monitoring plan include:

- the identification of analytical laboratories and reference laboratories;
- choice of analytical methods and validation of methods for determining residues;
- list of drug residues to monitor;
- choice of target tissue (muscle, fat, offal, urine and faeces); and
- description of sampling plans and systems.

Analytical methods may include methods for initial screening, which can be performed rapidly, at low cost and be decentralised; and

A more specific confirmatory method should be used when a positive result during screening has been noted. The screening method need not be very specific as long as it does not result in a false negative.

The confirmatory test must be thoroughly validated regarding specificity, precision, reliability, reproducibility, sensitivity and practicability.

The country’s monitoring programme falls under the Directorate of Veterinary Public Health at the Department of Agriculture, Forestry and Fisheries.

At present, the directorate undertakes random monitoring of products for use in South Africa as well as for export purposes.

In addition the commercial sector including both producer associations (e.g. pork and poultry) and buyer organisations (large supermarket chains) also have residue monitoring programmes in place to further protect the South African public.
GOOD DISPENSING PRACTICES

Dispensing is the procurement, preparation and distribution of medicines or drugs for use in a patient. It also includes the subdivision and repackaging of larger pack or container sizes. This is normally the function of a pharmacist but may also be performed by a veterinarian under prescribed conditions.

REQUIREMENTS AND RESPONSIBILITY

The rights and responsibilities of a dispensing veterinarian are contained within the various Acts regulating veterinary products as well as in the Veterinary Act. Manufacturers and suppliers take no responsibility for products that have been subdivided or repackaged due to possible problems relating to stability and contamination. Responsibility and liability reverts to the person(s) or the practice responsible for these activities.

GOOD DISPENSING PRACTICE

Good dispensing practice involves the whole process of medicine procurement, storage and supply of medicine. Good dispensing practice could therefore require adherence to minimum standards for dispensary premises and equipment; the procurement and sources for materials; the dispensing procedure; and the supply of advice to ensure that the patient or its caretaker receives and understands sufficient written and oral information or provide maximum benefit from the treatment.

The rules of the veterinary act, stipulate the following as the minimum standard viz. The dispensary must comply with the following, which must be read in conjunction with the Medicines Act:

a. It must be a separate room dedicated to the storage of medicines within the practice;
b. If medicine is stored in a cupboard in the consulting room, the following will apply:
   i. All reference to temperature, climate control and practicality in Rules (d ) to (r) below will equally apply to the room in which the cupboard is located;
   ii. The cupboard must be locked at all times when a veterinarian is not present;
   iii. Only schedule 2 to 4 medicines may be stored in this cupboard. Schedule 5 and higher medicines must be locked in a safe as prescribed by the Medicines Act; and
   iv. The amount of medicine stored must be limited to two containers each of a maximum of fifty medicines.
v. Light conditions, temperature and humidity within the dispensary or medicine room must comply with the requirements for the storage of medicine, other pharmaceutical products, and packaging materials;
c. The working surface area in a dispensary must be sufficient to accommodate the volume of prescriptions dispensed;
d. All medicines must be stored at the prescribed temperature i.e. at room temperature with heating and cooling as required;
e. A wash hand basin must be accessible, which may be in another room;
f. No medicines may be stored on the floor;
g. Schedule 5 and higher scheduled medicines must at all times be under direct supervision of veterinary professionals and locked away in a safe when a veterinarian is not on the premises (and kept in a locked box when in transit);
h. Storage areas must be large enough to allow orderly arrangement of stock and proper stock rotation;
i. A suitable means of counting tablets and capsules. This equipment must be cleaned regularly so that cross-contamination between products is avoided;
j. Refrigerator must be accessible (even in another room): must be equipped with a suitable thermometer and capable of storing medicines at temperatures between 2°C and 8°C. The refrigerator must be cleaned, defrosted and checked regularly to ensure efficient running. This refrigerator must be used only for storing pharmaceutical products (For a mobile clinic this requires a portable fridge or a suitable cooled box);
k. A suitable range of dispensing containers for medicine;
l. Dispensed medicines must be sold, and correctly labelled in a package containing the following information:
   i. the proprietary name, approved name, or the name of each active ingredient of the medicine, where applicable, or constituent medicine;
   ii. the name of the owner, as well as the name of the patient, if available, for whose treatment such medicine is sold;
   iii. the directions for the use of such medicine;
iv. the name and business address of the dispensing veterinarian; and
v. date of dispensing.
m. Empty, time expired/or broken containers of medicines must be disposed of as legislated for dangerous substances in legislation controlling these substances;
n. Records of medicines purchased need to be kept for a period of 5 years;
o. The receipt of medication for restocking of the dispensary is the responsibility of the veterinarian, and not the lay persons at the practice; and
p. Have access to the pharmacological reference sources, and in the case of compounding, access to protocols for the compounding of medication.

Further guidance to assist in the interpretation of standards can be obtained from the South African Pharmacy Council, under their Good Dispensing Practice Guidelines.

GOOD DISPENSING PRACTICE OF THE PHARMACY COUNCIL

Standards for dispensary premises

Appearance of premises
The external and internal appearance of dispensary premises must inspire confidence in the nature of the health service is provided.

Safety of premises
Working conditions must be so arranged as to protect the safety of the public and people working on the premises

Condition of premises
All parts (walls, floors, windows, ceiling, woodwork and others) of the premises must:
- be kept clean
- be kept in such good order, repair and condition as to enable them to be effectively cleaned and to prevent, so far as is reasonably practicable, any risk of infestation; and
- walls must be finished in a smooth impervious material.

Tidiness of premises
All parts of the premises must be maintained in an orderly and tidy condition.

Environment
- Products must be protected from the adverse effects of light, freezing or other temperature extremes and dampness.
- Levels of heat, light, noise, ventilation, etc., must exert no adverse effects on personnel.
- All parts of the premises must have suitable and effective means of heating, lighting and ventilation. If windows are capable of being opened, they must be securely locked when the dispensary is closed.

Size of dispensary
The size of the dispensary must reflect the volume of prescriptions dispensed and allow a safe and efficient flow of work and effective communication and supervision.

