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Article

Inconsistencies in the quality of the information on package inserts of medicines for veterinary use commercialized in Brazil

Vanessa Cola Thomazini[1], Vitória Ribeiro Mantovanelli[2], Marcela Saager Dias[2], Letycia Fernandes Franklin Ávila[2], Vinycius Fernandes da Rocha[2], Nayhara Madeira Guimarães[1], Gabriel Mendes da Cunha[3], Cristiane dos Santos Giuberti[3], Janaína Cecília Oliveira Villanova[1,2,3*]

[1]Graduate Program in Veterinary Sciences, Center for Agricultural Sciences and Engineering, Federal University of Espírito Santo, Alegre, Espírito Santo, Brazil, [2]Pharmaceutical Product Development Laboratory, Center of Exact, Natural and Health Sciences, Federal University of Espírito Santo, Alegre, Espírito Santo, Brazil, [3]Graduate Program in Pharmaceutical Sciences, Center of Health Sciences, Federal University of Espírito Santo, Alegre, ES, Brazil

This study examines the adequacy, readability, and quality of the information provided on package inserts for veterinary medicines in Brazil. It aims to identify the essential information required in these documents and assess non-compliance with regulatory standards. Initially, a documentary analysis was conducted to identify mandatory information as per Federal Decree No. 5,053/2004 and Normative Instruction No. 26/2009 of the Ministry of Agriculture, Livestock and Supply. Subsequently, 256 package inserts were analyzed to evaluate their suitability using descriptive quantitative analysis. This analysis showed a lack of essential technical and scientific information, necessary for the rational use of veterinary medicines. Mandatory elements supporting the correct use of veterinary medicines and essential information, such as a qualitative description of excipients, equivalence factors, the mass of active pharmaceutical ingredient per volume (when applicable), and information about the customer service center, were absent from these documents. This study found at least one non-conformity in the 252 evaluated package inserts. These findings underscore the significant lack of adherence to established rules and the low quality of technical-scientific information, reducing the comprehension of both prescribers and owners. The authors highlight the need for regulatory agencies to review and improve the guidelines that govern the format and content of package inserts.

Keywords: Package insert. Legibility. Health communication. Veterinary pharmacy.

INTRODUCTION

The market for veterinary products has experienced a marked growth in recent years, with a forecast increase of 7.4% from 2023 to 2024. Around the globe, the commercialization of medicines exclusive for veterinary use is expected to generate more than $42 billion by 2028. The factors driving this growth include personalized medicine in veterinary care focused on preventive medicine, regulatory compliance, and investments in the discovery of new drugs and the design of alternative and innovative pharmaceutical dosage forms (The Business Research Company, 2024). In this scenario, attention must be paid to the rational use of medicines in veterinary practice, which includes preparing package inserts that will contribute to maintaining the quality of medicines and the safety and effectiveness of pharmacotherapy.

The Brazilian Health Regulatory Agency (ANVISA) and the Ministry of Agriculture Livestock

***Correspondence:** J. C. O. Villanova. Laboratório de Desenvolvimento de Produtos Farmacêuticos. Centro de Ciências Exatas, Naturais e da Saúde (CCENS). Universidade Federal do Espírito Santo (UFES). Avenida Alto Universitário, S/N. CEP: 29500-000, Guararema, Alegre, Espírito Santo, Brasil. Phone: +552835528769. E-mail: pharmacotecnica@yahoo.com.br. ORCID: https://orcid.gov/0000-0001-6166-1724

and Food Supply (MAPA) are the agencies responsible for regulating the manufacture of medicines for exclusive veterinary use (MEVU). A Joint Technical Note issued on April 23, 2012, regulated the manufacturing of MEVU in the same pharmaceutical laboratory licensed to manufacture medicines for human use if the active pharmaceutical ingredients (API) are for animal and human use, considering the availability of data on toxicity and safety of use in the latter population. In these cases, manufacturers are subject to inspections by both aforementioned agencies. In the case of APIs for exclusive use in veterinary pharmacotherapy, facilities, equipment, and manufacturing lines must be segregated. Moreover, only MAPA can establish manufacturing standards and carry out health inspections (Ministério da Agricultura, Pecuária e Abastecimento, 2012). The registration of MEVU in Brazil is the sole responsibility of MAPA, in accordance with Decree-Law No. 467 of February 13, 1969 (Brasil, 1969).

