Assessment of Veterinary Pharmaceutical Products Registered in Kenya based on their routes of administration and dosage forms.

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Abstract
The aim of this study was to assess the veterinary pharmaceutical products that have been registered in Kenya in order to determine the most common routes of administration and the type of marketed dosage forms. Registered veterinary products were first categorized by route of administration and then sub-categorized by the dosage form. Veterinary pharmaceuticals delivered by oral and parenteral routes were the most common, collectively accounting for 87.7% of all registered products. Topical, intramammary, intrauterine and ophthalmic routes accounted for 4.7%, 3.3%, 1.0% and 0.1% of the registered products respectively. Products that could be delivered by more than one administration route comprised 3.2% of the registered products. For most routes of administration, a variety of specific dosage forms were available. Dosage forms for oral administration included solids (53.4%) namely powders, tablets, boluses, freeze dried products, granules; liquids (46.3%) namely suspensions, solutions, syrups and semi-solids (0.3%) namely pastes. Topically administered dosage forms included solutions, sprays, ointments, creams, shampoos and powders, while those delivered via the intrauterine route included pessaries, solutions and suspensions.

Keywords: dosage forms, administration route, veterinary pharmaceutical products, animal species, drug delivery

Introduction
Veterinary medicine encompasses the health, care, and treatment of animals. Animals may be classified as domestic (livestock and companion animals) or wildlife. Livestock are used to supply food, fibers (e.g., wool), hides, or labor. Common examples of livestock in Kenya are cattle, goats, sheep, camels, and chicken. Other livestock found locally include pigs, rabbits, ducks, and turkeys. Non-mammalian and non-avian animals of economic importance locally include fish and honey bees.

Livestock has been reported to account for 12% of the Kenya’s gross domestic product [FAO Livestock Sector Brief - Kenya, 2005]. Companion animals (e.g., dogs and cats) are used as pets. Dogs may also serve as working animals (e.g., guard dogs). Wildlife (through tourism) is a major contributor to the Kenyan economy. Wild animals, to a lesser extent than domestic animals, may also receive veterinary services (e.g., during translocation, disease surveillance, and vaccination). When one considers the economic impact of all these animal species, the importance of maintaining their health is readily appreciated. Veterinary medicine has a critical role in the healthcare of animals. An important component in the practice of veterinary medicine is the use of pharmaceutical products.

Diverse animal species display anatomical, physiological, pharmacological, and pharmacokinetic differences, which influence the selection of a drug delivery system and administration route [Toutain et al., 2010]. The same medicinal agent may need to be delivered at different dosages, via different routes of administration and dosage forms to different animal species in order to obtain an optimal therapeutic effect.

The medicinal agent refers to the active pharmaceutical agent (API) or drug, while the dosage defines the amount of API given to the animal. The dosage form refers to the vehicle used to deliver the API into the body while the administration route denotes the path of delivery. For example, an API may be formulated as a water-soluble powder for dilution into poultry drinking water, while in cattle the same API may be administered as an
injection intramuscularly. In this case, the dosage forms are a water-soluble powder (poultry) and an injection (cattle), while the routes of administration are oral (poultry) and parenteral (cattle). Some dosage forms (e.g., tablets, solutions, injections, creams, ointments) are used in both humans and animals for drug delivery. Other dosage forms, such as topical pour-on (or backliner) and spot-on solutions, ruminal boluses, flea collars, ear tags, feed premixes, medicated blocks and intramammary infusions, are unique to animals.

The choice of dosage form and administration route of a drug influences both the intensity and the duration of its pharmacological effect [Baggot, 1992]. While consideration of drug pharmacokineti/cpharmacodynamic profiles is important for all drug classes [Martinez et al, 2010], it is critical for drugs such as anti-infectives and anti-parasitics whereby exposure to sub-therapeutic doses may promote the development of drug resistance by target organisms [Mckellar et al, 2004]. Widespread resistance has been seen with antimicrobials such as penicillins, aminoglycosides among others [Morley et al, 2005] and anthelmintics like benzimidazoles, levamisole, pyrantel, and ivermectin [Kaplan, 2004].