Hygiene
- Adequate toilet facilities must be available and must be kept clean and in good order. A vented lobby must be provided for entrance to a toilet. Toilets must not in any case open directly into the dispensary.
- Hand-washing facilities must be provided in the toilet area or the lobby together with a conspicuous notice requesting users to wash their hands. Facilities must include readily available hot water, soap, nailbrush and clean towels or other satisfactory means of drying the hands.
- Toilet areas must not be used for storage or as a source of water for dispensing.

Standards for dispensary design and equipment

Suitability of dispensary
The dispensary, its fittings and equipment must be adequate and suitable for the purpose of dispensing.

Work surface and shelves
- Working surfaces, cupboards and shelves must be in good state of repair and in a clean and tidy condition. They must be smooth, washable and impervious to moisture. The work surface must have a minimum number of joints which must be sealed to prevent ingress of moisture or liquids.
- A clear area of bench space at a comfortable height must be set aside for dispensing.
- Care must be taken to avoid obstruction by labelling and other equipment.

Floor covering
The floor covering in the dispensary must be kept clean.
Water supply
- The dispensary must be provided with a source of potable water.
- A sink, of durable material (e.g. stainless steel) must be provided in the dispensary, with readily available hot and cold water. The sink must have a plumbed-in waste pipe.

Waste disposal
- A suitable and adequate means of waste disposal must be available and in use.
- Waste material must not be allowed to accumulate and should be collected in suitable, covered receptacles for removal to collection points.
- Care must be taken to segregate any special Waste.

Dispensing equipment
There must be adequate, suitable equipment in the dispensary. Each item must be clean in good repair and of suitable material. The list below is a minimum list and must be extended according to the requirements of the dispensary.
- A suitable means of counting tablets and capsules. This equipment must be sealed regularly so that cross contamination between products is avoided.
- An accurate dispensing balance.
- A range of graduated, stamped glass measures.
- A refrigerator equipped with a maximum/minimum thermometer and capable of storing products at temperatures between +2 and +8 degrees EC. The refrigerator must be cleaned, defrosted and checked periodically to ensure efficient running. Unless there are adequate arrangements for separating various items to avoid cross contamination, the refrigerator must be used only for pharmaceutical products.
- A suitable range of dispensing containers for medicinal products and child resistant closures.
- A means of mechanically printing dispensing labels. Additional warning slip labels must be available, unless those warnings are printed on the dispensing labels. Where computer software is relied on for warnings/interactions, this could be the latest version available.

Reference source
The following reference material in their latest editions must be available for consultation in all dispensaries:
- Martindale: The Extra Pharmacopoeia.
- IVS and IVS Desk reference
- A comprehensive handbook on pharmacology; and
- Compendium of Laws and Regulations (PSSA)

STANDARDS FOR PROCUREMENT AND SOURCES FOR MATERIALS

Definition: Materials mean raw materials, containers and closures, prescription ingredients, finished products, proprietary preparations and any other medicinal substances purchased for the purpose of use in dispensing.

Responsibility for procurement
The pharmaceutical aspects of the purchase of all medicinal products and related materials must be the responsibility of a veterinarian.

Sources of supply
- A veterinarian has a professional responsibility to exercise control over all medicinal and related products that are purchased or supplied.
- A veterinarian must not purchase, sell or supply any medicinal product where the veterinarian has any reason to doubt its safety, quality or efficacy.
- A veterinarian must be satisfied that both the supplier and the source of any medicine purchased are reputable. Due regard must be given to the storage conditions before purchase and to the labels, leaflets, appearance, origin and subsequent chain of supply of the medicine concerned.
- In South Africa, veterinary practice can only source their registered finished products from a pharmaceutical wholesaler registered with the SAHPRA for subsequent patient use. The purchase and use of medicines from other sources is illegal, unless supported by a section 21 permit from the SAHPRA.

Safe systems of work
A veterinarian must conform to the guidelines or codes of practice appropriate to the relevant field of work.
Standards for dispensing procedures

**Definition:** Dispensing includes all of the activities which occur after the prescription has been handed in at the dispensary until the medicine or other prescribed items have been collected.

Supervision of dispensing and sales
- Dispensing must be under the supervision of a veterinarian.
- In a dispensary, with only one veterinarian present, this veterinarian must be able to supervise activities in the medicines sales area at the same time as supervising dispensing.
- A veterinarian responsible for supervising the dispensing, sale or supply of any medicine in a dispensary bears the associated legal and professional liability.
- A veterinarian may only dispense medication for their own practice, veterinarian (permanent or locum) employed at the practice. It is not legal (Veterinary Act) for a veterinary to dispense on behalf of another veterinary practice i.e. a veterinary dispensary cannot operate as a pharmacy for open sale.
- The veterinarian must exercise judgement to ensure fulfilment of professional duties to the patients in the best possible way. The veterinarian must thus be able to delegate to suitably trained staff those tasks that he is confident can be undertaken by them. The veterinarian must be available in the dispensary to intervene, to advise and to check the dispensing of any prescription under his supervision.
- Where the veterinarian determines that the advice of a veterinarian needs to be given, a veterinarian must hand out the dispensed item personally.
- Systems must be developed to ensure that the distribution of medicines is reliable and secure to the point of delivery.
- Delivery of medicines: The best pharmaceutical service is provided where the opportunity exists for direct contact between patient and veterinarian, which would normally take place in a dispensary. Before commencing deliveries to a patient, the veterinarian should speak with the patient’s caregiver to ensure that the medicines will be administered correctly, to confirm the delivery address and to make arrangements to ensure the safe delivery of the medicines. The veterinarian should also discuss acceptable alternative delivery arrangements, should there be no one at home at the time of delivery. No medicine should be left with neighbours unless authorized by the patient’s caregiver.
- When medication cannot be dispensed in its original packaging, it is currently only legal for a veterinarian to dispense the medicine in its new packaging (re-packaging) at the time of seeing a patient. It is unacceptable for a veterinarian to pre-prepare medication packages (pre-packaging) for dispensing (so called patient ready packs) for future dispensing.