ANVISA and MAPA standards show divergences on the regulation of topics related to medicines manufacture, for example, the preparation and approval of packaging, which must be prepared by marketing authorization holders and approved by health agencies. Package inserts are legal documents that accompany medicines. The Brazilian regulatory agencies require them for registration grants and license requests for the commercialization of medicines for human and veterinary use (Brasil, 1969; Agência Nacional de Vigilância Sanitária, 2022a). Due to reports regarding difficulties reading and understanding the information on package inserts and the constant updates of standards to the manufacture and registration of medicines, ANVISA frequently updates its guidelines for the preparation of packaging of medicines for human use. In 2022, ANVISA (2022a, 2022b) published standards that are considered regulatory marks for medicine packages, aiming to increase patient safety and mitigate possible medication errors arising from inconsistencies and difficulties reading and interpreting such information. One of the main advances of RDC No. 768, of December 12 of 2022 (RDC 768/2022), refers to the definition of criteria to improve the form and content of labeling for all medicines in Brazil, guaranteeing access to suitability and safe and clear information. RDC No. 768/2022 also standardized packaging to systematize information about specific medicines (such as phytotherapeutic, generic, and similar medication) and established the creation of electronic package inserts (Agência Nacional de Vigilância Sanitária, 2022a). RDC No. 770, of December 12, 2022 (RDC 770/2022), also regulated another relevant advance, which standardized the inclusion of warnings related to the presence of APIs and concerning excipients on package inserts and labels (Agência Nacional de Vigilância Sanitária, 2022b). Contrary to the evolution of ANVISA rules and guidelines, MAPA standards for MEVU packaging have undergone no updates in the last decade, although a public consultation was carried out to approve a new regulation for granting registration and for the use and inspection of products for veterinary use in the country (Ministério da Agricultura, Pecuária e Abastecimento, 2022).

Packaging can be classified as primary or secondary: primary packaging lies in direct contact with the medicine to protect and maintain its stability, whereas secondary packaging contains the primary packaging and includes cartons, labels, and package inserts to provide information about the medicine to patients, users, caregivers, owners, prescribers, and other health care providers involved in medicine administration (Allen, McPherson, 2021; Mengesha, 2021). Since the main objective of package inserts is to guide the rational use of medicines and provide information on precautions for their correct use and storage to guarantee their quality, effectiveness, and safety, these documents have value as instructional material. The information manufacturers or marketing authorization holders provide on package inserts is often the only data available to clinicians, healthcare professionals, patients, and owners. Therefore, this information must be reliable, easily accessible, written in an objective and clear manner, easy to read and understand, with updated information, and based on technical and scientific knowledge. The format must

also comply with legal guidelines, including letter font and size, spacing, paper color standards, among others (Agência Nacional de Vigilância Sanitária, 2022a; Agência Nacional de Vigilância Sanitária, 2022b; European Comission, 2009; European Medicines Agency, 2012; Food and Agriculture Organization, 2016; Mengesha, 2021). Difficulties reading and understanding the information on package inserts represent one of the main sources of medication errors and contribute to failures and low adherence to pharmacotherapy, requiring regulatory agencies to constantly update their rules, guidelines, and templates for this document (Al Jeraisy *et al*., 2023; Hoeve *et al*., 2020; Pires, Vigário, Cavaco, 2016; Zini *et al*., 2018).

The literature contains several reports that aimed to evaluate the readability and suitability of the information on the package inserts of medicines for human use. Many studies also report the likely impacts on human health resulting from the observed inconsistencies. On the other hand, few studies have evaluated inconsistencies in MEVU package inserts, mostly referring to antimicrobials given the global concern about antimicrobial resistance and the One Health context (Guimarães, 2019; Gulwako *et al*., 2023; Riet, 2021; Tufa *et al*., 2018; Silva *et al*., 2023; Souza *et al*., 2015). Therefore, this study aims to highlight the importance of regulating MEVU package inserts in Brazil.

MATERIAL AND METHODS

This exploratory documentary investigation was characterized by qualitative and quantitative approaches in two stages. In its first qualitative stage, the MAPA Federal Decree and Normative Instruction were consulted to prepare a list of information that must appear on MEVU package inserts (Brasil, 2004; Ministério da Agricultura, Pecuária e Abastecimento, 2009). In its second stage, a quantitative evaluation was conducted on 256 package inserts of veterinary medicines commercialized in Brazil to assess their compliance with the regulatory standards in force in 2023 (Federal Decree No. 5,053/2004 and Normative Instruction No. 26/2009 of the MAPA) and to identify the presence of elements considered relevant for the safe use of medicines by the animal population. Specific regulations on the package inserts of biological and biotechnological vaccines and medicines were ignored by this study. Both stages aimed to establish correlations between the collected information and the potential impact of the observations on animal health.

Unlike ANVISA, MAPA has no electronic repository of package inserts for free consultation. Therefore, the package inserts were directly sourced from the websites of national pharmaceutical laboratories, whose names were kept confidential for ethical reasons. Only package inserts for veterinary medicines that are manufactured in Brazil were analyzed. This study focused on medicines from the therapeutic classes that are most prescribed for the animal population, including analgesics, antiparasitics, anti-inflammatories, antiemetics, antihypertensives, antidepressants, and antimicrobials. The analysis was limited to conventional pharmaceutical dosage forms (liquid, solid, or semi-solid) for internal and external use, which are orally, parenterally, topically, ophthalmically, intramammary, pulmonary, or transdermally administered, aimed toward local or systemic action. Package inserts containing associated APIs were not included. In cases in which more than one veterinary medicine product containing the same API was manufactured by different laboratories, only one package insert was examined. Descriptive statistics were used to analyze the data, and the variables examined regarding MEVU package inserts were derived from the regulations analyzed in the first stage of this study.

RESULTS

Table I shows the mandatory information that must be included on MEVU package inserts (except for specific medicines such as vaccines, biologicals, and antimicrobials) based on regulatory rules.