For food (or fiber) producing animals, the dosage form and route of administration is important because it influences the amount of residual drug in the food (or fiber) provided by the animal and thus withdrawal times, for example ivermectin has a slaughter withdrawal time of 35, 48 and 180 days after administration via subcutaneous injection, topical and oral bolus respectively. The differences in withdrawal times are due to variations in the release of ivermectin either from residues accumulated in the animal tissue as seen at the injection site and skin, or from the sustained release dosage form [KuKanich et al., 2005].

Knowledge of the dosage forms, which are used to deliver veterinary medicines that are available in a particular market, is beneficial to academicians in designing of their training programs. For the pharmaceutical industry, knowledge of the available dosage forms may help in identifying gaps in the market for new product opportunities. For regulatory bodies, this knowledge may help in guiding drug regulation/surveillance programs and future drug registration.

Therefore, the aim of the present study was to analyze the veterinary pharmaceutical products that have been registered in Kenya and categorize them by: 1) route of administration and 2) type of dosage form. The paper also provides a brief overview of the main pharmaceutical products delivered by specific administration routes and dosage forms. Finally, the general advantages as well as disadvantages of these administration routes and dosage forms are outlined.

Materials and Methods

The information on the drug dosage form and administration route was obtained by analyzing the Pharmacy and Poisons Board online database of registered veterinary drugs in Kenya [PPB - Registered Veterinary Drugs, 2012]. The products were first characterized by administration route, and then by the dosage form. Oral products were also categorized into solids, semi-solids and liquids. The routes of administration screened for products were oral, parenteral (injections), nasal, transdermal, otic, ophthalmic, intravaginal, sublingual, topical, intramammary and intrauterine routes. The dosage forms used for the classification included powders, tablets, boluses, freeze dried products, granules, solutions, suspensions, syrups, emulsions, creams, ointments, shampoos and pessaries.

Results and Discussion

The registered veterinary products (682 entries) on the database were categorized according to the route of administration. 97.2% of these products (663 entries) were classifiable by route of administration. The remaining 2.8% of these products (19 entries), which were either environmental (e.g. disinfectants for aerial fogging and cleaning of floors/surfaces of the animal shelters) or which could not be classified due to insufficient/conflicting information on the database, were excluded from the study.
Figure 1 shows the percentages of registered products classified by their route of administration. Oral (48.9%) and parenteral (38.8%) routes accounted for majority of the products. The collective percentage of 87.7% shows that both oral and parenteral routes are quite popular in veterinary medicine. This could be due to a combination of factors. The oral route is generally more convenient and safer to use, while the parenteral route offers advantages such as high bioavailability and rapid onset of action. However, oral administration in animals is often more complicated than it is in humans, since many species will not readily ingest pharmaceutical products.

![Figure 1: Percentages of registered products classified by route of administration](image)

In the present study, the products delivered by the parenteral route mainly comprised antimicrobial agents, e.g., penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, sulfonamides, fluoroquinolones e.t.c., for treatment of systemic conditions in ruminants. Indeed it has been reported that the parenteral route is the most efficient route for administration of antimicrobials to ruminants, whose gastrointestinal system may lead to poor drug absorption [Johnston, 1998]. Majority of the locally registered products administered via the oral route comprised of anthelmintics for the control of parasitic nematodes in ruminants or companion animals and products for use in poultry. The anthelmintics for ruminants or companion animals included a range of classes such as benzimidazoles, imidazoles-tetrahydro pyrimidines, avermectin -milbeycins among others. The dosage forms of the oral anthelmintics were tablets, boluses, suspensions, solutions and powders. The oral route is ideal for control of nematodes as this route delivers a high concentration of the drug to the gastrointestinal system, which is the local site of colonization, thereby optimizing treatment. Products for administration to poultry included antimicrobials, multivitamins and vaccines among others, mainly available as powders for dissolution in drinking water or as feed premixes.