Dispensing containers/packaging
- The container must be appropriate for the product dispensed, bearing in mind the need to protect the product from moisture and sunlight as well as from mechanical stresses imparted by transport and use of the product.
- All containers intended for medicinal products must be protected and kept free from contamination.
- All solid dose oral preparations should ideally be dispensed in either a reclosable solid container or in unit packaging of strip or blister type.
- All oral and external liquid medicines dispensed from bulk must be supplied in a re-closable container.

Re-use of containers and other medical material
- Plastic containers and caps for solid or liquid dose preparations must not be re-used as satisfactory cleaning cannot be ensured.
- The re-use of disposable medical administration equipment such as syringes is also not considered a safe practice
- Under no circumstances may re-closable child resistant closures be used more than once, as continued use affects the child resistant properties of the closure.
- Glass containers are capable of being reused only after satisfactory cleaning and drying. High standards must be maintained, which may make reuse uneconomical.

Reuse of medicines
A veterinarian must use his professional knowledge in relation to the re-use of medicines brought in by caregivers for the caregiver’s patient. All such medicines are, however, the caregiver’s own property and should under no circumstances be considered for the re-use for any other patient even if for welfare reasons. It is also illegal to accept unused medication or offer a refund for return of medication for re-use by the practice as these medication have been out of control of veterinarian.
- Standard labelling requirements are laid down by the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965) and all medicinal products must be labelled in accordance with this Act. In addition, there are special requirements, including warning and cautionary labels, for certain classes of medicines and dispensed medicines must also bear this additional cautionary and advisory labelling, where appropriate.

- The labelling requirements for medicinal products for human use, which are dispensed medicinal products, apply equally to veterinary medicines. There is, however, one additional requirement: “For animal use (treatment) only” must be on the label of every veterinary medicine, unless the container or package is so small that it is not reasonably practicable to show such words.

Storage

- Materials must normally be stored in the manufacturer’s original containers. If, in exceptional cases and with due consideration of the nature of the product concerned, the contents need to be transferred to other containers, care must be taken to avoid contamination and information must be marked clearly on the new container.
- All materials must be stored under suitable conditions, appropriate to the nature and stability of the material concerned. Particular attention must be paid to protection from contamination, sunlight, atmospheric moisture and adverse temperatures.
- A veterinarian must exercise his/her knowledge of stability of materials to segregate for disposal and destroy any substances that have deteriorated, or which have been in stock for unduly long periods, or which have reached their expiry dates (refer MCC).

Recalls

A veterinarian must comply immediately with any warning or recall about defective medicines.

Personal hygiene

- High standards of personal cleanliness must be observed in dispensing.
- Direct contact between the dispensed product and the operator’s hands must be avoided.
- Cuts or abrasions on dispenser must be covered with an open lesion or readily transmittable infection must report to the veterinarian who will decide whether they may be engaged in the dispensing process.
- no personnel may smoke, or prepare or consume meals in any area where medicines are dispensed, sold or supplied.

Standards for counselling/advice to ensure patient safety

Safe and effective medicine therapy is best ensured when patients (care-givers) are well informed about medications and their use. Veterinarians’ medicine consultations with care-givers should be aimed at improving therapeutic outcomes by maximizing proper use of medications.

The following is of importance in achieving this goal:

- The veterinary should provide all information necessary for the safe, correct and effective use of a medicine by information tailored to individual needs.
- In addition to oral communication, information and advice should be backed up in writing or by appropriate supporting materials.
- Contra-indications, interactions or possible side effects should be explained when the dispensed medicine is handed out.
- The veterinarian should seek to ensure that the care-giver of a patient has no doubts as to the action of the medicine, the manner in which it is to be taken (how, when and how much), the duration of treatment, possible adverse effects, interactions and special precautions.

Inspections

Veterinary practices are subject to inspection by the SAHPRA, Act 36 and the South African Veterinary Council and for adherence to good dispensing and sale practice.

Inspectorate

The inspectorate of SAHPRA is responsible to ensure that the provisions of manufacture and sale of a veterinary medicines or scheduled substance is complied with in terms of the Act. Inspectors appointed in terms of Act 36/47 are responsible for inspection of stock remedies.

Veterinarians and any authorised dealer are subject to inspection i.r.o. the dispensing, prescribing and recording of medicines used.
Adverse reactions can arise from a wide variety of possible circumstances. This will include untoward reaction from:

- the correct utilisation of drugs,
- the use of human preparations,
- any extra-label use of drugs,
- the use at incorrect dosages,
- the failure to produce an effect at the recommended doses,
- products failing to meet the reported withdrawal period or
- reactions occurring in people following use of veterinary drugs (either accidental or intentional).

Adverse reactions should be reported, either by post or electronically, to the MCC and the registration holder. Details from each report are logged onto a drug database, as reported by the sender. With the aid of electronic tracking, any trends in the occurrence of ADRs are followed. It is a condition of registration of Act 36 that a registration holder must submit all product ADR information directly to the Registrar. The registration holder must investigate the complaint and its cause. The MCC or the registrar of Act 36 will determine if any action is necessary. Adverse Drug Reactions (ADRs) are addressed in terms of both Act No. 101 of 1965 and Act No. 36 of 1947. The new regulations of Act 101 pertaining to adverse drug reactions have been expanded to include veterinary medicines.

It is a condition of registration for Registration Holders of Stock Remedies to forward to the Registrar of Act 36 reports of suspected adverse reactions. In the South African context a wide variety of conditions are regarded as ADRs. This will include untoward reaction from:

- the correct utilisation of drugs,
- the use of human preparations,
- any extra-label use of drugs,
- the use at incorrect dosages,
- the failure to produce an effect at the recommended doses,
- products failing to meet the reported withdrawal period or
- reactions occurring in people following use of veterinary drugs (either accidental or intentional).

Previously a Veterinary Pharmacovigilance and Medicines Information Centre (VP & MIC) was established in the Faculty of Veterinary Science, University of Pretoria, but due to insufficient funding, this centre has been disestablished.