TABLE I - Minimum information that must be present on MEVU package inserts according to the Brazilian regulatory agency*

Information for product identification	1	Trade name
	2	Name of API or each API in an association
	3	Quantity (number of dosage units, volume, or weight)
	4	Concentration (amount of API or each API in the association)
Technical information that supports correct use by owners and prescribers	5	Etiological agents and susceptible animal species (when relevant)
	6	Dose by target animal species
	7	Indications for use
	8	Posology and duration of treatment
	9	Withdrawal period (if any)
	10	Drug interactions
	11	Contraindications
	12	Side effects
	13	Precautions and warnings
	14	Antidotes
	15	Instructions for use
	16	Summary information about the pharmacodynamics and pharmacokinetics of APIs (for antimicrobials)
	17	Storage conditions (temperature, humidity, and light)
Information about the marketing authorization holder or manufacturer and legal statements	18	Type of sale (with or without prescription)
	19	Marketing authorization holder
	20	Manufacturer information (name, CNPJ code, and address)
	21	Data of the responsible technician (name and register number)
	22	Batch, manufacturing date, and expiration date
	23	Legend: "VETERINARY USE"
	24	Legal and/or special words and warning phrases (when relevant)

*The information required for the package inserts of vaccines and biological and biotechnological medication for veterinary use were ignored.

The comparison of MAPA standards with those of other regulatory agencies showed a lack of essential information to ensure the quality of products and support their correct use, therapeutic efficacy, and animal safety. The main information MAPA standards failed to require include route of administration; type of administration (internal or external; local or systemic); pharmacological and pharmacokinetic data of APIs or their combination; adverse reactions (ARs) of APIs or their combination; qualitative description of the formulas' excipients; conversion factor between different forms of API (when applicable); relations between the number of drops and the dose to be administered in the case of liquid pharmaceutical forms, such as solutions and suspensions

(when applicable); and data from the Customer Service Center (CSC) of the marketing authorization holder.

The second phase of this study reviewed 256 package inserts for MEVU sold in Brazil to evaluate the compliance of the information with the items in Table I and to identify the presence of other information outside the evaluated MAPA standards but considered essential for animal safety. Out of all package inserts, 78 were of solid pharmaceutical dosage forms (tablet, capsule, powder), 154 were of liquid dosage forms (solution and suspension), and 24 package inserts were of semi-solid products (cream, paste, ointment, and gel). The 252 package inserts included at least one inconsistency, failing to comply with current regulations.

Regarding product identifying information, all evaluated package inserts correctly indicated the trade name, the names of the APIs (according to the Brazilian Common Denomination), and the total quantity (unities, volume, or mass) of the medicines. As for the elements that support the correct use of MEVU, only the indication for use and summarized information about pharmacodynamics and pharmacokinetics of APIs for antimicrobials met established standards. All other items showed non-conformities on one or more package inserts. In agreement with the technical information on medicine registration, all items in Table I fully complied with national standards regarding data on marketing authorization holders, manufacturers' address and CNPJ code, product registration numbers, information about responsible technicians, type of product (over-the-counter or prescribed), and manufacturing and expiration date. All package inserts included the warning "VETERINARY USE" and the legal statements: "Keep out of the reach of children and animals", "Caution: use by humans may cause serious health risks", "Sale under prescription from a veterinarian, with mandatory retention of the prescription notification", "Attention: prohibited use in pregnant animals", and "Pregnant women cannot come into contact with the medication as the substance can cause serious defects in fetuses", when applicable. This study found that the main lacking information on package inserts referred to their section about technical information supporting their correct use. Figure 1 graphically describes these data.

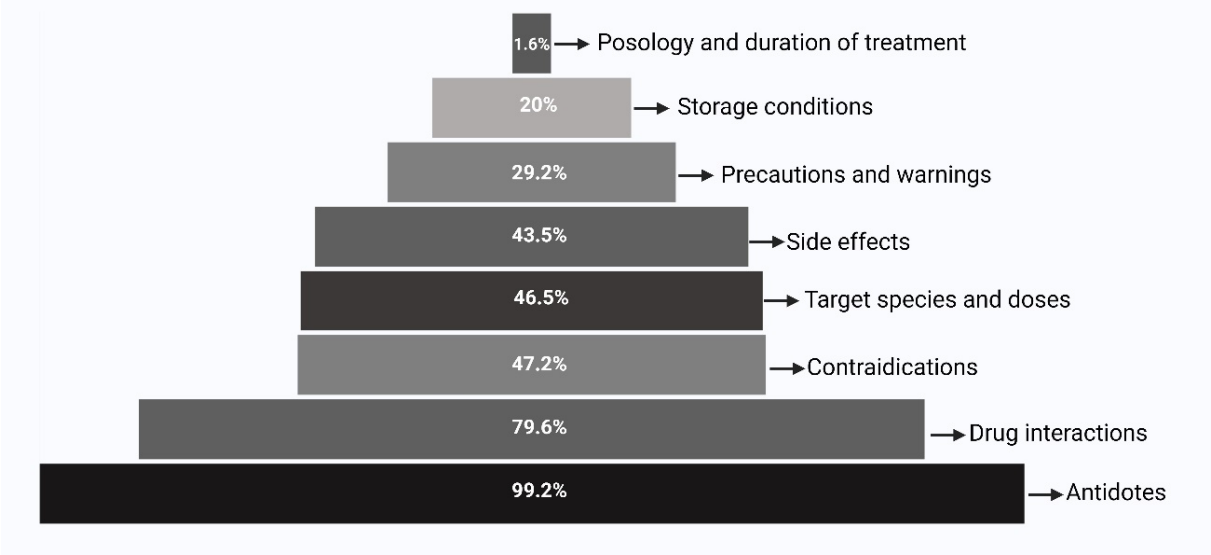

FIGURE 1 - Percentage of package inserts lacking technical information supporting correct use by owners and prescribers, according to Table I.