The topical route of drug administration accounted for 4.7% of the registered products, while intramammary, intrauterine and ophthalmic routes accounted for 3.3%, 1.0% and 0.1% respectively. Topical, intramammary, intrauterine and ophthalmic routes are usually used to deliver drugs intended for local action, thereby reducing the incidence of systemic side effects. Drugs that could be administered via more than one route were designated ‘multiple route’ and this group formed 3.2% of the registered products.

Figure 2 shows the categorization of oral dosage forms into solids, semi-solids and liquids. The majority of the oral dosage forms were either solids (53.4%) or liquids (46.3%). Solid dosage forms delivered orally included tablets, capsules and powders. They offer advantages of portability, manufacturability, affordability (relative to other dosage forms) and physical/chemical stability. Liquid dosage forms administered orally, which includes suspensions, solutions and syrups may be more suitable for animals that cannot readily swallow tablets or capsules such as birds (poultry) as well as larger animals (cattle, goats and sheep) in some circumstances. Liquid dosage forms provide a faster onset of action than solids as they do not undergo disintegration. Liquids dosage forms administered orally are however bulkier and less physically/chemically stable than solids. Semi solid products such as pastes, which consist of a drug powder dispersed in an aqueous or fatty base, comprised only 0.3% of total oral products. Pastes are used for animals such as cats and horses.
Tablets and boluses accounted for 22.0% and 20.8% of the oral solids respectively. Conventional or chewable tablets are often used to deliver drugs to dogs and cats. Specific flavors (e.g., yeast or meat-based flavors) are sometimes incorporated into tablets to make them more palatable.

However the odor of a formulation may be more important than its taste in determining acceptance by dogs, necessitating odor masking strategies. A bolus is a controlled release tablet or device, which is designed to be retained in the rumen of ruminating animals and release the drug over an extended period of time (e.g., up to 6 months or longer) thus reducing cost and frequency of treatment. The release of drug is dependent on the bolus design occurring via mechanisms such as erosion, diffusion from an insoluble matrix or via osmotic pumps.

Pulsed release boluses designed to release the drug at specific times are also available. Boluses are delivered to the back of the throat of a restrained animal, via means of a balling gun, before being swallowed and descending to the rumen. The rumen is a large fermentation chamber containing large volumes of fluid and good mixing conditions thereby enhancing drug release from the bolus [Rathbone, 2012].

Freeze dried products (1.7% of oral solids) are meant for reconstitution with appropriate diluents before oral administration. These products are usually vaccine products. Granules comprised 0.6% of oral solids.

Figure 4 presents the individual types and percentages of oral liquid dosage forms. Suspensions (72.7%) accounted for the majority of products, followed by solutions (26.7%). Syrups only accounted for 0.6% of the oral liquids. Suspensions and solutions are liquid dosage forms in which the drug particles are either dispersed or dissolved in liquid media respectively. Syrups are viscous liquids containing a high concentration of sugar.
The high sugar content in syrups is useful in masking the taste of bitter drugs in human pharmaceuticals; however animals tend to have different taste sensations.

**Figure 4:** Type and percentages of liquid dosage forms administered by oral route.

The parenteral route accounted for a large percentage (38.8%) of registered veterinary products. Though the term parenteral means any route other than oral, parenteral here refers to products delivered via injection for systemic action. The observed injections comprised of solutions, suspensions, emulsions and powders for reconstitution. Suspensions may be delivered intramuscularly or subcutaneously, while only solutions may be delivered intravenously. The parenteral route is important in emergencies, severe infection, and for drugs that cannot be administered orally due to degradation in the gut.