Table 1: Criteria used for assigning causality

<table>
<thead>
<tr>
<th>Causality classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>There is a plausible time relation between the administration and the adverse event, which cannot be explained by the concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) is clinically plausible and the event is definitely pharmacological or phenomenological, using a satisfactory re-challenge procedure if necessary.</td>
</tr>
<tr>
<td>Probable</td>
<td>There is a plausible time relationship between the administration of the drug and the adverse event, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follow a clinically reasonable response on withdrawal. A positive re-challenge is not required to fulfil this definition.</td>
</tr>
<tr>
<td>Possible</td>
<td>There is a plausible time relationship between the administration of the drug and the adverse event, but the event could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>An adverse event with a temporal relationship to drug administration that would make a causal relationship improbable, and which other drugs, or chemicals or underlying disease provides plausible explanation.</td>
</tr>
</tbody>
</table>
It is the responsibility of the veterinarian to submit reports of adverse drug reactions. Therefore if a veterinarian, in his professional opinion, feels that an ADR has resulted then a full report on that reaction should be submitted.

Report forms can be found in the IVS and on the MCC website. Registration holders (pharmaceutical companies) also have ADR forms allowing them to follow up on these events and report such events internationally. The registration holder must investigate all complaint and its cause.

Addendum 1: Compounding of Veterinary Medicines (Published in Vet News)

Introduction
The practice of the veterinary profession is highly dependent on the use of commercial veterinary remedies. While a large number of these drugs are currently available as either stock remedies or veterinary medicines, the drugs available do not cover the entire spectrum of therapeutic agents required in the management of animal disease. Whilst a number of different factors may be responsible for the absence of required medication, the most common has to do with the size of the veterinary market i.e. the local market is not large enough to support the sale of these remedies.

As a result of the non-availability of veterinary remedies, veterinarians have been afforded the privilege to use drugs extra-label, which essentially allows one to use non-registered drugs for animal use in South Africa. While in the main, this implies the use of human medication in animals, this also encompasses the process of drug compounding. In addition to non-availability mentioned above, other factors that favour compounding usually include an inability to obtain correct dosage forms e.g. only tablets available when oral solutions may be required, or when current dosage concentrations are too high to safely allow for use in small animals.

What is Drug Compounding?
Compounding is a veterinary privilege afforded by the Medicines and Related Substances Control Act (Act 101 of 1965). Whilst the Act does not strictly define compounding, this process may be defined as the manipulation of an available medicine or pure chemical substance to obtain a new dosage form. In the case of registered medicines this would also include any product manipulation that results in alternate instructions other than those already provided on the approved drug packaging. As such veterinary compounding may be simply defined as the self-preparation of a medicine for animal use such as the formulation of a new veterinary medicine from self-sourced raw material and/or the reformulation of an available remedy viz. drug dilution, crushing of tablets into food, mixing of drugs for wildlife capture, etc. In addition, as vets we not only have the privilege of being able to compound drugs in house, we may also instruct a pharmacist to compound on prescription.

The legalities of registered medicines
As in almost every country in the world, drug availability is highly regulated. This is important as the registration process ensures that commercial products are of adequate quality, safety and efficacy:

- Quality: Most drugs are mixture of chemicals with the exception of the newer high molecular weight protein drugs like erythropoietin. Nevertheless, despite the source of the product, medicines are produced by manufacturing companies under laboratory or factory conditions. As a result of the production process, it is possible that foreign contaminants such as endotoxins or other foreign chemicals could inadvertently enter into the final raw or finished product thereby resulting in an inferior and possible hazardous medicine e.g. the recent contamination of pet food with cyanuric acid/melamine highlighted the dangers of this process. Therefore to ensure the quality of manufactured product, every aspect of drug production is strictly controlled by the quality process known as Good Manufacturing Practice (GMP).

- Efficacy: Drug formulations are complex mixture of active and inactive ingredients. As a result of these differences, formulations with the same active ingredient may not necessarily produce the same effect as their inactive may well differ e.g. medical oral clavulanic formulations are not considered equivalent to the veterinary formulations. As a result of this well understood pharmaceutical factor, every formulation has to be extensively tested prior to registration. While for new chemical entities (NCE) this would entail exhaustive studies in a few hundred animals, the pharmaceutical alternative/similar products (generic products) may be registered based on strict bioequivalence guidelines. As a result registered products are usually effective in 80% of the recommended target population (Natural population variation), at the recommended dose barring external factors such as microbial resistance.

- Safety: Since different formulations are manufactured by different companies, they will always to some
extent differ. With these differences lying mainly in the specific combination of active and inactive ingredients, every formulation has to be initially tested for its potential to be toxic, irritant or harmful in the target population (Target animal tolerance studies). These tests are in addition to full preclinical safety testing of the active ingredient as pure chemicals in laboratory animals, as well as meeting manufacturing criteria controlled by GMP. For these studies, the target species is exposed to the product at various doses above that recommended to elucidate all known side effects, which may then be recorded on the package insert. At present this is the only means of evaluating the side effects that a drug formulation could potentially have. In addition the pharmaceutical industry and veterinarians are legally obliged to report any adverse reaction that results from the use of a veterinary medicine or stock remedy in the aim of improving product safety.

While the necessity of drug regulatory control has often been questioned, incidents in other countries where no control exists have highlighted the dangers of open markets, such as the unscrupulous marketing of fake products to the veterinary communities. In another instances, random sampling has shown deficiencies in not only the quantity but the quality of the active ingredients. More importantly since these fake/counterfeit products are freely marketed at lower prices, they essentially kill the market for ethical good quality products as well as commercial veterinary industry. Therefore drug regulatory control is essential to protect the availability of drugs to the veterinary market as well as the veterinary market itself.

Why should we compound?
- As mentioned above the privilege of compounding allows veterinarians the ability to treat animals with available human medical drugs.
- In addition the process makes it possible to manage wildlife as dart cocktails need to be made up for specifically for the species being managed.
- In small animal practice it can allow for the easier dosing of tiny animal with diluted concentrated solutions that would otherwise not be possible.
- Most importantly it allows for the use of certain medication in animals that are not currently available for use in South Africa.