DISCUSSION

Lack of essential information on MEVU package inserts according to the current Brazilian legislation

According to the European Commission (2001), package inserts in medicines for human use must contain six sections summarizing the following information: (i) what the medicine is and what it is used for; (ii) what patients must know before using the medicine, including a list of warnings and precautions, explanations, and most common symptoms of conditions possibly arising from their use; (iii) the correct way to use the medicine; (iv) possible ARs — classified by frequency of occurrence according to clinical trials; (v) how to store the medicine; and (vi) the contents of the packaging and other information, including on product registration marketing authorization holders and/or manufacturers. ANVISA (2022a) stipulates two types of package inserts for medicines for human use: one designed for prescribers and healthcare providers and the other, simplified but complete, for patients. For the European Medicines Agency (EMA, 2012), the information on MEVU package inserts must resemble that required for medicines for human use. In Brazil, MEVU package inserts must contain a minimum of 24 items distributed in three sections: (i) medication identification; (ii) information for users, and (iii) technical information for prescribers (Brasil, 2004; Ministério da Agricultura, Pecuária e Abastecimento, 2009). Brazilian rules for MEVU agree with those of the United Nations Food and Agriculture Organization (2016).

MAPA requires neither the important information supporting the quality of medicines nor their therapeutic efficacy and safety for the animal population. The lack of information regarding the route of administration and indication of use (internal, external, local, or systemic) reduces owners' understanding of the correct way to use medications, impacting the efficacy and safety for the animal. On the other hand, the pharmacological characteristics that describe the pharmacodynamic and pharmacokinetic parameters of APIs or their associations are especially important for prescribers as they enable the correlation of API variables, such as action mechanisms, absorption time, plasmatic half-life, elimination routes, biotransformation, binding to plasma proteins, among other useful parameters for monitoring therapeutic and pharmacovigilance actions. Information about the mechanisms of action and values of plasma and elimination half-lives helps defining API associations, establishing correct dosages, posology, and duration of treatment, which can be compromised if the information is not easily available to veterinary prescribers (Ahmed, Kasraian, 2002).

Current Brazilian rules does not require the inclusion of ARs on MEVU package inserts, unlike information on side effects, which are considered necessary. Although used colloquially as a synonym for AR, side effects refer to a secondary therapeutic effects resulting from the use of medicines regardless of dose, i.e., possibly harmful effects unlike those expected or observed in tissues or organs other than those anticipated. Some medicines are prescribed based on their side effects: mirtazapine (prescribed as an antidepressant), for example, can stimulate weight gain, being administered as an adjuvant in the treatment of anorexia in cats (Poole *et al*., 2019). On the other hands, ARs are defined as any unintended, unwanted, or harmful events that occur after the administration of the recommended doses of MEVU, requiring the discontinuation of pharmacotherapy (Aronson, Ferner, 2003). Regulatory agencies worldwide point out that ARs of veterinary medication must be described on MEVU package inserts and be classified as very common, common, uncommon, rare, and very rare, according to their frequency of occurrence (European Medicines Agency, 2012; Food and Agriculture Organization, 2016).

A controversial and underexplored aspect of veterinary pharmacotherapy is the potential for ARs due to excipients in MEVU. Historically, excipient safety has been overlooked but research now finds that the toxicity of certain excipients to target animal populations should be considered (Thomazini *et al.*, 2023). According to Abrantes, Duarte, and Reis (2016), excipients are chemically and pharmacologically active, and assessing their safety is complex due to their chemical nature, production sources, potential

for secondary products and contaminants, and the various technological functions they can perform in formulations. The veterinary literature includes reports showing ARs to commonly occur due to excipients used in MEVU, such as benzalkonium chloride, benzoic acid, ethanol, mannitol, mineral oil, polyethylene glycol, polysorbate, sodium benzoate, sodium lauryl sulfate, sulfites, xylitol, and others (Thomazini *et al*., 2023). Davidson (2017) warns that excipients can harm certain animal populations, even if they are Generally Recognized as Safe (GRAS) and used correctly (concentration, dosage form, and route of administration). Therefore, it is important for MEVU manufacturers to ensure the safety of exposure to excipients for animal populations, which can be achieved by providing this information on package inserts (European Commission, 2001; European Medicines Agency, 2012). According to EMA (2012), knowing the qualitative composition of excipients is crucial for the proper administration of veterinary medicines. Package inserts should use the usual common name or chemical description of these components and include a warning in their "contraindications" section, stating that the medicine should be avoided in cases of AR or hypersensitivity to any excipient. Golightly *et al.* (1988) recommend that all drug manufacturers publish the list of excipients in their package inserts, making this information easily accessible to prescribers, healthcare providers and drug information centers.