Figure 5 shows the percentages of products delivered via all routes of administration excluding oral and parenteral routes. The topical route was the most popular accounting for 37.8% of these other products (excluding oral and parenteral), while the intramammary, intrauterine and ophthalmic routes accounted for 26.8%, 8.6% and 1.2% respectively. Pharmaceuticals that could be delivered via multiple routes (e.g., some poultry vaccines which could be delivered either via oral, occlusal or topical routes) comprised 25.6% of these other products (excluding oral and parenteral routes). The different routes of administration of the poultry vaccines are occasioned by the size/age of the birds.

**Figure 5:** Percentages of registered products (excluding oral and parenteral products) classified by route of administration.

The intramammary route, whereby the drug formulation is directly infused into the teat canal, delivers a high drug concentration to the local site of infection. All infusions observed in this study were intramammary antibiotic suspensions intended for the prevention/treatment of mastitis. Pharmaceutical factors such as drug solubility, lipophilicity, ionization, particle size, and vehicle base as well as animal factors like severity of mastitis and milk production volume influence the drug disposition and hence the success of treatment [Gehring et al, 2006]. Disadvantages of intramammary drug administration include the possibility of infection or injury of the teat canal, uneven drug distribution in the udder quarters, and long milk withholding times due to persistence of drug residues in milk.

Topical, intramammary, intrauterine and ophthalmic routes are often employed for local delivery, thus reducing the incidence of side effects. Ophthalmic dosage forms include ointments, drops, sprays or powders – in this study only one ophthalmic powder, an antibiotic specifically designated for treatment of pink eye (infectious bovine keratoconjunctivitis), was observed. Eye drops and ointments may provide better alternatives in the treatment of pink eye, as powders will further irritate the already inflamed eye.

Figure 6 illustrates the types and percentages of topical dosage forms. The topical route is a simple and convenient route often employed for local action either in treatment of skin conditions or in prevention of external parasites (e.g. mites, ticks and fleas). The major
topical dosage forms observed were solutions (32.3%), sprays (29.0%), and ointments (19.4%). Formulations intended for control of external parasites, are termed pour on (or backliner) and spot-on, depending on the mode of application. Ointments are petroleum based semi-solid formulations used to deliver a medicament and/or provide lubrication to skin surfaces. These formulations include milking salve used to prevent drying and chapping of cow teats. Creams, shampoos and powders accounted for the rest of the topical products comprising 9.7%, 6.4% and 3.2% respectively.

Creams differ from ointments in that they are water based and of lighter consistency. Shampoos are surfactant based washes used in the cleaning of animals' coats and fur.

![Figure 6: Type and percentages of dosage forms administered topically.](image)

Figure 7 gives the types and percentages of intrauterine dosage forms. In cattle, the intrauterine route is often employed, for local action, in treatment/prevention of postpartum disorders such as endometritis. Pessaries/oblets (tablets designed to foam on contact with moisture) containing medicaments such antibiotics accounted for 71.4% of the uterine products. Suspensions and solutions each accounted for 14.3% of the intrauterine products.

![Figure 7: Type and percentages of dosage forms administered by intrauterine routes.](image)

Fifty five products were listed as vaccines. The administration routes of these vaccines varied according to the type of vaccine and animal. Cattle vaccines were mainly for parenteral administration via the intramuscular or subcutaneous routes, while poultry vaccines could be administered orally, oculonasally, topically, and even parenterally. Only one product listed as an implant was observed. The implant was Crestar® (norgestomet) used for oestrus control in dairy cattle.

No products intended for delivery via the rectal, transdermal, otic, pulmonary, intravaginal or sublingual routes were observed.

Conclusions
The study found that there is a wide variety of dosage forms of locally registered veterinary pharmaceuticals in Kenya and that these products are administered by various routes. Oral and parenteral routes of administration accounted for the majority of the products. The type of animal, site of infection and the drug pharmacokinetics influenced the delivery options, dosage forms/routes of administration, available for a particular drug.
References