What Should I be wary of in Compounding?
- Formulation Differences: As mentioned above drugs are formulated in very specific manner by the drug companies. While in many cases these formulations are designed to control the release of the active ingredient, they are also important in protecting the active ingredient. Therefore if the compounded product lacks a specific inactive ingredient, the clinical effect of the active ingredient is automatically reduced e.g. erythromycin is sold commercially as an enteric coated tablet to protect the molecule from the low gastric pH. By crushing these tablets, the outer coating is damaged, which subsequently leads to a high presystemic elimination.

Another important concept in pharmacology is the bioavailability of the active ingredient i.e. failure in absorption will automatically result in the failure of the product. In pharmaceutics and pharmacokinetics (study of biopharmaceutics) the interrelation of the formulation and absorption is widely accepted. As such any modification to the formulation could therefore result in decrease bioavailability and inefficacy e.g. the use of fentanyl patches in dogs are not always effective as its release characteristics is specific for human skin.

- The pH of the formulation. In pharmaceutical manufacture the specific salt of the active ingredient is selected for its stability in formulation. By using a different salt during compounding, one can alter factors such as formulation pH, ionization, stability and absorption. Even preservatives added to a formulation need to be tested for their influence on the pH e.g. the preservative may chemically neutralize the active ingredient. Another important consideration is the use of product for intramuscular administration. Any changes in the pH can cause severe pain, irritation and or muscle damage on administration.

- Chemical Contamination: Since the source of the active ingredient in the formulation is not under strict GMP control, the potential for contaminants to enter into the formulation is always present (It has been speculated that some foreign chemical manufacturing companies intentionally profiteer through the sale of poor quality chemical products). While some of these contaminants
can be minor toxins, others are very potent and result in mortality. Unfortunately the degree of contamination of the product cannot be tested, as the current tests can only look for certain chemical i.e. you can’t test for everything.

- **Microbial contamination.** A major concern with any formulation is their potential contaminations with a micro-organism e.g. fungal organism grow remarkably well in drug vials. In addition to the microbial contamination directly, metabolic products like endotoxins are also a major concern. The production standard for the preparation of sterile parenteral drug products which pharmaceutical companies follow is clearly stated in the pharmacopoeias. Therefore if parenteral formulations are to be compounded, veterinary dispensaries or pharmacies must meet these strict requirements. This is important to prevent septic or endotoxic complications in treated patients.

**The Vet’s legal responsibilities with regards to compounding**

Since compounded products usually do not comply with the strict testing requirements, enforced for registration by South African law, the use of compounded products is controlled in the following manner:

- **The Medicines and Related Substances Control Act (Act 101/1965):** A veterinarian may compound or request a pharmacist to compound (via a valid prescription) any product contained within its schedule up to schedule 4, on condition that this is per patient (Patient as defined in the Veterinary Act). More importantly compounded products must have a specified shelf-life of only 30 days i.e. these products expire within 30 days of compounding irrespective of the batch size produced. The Act does not allow or make provisions for veterinarians to stock compounded product on shelf per chance it be required i.e. compounding may only be undertaken after consultation. The stocking of compounded product is the responsibility of only the pharmacist. Most important, all compounded medicines are subject to the rules and regulations that govern the schedule (or highest schedule) in which the chosen active ingredient(s) belongs.

- **The Veterinary and Paraveterinary Professions Act (Act 19 of 1982):** According to this Act, veterinarians may not run an open pharmacy. As such the selling or stocking of these compounded remedies in bulk is illegal. The Act also indicates that scripting is a component of the consultation process, and therefore the owner may not be charged additionally for this service if a consult fee has already been levied. In addition the Act also regulates the extra-label use of medicines. **Veterinarians may only use an animal product extra-label if the informed owner consent is received and at that on condition that an alternate veterinary product is not already registered for use in the country.** Lastly the Act states that the vet must protect public health. Therefore the use of compounded products in animals may not be undertaken without taking cognisance of the consumer safety and food drug residues.

- **The Foodstuffs, Cosmetics and Disinfectants Act.** (Act 54 of 1972): This act protects the consumer from potential residues of veterinary remedies in the human food chain. This act states that no person may use any remedy in a food producing animal if an adequate withdrawal period has not been set. This therefore implies that the veterinarian must set a new withdrawal period whenever a product is used extra-label or being compounded.

**Practical tips when compounding (NB)**

**Companion Animals**

With the current constraints in companion animal practice, compounding will always be a part of the veterinary profession. Therefore when using drugs in this group of animals, ensure that the owner is informed on the extralabel nature of the product, preferably in writing (notes must always be kept in the patient record). Be aware that you are legally responsibility for any negative outcome from the use of the said remedy, even if the remedy is prepared by a pharmacist. Avoid using compounded parenteral formulations as they have a greater chance of causing harm.

**Production Animals**

The use of compounded remedies in production animals is not generally supported due to food safety issues, but the latest compounding guidelines from the SAVC is that a compound product may be used in an individually
diseased animal. Whenever any compounded product is used, an adequately scientifically determined withdrawal must be set by a person experienced in pharmacokinetic extrapolations and interspecies scaling. Alternatively, the veterinarian should enforce a withdrawal period of at least three to six months depending on the nature of the compound in use. This applies equally to the wildlife industry, where the potential exists for trophy kills to end up in the food chain, soon after immobilisation.

Suggestions for the use of compounded medicines
• Compounding should not be used as a cheap alternate source of medication.
• Compounding should be used when no alternate/suitable remedy is available.
• Ensure that owners are fully informed when compounded products are being used.
• Compounding should preferably be avoided in production animals. When used, it should be reserved as a last resort and on condition that public safety is ensured i.e. set an adequate withdrawal period.
• Compounded drugs have a legal shelf life of only 30 days.
• Compounding is patient specific and therefore compounding product should not be kept of shelf for routine dispensing.

Addendum 2: Are all generics created equal?
(Published in Vet 360)

Bioequivalence is the comparison of the plasma profile between the test and reference product. A generic product is bioequivalent to the innovator product and it thus essentially identical - in a species group. There is no pharmacokinetic evidence to support human medicines being generics for veterinary species.