In Brazil, only biological medicines require the inclusion of a list of excipients in the package inserts of MEVUs. Other products must describe excipients in the product dossier for registrations and post-registration changes. In its Normative Instruction 23/2016, MAPA establishes that changes in the type and quantities of excipients in liquid, solid, and semi-solid pharmaceutical products can only occur after a request for registration changes has been approved by the agency. Data on bioavailability and efficacy of medicines must be presented when relevant, and toxicological information on excipients must be provided (Ministério da Agricultura, Pecuária e Abastecimento, 2016).

Information regarding equivalent (EqF) or conversion factors (ConvF), although relevant for the efficacy and safety of the medication, is not mandatory in the package inserts of MEVUs. EqF is a dimensionless number used to convert the mass of an API from one form to another, such as free base, salt form, esterified form, hydrated form, or anhydrous form. This information helps make API doses unambiguous for prescribers, dispensing professionals (Allen, McPherson, 2021). The Brazilian Federal Pharmacy Council regulates the calculation and application of these factors, with legal sanctions for pharmacists who fail to apply them correctly during manufacturing or compounding medicines (CFF, 2016). The United States Pharmacopeia (USP, 2022) categorized non-sterile product compounding complexity into three types: simple, moderate, and high. The compounding procedures that require special calculations, such as the application of conversion factors, configures an activity of moderate complexity. Furthermore, when the pharmacopeial monograph of an API is unavailable for EqF value verification, understanding how the API dosage should be expressed may require the consultation of the package insert of a medicine. Numerous APIs for veterinary use have an EqF that must be known not only to guarantee the administration of its correct dose, but also to ensure that pharmacists responsible for preparing master formulas in pharmaceutical laboratories or in compounding pharmacies adjust the masses in the formulations. Table II provides some examples of APIs with an EqF.

TABLE II - Examples of APIs for veterinary use that have a tabulated EqF

Base	Salt, ester, or hydrated form	Tabulated EqF
Amoxicillin	Amoxicillin trihydrate	1.15
Interpretation	575 mg of amoxicillin trihydrate are equivalent to 500 mg of amoxicillin	
Flunixin	Flunixin meglumine	1.66
Interpretation	8.3 mg of flunixin meglumine are equivalent to 5 mg of flunixin	
Azithromycin	Azithromycin dihydrate	1.05
Interpretation	524.10 mg of azithromycin dihydrate are equivalent to 500 mg of azithromycin	
Doxycycline	Doxycycline hydrochloride	1.13
Interpretation	93.32 mg of doxycycline hydrochloride are equivalent to 80 mg of doxycycline	
Atropine	Atropine sulfate	1.03
Interpretation	0.2566 mg of atropine sulfate are equivalent to 0.2500 mg of atropine	

Likewise, another piece of information that could compromise the safety and effectiveness of veterinary pharmacotherapy refers to package inserts suppressing the relation between the volume of a liquid medicine, the number of drops contained in the volume to be administered, and the dose of API in each drop or in the total volume to be administered. Liquid pharmaceutical dosage forms as solutions or suspensions intended for administration as drops require that the product formulation phase calibrate the number of drops in each volume of the formulation (usually 1 mL) since densities vary across pharmaceutical formulas. Thus, the dose of drug in each drop varies according to product density, and package inserts must include this relation to ensure the administration of the correct dose of the API (Costa *et al*., 2021).

Various studies have explored the effect of parameters on drop mass or volume, highlighting the risks of incorrect dosing and associated negative pharmacotherapy outcomes. Costa *et al.* (2021) assessed the variations in the masses of drops from commercially available lubricating eye drops. They found significant differences between products, suggesting potential dosing discrepancies that could compromise treatment effectiveness. Drop masses ranged from 16.5 to 19.7 mg, which the authors attributed to factors such as bottle positioning and dispensing force, mentioning lack of standardization in packaging materials, shapes, and nozzle diameters as sources for such variation. From a pharmacotechnical perspective, formulation aspects such as density, viscosity, and surface tension also impact drop variation (Attebäck, Hedin, Mattsson, 2022). In addition to these parameters, the information provided to users on the correct way to utilize the dosing bottle and to prescribers on the relation between the number of drops and the dose of each formulation reduces the possibility of medication errors and increases the chance of pharmacotherapy success (Peacock *et al*., 2010). In this context, MAPA should perhaps consider the consequences of varying the mass of APIs in drop medicine and include standardized information on MEVU package inserts. The number of drops can be determined by the "dripping test," described by the United States Pharmacopeia (2022). The test serves to determine the relation between the number of drops per milliliter (1 mL) and the amount of API per drop for liquid pharmaceutical forms packed in containers with an integrated dosing device, ensuring the administration of the correct dose in relation to the dosage of the medicine.