Introduction
A good way to start this article, would be for you to close your eyes and contemplate the valuable role veterinarians play in the health and welfare of animals. At this point, you would probably agree that veterinarians play an invaluable role of the diagnosis and treatment of animal disease or disease conditions. However have you ever considered what the function of the veterinarian would be, if we as a profession, had no medication available to treat our patients?

Probably very little, and even less so since the profession has moved away from the use of Materia Medica (books describing how to prepare one’s own medicines).

So what has changed? The answer is simple and reflects our acceptance of modern pharmaceutical science as the means of treating disease.

These prepared formulations offer a number of benefits over practice-based drug preparations. These include:
• Ready availability (e.g. does not need to be prepared which save times and the need to keep raw ingredients as in an apothecary);
• they have long shelf lives (which means one does not need to keep restocking with new/fresh ingredients);
• one could rely on the use of synthetic chemicals (that would otherwise not be readily available)
• purer formulations (in that they’re not contaminated with foreign material or bacteria);
• potential for parenteral administration for rapid or sustained effect (since they’re sterile and pure) and lastly,
• they control for variable effects that can result from inconsistencies in absorption.

All of which is possible through our better understanding of various aspects in pharmacology, such the drug’s pharmacokinetic profile, mechanisms of action, the interaction between pharmacokinetics and effect and the importance of biopharmaceuticals in the effects of medication.

How do drugs produce their effects?
Drugs produce their effects by interacting with receptors in the body. These receptors are typically proteins on the cell surface. When the drugs bind to these receptors, they essentially instruct a cell to bring about a change in function or activity, which we would interpret as a clinical effect. The effect is considered agonistic if it mimics or causes an increase in normal cellular function or antagonistic if it opposes or reverses normal physiological function. While the clinical effect is simple to interpret, at the cellular level, this can take effect at various levels, which is beyond the scope of this publication. The study of a drug's effect is known as pharmacodynamics. From pharmacodynamic theory we know that the final effect is dependent on the number of receptors on/in the cell, the concentration of drug achieved at the site of my receptors (biophase) and the internal cellular processes. In the majority of cases we cannot control the number of receptors on the cell surface (I would not say impossible as we do
this in certain cases such as COPD management, when a beta agonist and a steroid are used in combination) or the internal cellular processes (One again some drugs can, but rarely). So in pharmacological development we chose drugs that activate our required process, and vary the effect by controlling the concentration of drug reaching the cell receptor and/or we can chose drugs that have an inherent lower/higher ability to activate the receptor. This study is known as the receptor-drug interaction and is commonly referred to as receptor affinity. The effect the drug has on a receptor, would be drug's intrinsic activity which can be partial activation, full activation or inactivation.

Pharmacokinetics
Pharmacokinetics is the study of the movement of drug through the body, from the site of administration, to the site of effect and finally to the method of elimination. Of these absorption is dependent on the site of administration, the amount administered, the ability of the body to remove the drug before it is absorbed and drug's chemical profile. Similar factors determine whether the drug gets to the site of action, while elimination is dependent on the need for the drug to be metabolised or excreted.

The processes involved in the pharmacokinetics of a drug are studied by following the change in concentration of drug in the plasma of time (Figure 2). Using differential calculus, one can follow the change characteristics of the curve and establish mathematically how the drug is absorbed, distributed and/or eliminated. In pharmacokinetics the key controlling aspects is the drug formulation which controls absorption and elimination, and the endogenous/systemic processes which control elimination.

The dotted line represents the relationship of the plasma concentration with the effect concentration (For the latter, one can see that it's' not only the ability to reach said concentration that is important, but the duration of time that the concentration can be achieved).

As one can see, since the drug concentration at the receptor site is important, and that the drug pharmacokinetics determines the drug concentration in the body, these the two process must interact to produce a drug effect. More importantly this principle states that if two drugs achieve the same concentration in the plasma, they should be equally as effective.

The formulation
Medication that are sold commercially, are sold as a mixture of ingredients that all interact to allow the said drug to have its effect. The formulation is there to ensure that the drug is adequately absorbed into the circulation and it can also control the rate of absorption. To place this into perspective, the formulation controls the time to a drug's first effect, the degree of effect and thus the degree of side effects. The formulation has a number of potential components, which all fulfil different roles in allowing the active ingredient to be absorbed, as well as the shelf-life of the drug (Table 1).

Another important feature of the formulation is the actual chemical properties of the active ingredient, which also has an impact on drug absorption, chemical stability, interaction with excipients and at times even activity.

For the latter it's’ important to note that the active ingredient can also occur in different forms (e.g. amorphous versus crystalline) with some chemical forms being ineffective. The same can apply for chirals (L and D Isomers) with some isomers being inactive, more active or even toxic (e.g. dexmedetomidine is the active chiral of medetomidine).

Table 1: Some value potential of various excipients in the formulation

<table>
<thead>
<tr>
<th>Excipient (Components of a finished drug other than the active pharmaceutical ingredient)</th>
<th>Reason for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweeteners and flavourings</td>
<td>Improve the palatability of oral medication, to improve compliance in treatment.</td>
</tr>
</tbody>
</table>
In the formulation, the actives and inactives will interact with one another to control absorption (Figure 3).

From numerous pharmaceutical studies, we know that a change in the excipients or a change in the ratio of ingredients can result in different absorption profiles between formulations. The same can be said if a different form of the active (e.g. different salt, different size of molecular, different polymorph, different isomer) is in use.

As a given rule, no two formulations are identical until proven i.e. simply being told that formulation has the same active as another product is not sufficient to assume efficacy. This would need to be proven with validate methodology such as bioequivalence testing. Another important factor to be consider is the potential for the inactive and active to interact with one another with resultant inactivation, or change in tableting pressure that precludes the release of the active ingredient in the same period of time, or even the incorrect pH which can cause pain and tissue damage on administration.

Since we know that the formulation effect is extremely important, drug manufacturers have to ensure that their formulations are as uniform as possible. Most try and keep their drugs within a 5% variation of the expected from batch to batch (e.g a 5mg tablet may have 4.5 to 5.5 mg therein), which is lower than natural variation which can be as high as 10%. This process of control is known as Good Manufacturing Practice (GMP), and involves standardising as many factors as possible, from how the chemicals are sourced to how the equipment is handled, serviced and calibrated. It expects the manufacturer to undertake routine assays of their formulation at various steps in manufacture as well to ensure that staff are adequately trained.