Finally, MEVU package inserts have no obligation to include a toll-free telephone number or electronic mail address of the marketing authorization holder, although

MAPA recommends that consumers contact them directly by a CSC available on the label or package insert in case of ARs or side effects. It is worth mentioning that a page on the MAPA website refers to this recommendation as a veterinary pharmacovigilance action, although the agency fails to include it in its regulatory standard. According to the proposed draft of the Ordinance on the MAPA webpage, manufacturers and marketing authorization holders of MEVU must clearly present a CSC (which may be a toll-free telephone number or electronic mail address) on medicines labels. The draft has no mention of the inclusion of service channel data on package inserts (Ministério da Agricultura, Pecuária e Abastecimento, 2022). The main function of the CSC is to receive notifications of ARs observed by users during the use of a medicine after its introduction on the market, as well as to register technical complaints about the quality of these products. CSC data must be prominently made available at the end of package inserts to give visibility to this information and facilitate the direct contact between consumers and pharmaceutical laboratories. The CSC can also provide guidance and recommendations on the safe and effective use of veterinary medicines as it also configures a useful tool to compose the risk minimization plan industries propose to monitor the safety of the use of medicines after registration and commercialization (Food and Drug Administration, 2020). Therefore, MAPA must consider standardizing the inclusion of an indication of a CSC on MEVU package inserts.

Inconsistencies in package inserts of MEVU commercialized in Brazil

In the package inserts examined, we assessed the lack of information required or not by MAPA, but that impacts the rational use of medicines and safety of veterinary pharmacotherapy. The absence of essential information on package inserts compromises their essential role in the rational use of medicines and reduces their value as instructional material for prescribers and users (Al Jeraisy *et al*., 2023; Hoeve *et al*., 2020; Pires, Vigário, Cavaco, 2016; Zini *et al*., 2018). An aspect whose analysis is essential is the availability of information for MEVU storage conditions to guarantee their stability during their shelf lives. Around 80% of the MEVU package inserts this study evaluated correctly described the storage conditions for medicines, indicating the location and appropriate storage temperature, humidity, and incidence of direct sunlight. Adequate storage conditions ensure the stability of medicines, which, in turn, is related to maintaining their therapeutic efficacy and safety. Medicines should usually be stored at room temperature, away from direct sunlight and moisture, for the expiration date indicated on their labels and package inserts. However, some medication, e.g., reconstituted solutions or suspensions, small-volume sterile products for ophthalmic use, vaccines, and other biologicals products, may require different storage conditions, which must be clearly indicated on their labels and package inserts (Allen, McPherson, 2021; USP, 2022). Tufa *et al.* (2018) evaluated whether animal food producers correctly used antibiotics and anthelmintics. The authors showed, among other problems, inadequate storage practices and product use, which they attributed to the low quality of the information on package inserts and labels and producers' difficulties in reading and understanding the contained information, especially in imported medicines. Thus, these producers differentiated between the medicines by their color. For the authors, low education influenced their findings. According to Pires, Vigário, and Cavaco (2016), strategies such as the use of pictograms and illustrations support users' understanding of the information on package inserts, adherence to treatment, and the rational use of medicines. The authors analyzed the usability of illustrations and tables on package inserts of medicines for human use by formally educated people and observed this population's difficulty in understanding the information, which suggests that people from low literacy groups will have even greater difficulties. For the authors, it is advisable to update the standards that guarantee the readability of package inserts. Pharmacists and health information specialists can contribute to improving the quality, readability, and comprehension of this information, corroborating the importance of forming multidisciplinary professional teams at all stages of medicine use, i.e., registration, design, production, quality control, dispensing, and monitoring of efficacy and safety. Figure 2 illustrates the relation between the

functionality of package inserts as a document that guides the rational use of medicines and the attributes of legibility, comprehension, and adequacy of the technical and scientific content of the information. Gulwako *et al.* (2023) highlighted the importance of instructing producers on primary care for animal health and the relevance of understanding the information on package inserts, such as compliance with withdrawal periods, the correct temperature for storing medicines, and other important parameters for use efficacy and animal safety.

Although optional on the evaluated standards, the assessed package inserts included data on the usual maximum dose and overdose but showed no information on antidotes which, although mandatory, were absent in most documents. Absent or incomplete information about antidotes can result in complications and death for animals, reducing the informative value of package inserts. However, the standard fails to make it clear in which situations antidotes should be indicated.

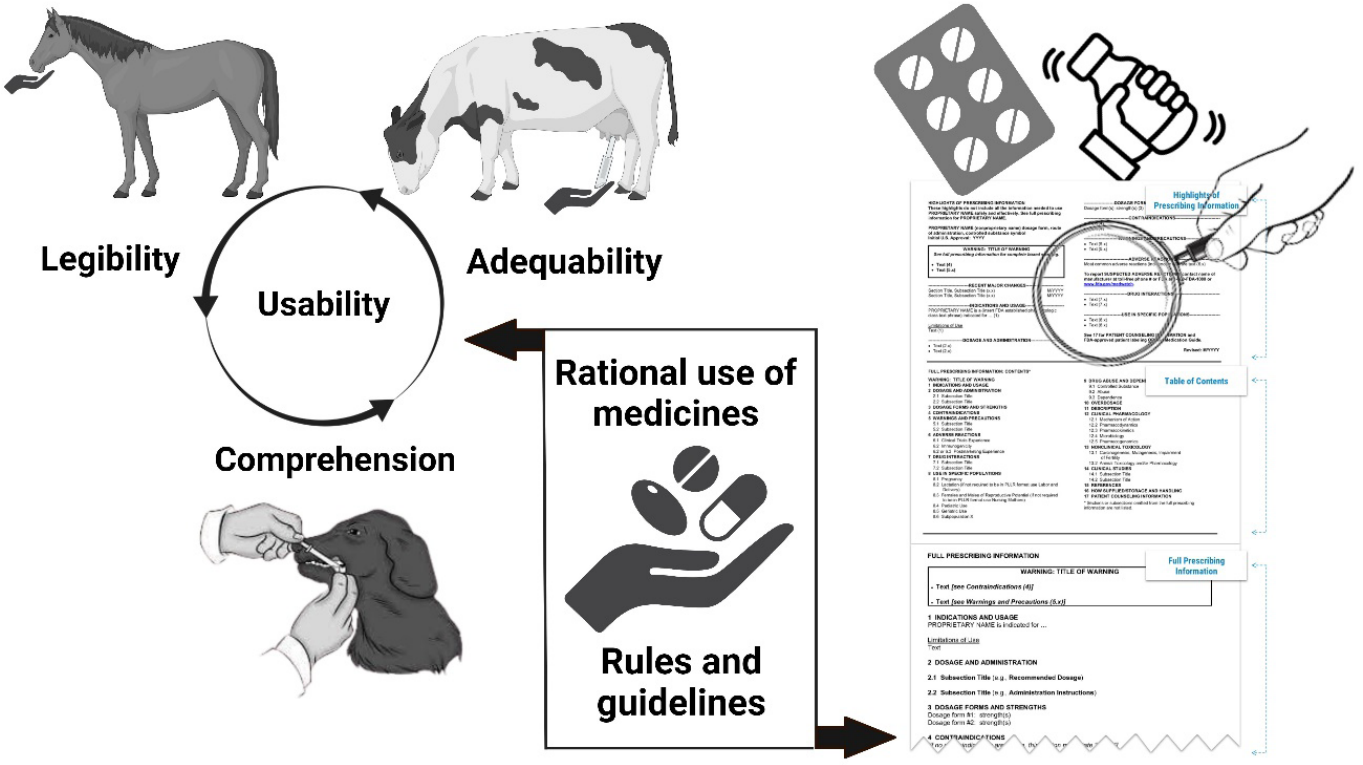

FIGURE 2 – Relation between the attributes required for package inserts of medicines for exclusive veterinary use and the promotion of safety in veterinary pharmacotherapy.

The indication of the number of dosage units in the product and the total volume or mass configures a legal MAPA requirement for package inserts and all evaluated documents complied with the legislation. On the other hand, 6.5% of the evaluated package inserts lacked an indication of API dose per pharmaceutical unit or volume/mass. The indication of doses for each animal species is important and must be clearly stated on package inserts to avoid the administration of doses that could result in ineffective treatments or animal poisoning (Ahmed, Kasraian, 2002). Moreover, all package inserts indicated administration route and pharmaceutical dosage form. Although optional, all evaluated documents made administration route explicit.

Among the analyzed MEVU package inserts, 13 were for medicines intended for the administration

of antimicrobials via intramammary infusion (IMM) to treat mastitis and all included the correct form of administration. In these package inserts, only one inadequately indicated its withdrawal period. Information on administration route and the correct insertion of cannulas into the animal teats can prevent a new unwanted IMM infection and favor the success of pharmacotherapy. The information on the withdrawal period aims to prevent the presence of API residues in foods, such as meat, milk, eggs, fish, and honey, above the limit considered safe for human health (Paula, Souza, 2020). Souza *et al.* (2015) analyzed package inserts of IMM MEVU to treat bovine mastitis and found inconsistencies regarding the withdrawal period and the correct insertion of cannulas into animal teats. They suggested that accurate technical information on insertion could help veterinarians to define different treatment protocols for clinical and subclinical mastitis. Machado *et al.* (2017) noted that about 58% of the MEVU package inserts they studied included no information on withdrawal period. They also found that using the product contrary to the recommended withdrawal period could lead to residues above approved limits, making the food unsuitable for consumption, as described in 31 package inserts. Guimarães (2019) stated that the lack of information such as antimicrobial therapeutic class, administration route, cannula insertion for IMM products, application period, and withdrawal period on package inserts can significantly influence the emergence of microbial resistance and the presence of antimicrobial drug residues in milk.

Special attention should be paid to suspension package inserts. Suspensions are liquid pharmaceutical dosage forms in which the insoluble or minimally soluble API must be dispersed in the vehicle, which requires the products to be shaken immediately before use to ensure a homogeneously distribute the API in the vehicle and uniformity of the dose (Allen, McPherson, 2021). All suspension package inserts must include the warning "Shake before using." Among the analyzed package inserts, 10 were for suspensions, of which 40% provided instructions for shaking the product before use.