Other important aspects include the source and purity of the chemicals in use e.g. what’s the purity, is it free of endotoxins, is it free of contaminants, it is free of bacteria, etc. While this process does add to the costs of production, it is well known that without these control measures the variation in the formulation can result in unpredictable variations in plasma concentrations, which could translate to ineffective treatment, treatment being toxic or even inconsistent treatment where one dose works and another fails.

![Figure 3: Interaction of the formulation effect, pharmacokinetics and pharmacodynamics of the drug.](image)

The figure shows the importance of the formulation in controlling the subsequent pharmacokinetic profile of the drug and its effect concentration achieved at the biophase

**PD** - pharmacodynamics - study of the biochemical and physical Effects of a drug
**PK** - pharmacokinetics - explains how the body affects a specific chemical after administration -
through the mechanisms of absorption, distribution, changes in enzymes for drug metabolism, and effects and routes of excretion of the drug metabolites.

Bioequivalence means that two drugs release their active ingredient into the blood stream in the same amounts and at the same rate.

General types of medicines
In the regulatory system, medicines generally fall into three categories: Innovator products, Generic products, and Compounded products. These three categories are controlled by the Medicines and Related Substance Control Act (Act 101 of 1965):

- **Innovator Products**: Are the first products that are brought onto the market. They are tested as the final formulation to prove that the active ingredient is properly released and that the formulation is effective. When registered, each indication is looked at individually and requires testing usually with actual clinical cases. The innovator company is generally allowed a period of 20 years from patenting, to sell their product with no competition. It is during this period that they recoup their investment. At all times, the manufacturer has to meet strict GMP requirements.

- **A Generic formulation**: Is a formulation that contains the same active ingredient as the innovator, and is registered through an abbreviated process known as bioequivalence or occasionally therapeutic equivalence. For the former process, the pharmacokinetics of the generic and the innovator formulation is compared. If the two formulations can be statistically proven to be bioequivalent, it can be registered as a generic to the innovator product. The underlying principle comes from the pharmacokinetic-pharmacodynamic interactions of the active mentioned above. If the two drugs allow for the same plasma concentration to be consistently achieved, there's no reason that they won't have the same effect. Since we do know that the manufacture of the formulation can influence the plasma pharmacokinetics, the formulation has to meet strict GMP conditions, to ensure batch to batch uniformity. Generics are thus cheaper than the innovator because they don't have to redo the efficacy and toxicity tests, as these have already been undertaken by the innovator company i.e. why retest for aspects that are already known. Since the pharmacokinetics of the generic formulation is unknown, this is what needs to be tested (Figure 4). With this said, the requirements for comparing the pharmacokinetic profiles of the generic to the innovator formulation is still very strict and has to comply with numerous requirements from the study design to the analytical chemistry part of the study.

![Figure 4: Illustration of how pharmacokinetics are applied in the process of proving bioequivalence of generic formulations (The graphs in question would be supported by a full statistical evaluation for registration purposes). In this case, two different generic formulations (T) (Each one has its own graph) are compared to the same reference product (R). In each of these cases the test and the reference product were compared to a reference produce in an independent two by two cross over study. As evident, the test generic formulation on the left clearly shows that the formulation is not bioequivalent as their profiles are not sufficiently similar. In contrast, the two formulations on the right are bioequivalent which is evident by the almost superimposed profiles.](image)

The principle of generic registration is considered to be highly sound, and has been used to bring numerous
generic medications onto the market over the last 40 years, with no proof existing that a generic is inferior when used for its registered indication. The science is so sound, that the innovator company also relies on the same methodology when they want to change their formulation e.g. when a tablet is changed to a palatable tablet, bioequivalence testing is used to save on costs and prevent retesting as once again, there is no need to repeat all the tests.

All in all, if a generic formulation is registered and the company follows GMP, there should be no difference between a generic and an innovator.

Nonetheless an important concept in generic medication development is the concept of switchability and prescribability.

- Generic are interchangeable and any of the registered formulation for a particular species can be considered a valid effective choice at the start or initiation of treatment in a patient. This is known as prescribability i.e. the choice is open when the drug is first prescribed.

- However this scenario changes when one is treating a chronic condition where the patient has been stabilised on treatment with a particular formulation e.g. epilepsy. Under these conditions, it is not advisable to switch formulations acutely (irrespective of whether it a generic or innovator) acutely. This acute switching can only occur if the products are tested for switchability, which most formations are not e.g. one can chose to use formulation A or formulation B initially (at this stage there is no difference). However at the end of the month, stick to the same formulation and don’t change acutely as this can be dangerous and result in destabilisation (i.e. for chronic patients, stock the same formulation). If you do need to change formulation, it’s always safer to phase out the old formulation while the new formulation is phased in.

- Compounded formulations: These are formulations that are meant for use in an individual patient and are tailor made drugs, usually made by a pharmacist on an as needed basis. Compounded formulations are generally simple formulations with the active dispersed in an excipient. These compounded products, due to their individualised nature, don’t need to legally comply with GMP requirements, and thus may be open to all the problems mentioned above. For this reason, the use of compounded products from a safety point to the patient and consumer, should not be used when there are alternate registered products i.e. legally one takes responsibility for the use. More importantly, it may be more difficult legally to demonstrate that the use of the compounded product use was prudent when there are GMP approved alternates available. Also of importance to consider is the product’s sterility and purity and shelf life. Since this may be a problem, compounded products should ideally be limited to oral or topical use; and they should not be used in production animals.

Is a Generic, definitely a generic?
This may seem as an odd question, in light of what has been said above. But it’s important to know the constraints of the process of bioequivalence. The foremost principle of bioequivalence is the comparison of the plasma profile between the test and reference product, and show that they’re essentially identical.

However as mentioned under pharmacokinetics, the PK of a drug is dependent on a number of factors such as absorption and elimination. This would mean that the profile is dependent on the species of testing and the metabolism of the drug. As such when bioequivalence is shown, each profile has to be determined for each the different route recommended and in each of the different species it is indicated for. As an example, a drug recommended for use by the subcutaneous and intramuscular in pigs, cattle and horses, will need to be tested in six separate studies to show that all the routes per species are bioequivalent.

Since it may not always be possible demonstrate bioequivalence in all these studies, some generic formulations will have curtailed claims. As such it is important to check what the recommendation are on the package instead of assuming that they are the same as the innovator (reference product).

Another important consideration is the use of human medication in animals. Firstly this extra-label use of the drugs has legal implications, as the person recommending this use, takes responsibility if something goes wrong (for registered veterinary drugs used correctly as stated on the package insert, the registration owner takes responsibility).

The use of human drug extra-label is nonetheless considered safer than using a compounded product, as good manufacturing practice is still in place as it’s a registered human product (i.e. same liability, but lower risk). As a veterinarian, it is incumbent on you to make use of your professional judgement when choosing to use a human formulation.
Firstly consideration must be given to the dose, which means that one needs to take into consideration the studies that have demonstrated that this extra-label use is prudent. For the latter consideration needs to be given to the sample size, as registered product use a substantial number of clinical cases to prove that the effect is real (as large as a few hundred animals) i.e. the published study on extra-label use may only have included a small number of clinical cases and not taken into consideration intra-subject variability in effect and side effects.

Another important consideration would be that the product used in the publication, may not necessarily be the same product that is sold locally e.g. There are numerous cases of companies choosing to market different formulations in different countries for various manufacturing reasons even though the name is the same.

It is possible that the published formulation may have a different response to the South African available drug, purely because they are of different formulation.

Another important scenario that comes up in South Africa is the cost of the medication. Under some conditions veterinary medications may be more expensive than their medical generics, due to lower costs on the medical side from larger scale production.

Can one use these human generics as cheaper therapeutic options? Firstly legally, the onus is on the treating veterinarian to let the owner know that there is a veterinary formulation and give them the option.

The reason for this, is that the medical product has been tested in only people and thus the veterinary profile may be unknown i.e. it may be possible that the drug has different profiles in the veterinary patient than in people.

When the GIT of man is compared to animals, there are major difference that can influence absorption between the species.

These difference may be anatomical in that there are different structure of the GIT; there may be difference in transit times; difference in content and thus non-specific binding; differences in bile salts; differences in pH amongst the different areas; differences in GIT bacterial content and/or species; differences in liver metabolic capacity; and most importantly differences in the transport proteins in the intestinal wall. The latter is also a major reason why veterinary drugs differ so much between species.

To illustrate the process, the innovator veterinary formulation of amoxycillin-clavulanate and Ran-Clav® (Ranbaxy) were compared at the same dose and the same route in the same six Beagles (in a cross-over study that was undertaken by myself).

The result for amoxycillin phase of the study showed a marked difference in absorptive profile between the two formulations. While the small sample size did result in significant variability in both groups, this was much more substantial (>80%) in the Ran-Clav® group.

This study illustrates the point that the non-veterinary formulation could not only differ in the extent of absorption, but more importantly could result in large intra-subject variability which could mean completely inferior treatment in some individuals.

This effect is addition to being potential dangerous, is also generally unknown until tested.

Figure 5: Average plasma concentration versus time profile for amoxycillin for a veterinary (R) and non-veterinary (T) amoxycillin formulation tested in the same group of six dogs in a 2x2 cross over study.

Conclusion
Drug regulation science, is a highly complex science that is focused on allowing the treating veterinarian the best chance of getting therapeutic success in a patient with the least chance of formulation failure.

This science extends to both innovator and generic formulations, but only so far as to the species and indication for which the product has been tested.

As such, when using a non-veterinary formulation, care should be practiced, as therapeutic success are affected by a number of unknown variables such as added excipients and exact structure of the active chemical / ingredient.
Table 2: Indication of how personal liability increases as different categories of medicines are used

<table>
<thead>
<tr>
<th>Category</th>
<th>Use</th>
<th>Benefits</th>
<th>Dangers</th>
<th>Liabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovator Vet Medicine/Stock Remedy</td>
<td>Registered Use</td>
<td>Proven safety, quality and efficacy</td>
<td>Poor storage can change product safety</td>
<td>If used and stored as per instructions: Falls to the manufacturer</td>
</tr>
<tr>
<td>Generic Vet Medicines/Stock Remedies</td>
<td>Registered Use</td>
<td>Proven safety, quality and efficacy</td>
<td>Poor storage can change product safety</td>
<td>If used and stored as per instructions: Falls to the manufacturer</td>
</tr>
<tr>
<td>Stock Remedies; Vet Med (innovator or generic) used extralabel</td>
<td>Used for non-registered purposes in the intended species</td>
<td>Proven quality. Safety known in target species if used at the recommended dose</td>
<td>Unknown efficacy when used for a new indication, and potentially safety concerns when used at a different dose.</td>
<td>Vet liable for extralabel use. Lower risk than other extralabel use, since use is in the intended species i.e. species safety usually known.</td>
</tr>
<tr>
<td>Stock Remedies; Vet Med (innovator or generic) used extralabel</td>
<td>Used for non-registered purposes in a non-indicated species</td>
<td>Quality of the product proven</td>
<td>Unknown efficacy as used for a new indication, and unknown safety concerns as used in an untested species</td>
<td>Vet liable for extralabel use. Risk increases as species safety usually unknown</td>
</tr>
<tr>
<td>Human Meds</td>
<td>Non-registered use</td>
<td>Quality of the product proven</td>
<td>Unknown efficacy and safety</td>
<td>Vet liable for extralabel use. Risks are the same as use of a veterinary medicine in non-indicated species.</td>
</tr>
<tr>
<td>Compounded Medicines</td>
<td>Non-registered product</td>
<td>Patient specific treatment option when no registered product is available</td>
<td>Unknown safety, efficacy and quality</td>
<td>Vet liable for use. Greater risk than extralabel use, since quality, safety and efficacy unknown</td>
</tr>
</tbody>
</table>