Moreover, two other relevant information interfere with the correct dose of APIs in the dosage unit or volume/mass: EqF and number of drops/mL, which package inserts must clearly express, as previously discussed. Among the MEVU package inserts in this study, 86% of the documents that should contain this information lacked EqF indication and only 20% described it correctly (Table II). Regarding the indication of the relation between the number of drops and the dose to be administered, of the 16 package inserts of oral and topical solutions for administration in drops, only one (6.25%) adequately described this relation.

Finally, the absence of information on the marketing authorization holders' CSC occurred in 60.2% of the analyzed package inserts, a worrying finding as this offers the means of communication between users and pharmaceutical laboratories, compromising reports of ARs and veterinary pharmacovigilance actions. It is worth noting that, despite the recommended inclusion of service channel data on MEVU package inserts and labels, current regulations fail to require it. The Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA, 2020) regulates and monitors veterinary pharmacovigilance actions and takes other measures to prevent medication errors in clinical practice. For this end, CSCs must report ARs and other problems arising from the quality or use of the medicines. Among the sources of medication errors, the agency lists problems with MEVU labeling, packaging, and nomenclature. For CMV, package inserts play a central role in the rational use of veterinary medicines. Before approving a MEVU for use, the CVM evaluates its package inserts for possible problems such as the quality of the content and the format of its package inserts, assessing the readability and the adequacy of the instructions to ensure their easy understanding. An example of a report received by the CVM involves the low quality of the instructions on the package insert of an oral medication containing dexmedetomidine, involving cases of overdose in dogs. Oromucosal gels were designed for administration by an oral dosing syringe. However, cases of accidental overdose have been reported, involving the functionality of the dosing syringe stop ring. Owners reported that, despite correctly handling the syringe, the device failed to function as intended and was considered difficult to use. To avoid further errors, the FDA and the manufacturer have improved the quality of usage

information on package inserts and made training videos available to educate veterinarians and owners (Food and Drug Administration, 2020). The regulatory agency draws manufacturers' attention to the responsibility of improving the quality of information on package inserts to guarantee animal and human health.

Few studies in the scientific literature report the analysis of MEVU package inserts regarding information readability, understanding, and adequacy according to legislation and its possible impacts on animal health but their results agree with those in this study. For Machado *et al.* (2017), the information on MEVU package inserts in Brazil showed technical-scientific inadequacies and non-conformities according to the current legislation. Guimarães (2019) evaluated package inserts for the antimicrobials available in the Brazilian market to treat bovine mastitis and found that most failed to fully comply with or only partially met MAPA requirements. The author suggests a delay or lack of action by registration holders to standardize the content of package inserts to MAPA standards. For Paula and Souza (2020), the flaws on MEVU package inserts reinforce the need and urgency for the regulatory agency to carry out actions to improve and ensure compliance with legal requirements since this document is an instrument to guarantee the safety of animals and humans. Riet (2021) evaluated 159 MEVU package inserts of antimicrobial, ectoparasiticide, endectocide, and anthelmintic medicine and observed that none met all regulatory guidelines, compromising the information on their rational use. The author also recommends that authorization holders introducing medicines on the market improve the quantity and quality of information on package inserts to provide prescribers and owners with sufficient information to make decisions on the safe and effective use of MEVU. Silva *et al.* (2023) classified South American countries according to regulatory criteria for parameters involving the manufacture of MEVU based on the standards of the World Organization for Animal Health (OIE), considering gold standards for antimicrobials and growth promoters, which includes packaging and storage conditions. The authors considered the Brazilian level of development regarding OIE rules as intermediate since the country failed to meet at least some gold standards.

In summary, this study compiled relevant information for the Brazilian regulatory sector as package inserts for exclusive veterinary medicines show inconsistencies that not only fail to ensure the efficacy of veterinary pharmacotherapy, but also compromise animal safety. Cases involving the use of medicines in the animal population intended for food production may also compromise the safety of human health. Therefore, the content of this study is also relevant to public health. Efforts are required to adapt the quantity and quality of information on package inserts so owners and prescribers can better comprehend their content. Few studies in the national and international literature have reported the search for inconsistencies on package inserts of medicines for veterinary use, which can be considered a failure given the importance of animal health and the relevance of the veterinary product market for the global economy. Neglecting these studies fails to encourage health surveillance agencies to update their rules, guidelines, and package insert templates to improve the quality of the content and format of this document and increase their instructional value. However, the adoption of ANVISA standards by MAPA, including the organization of the content and form of package inserts, may be relevant for the great quality and safety of final products for animals. Finally, the information in this study emphasizes the importance of the presence of pharmaceutical professionals in the regulatory process of veterinary medicines. In parallel with the growth of the veterinary products market, the role of veterinary pharmacists has gained prominence as these professionals are involved in every stage of the veterinary medicine supply chain, from product design to dispensing.

The main limitations of this study include the exclusion of standards for preparing package inserts for vaccines and medicines of biological and biotechnological origin, as well as the limited number of package inserts for exclusive veterinary medicines that were analyzed, which may not reflect the quantity of these commercially available products. Additionally, the lack of research on the readability and understanding of package insert content for owners can also be considered a limitation. For future studies, it is highly recommended to expand the scope of regulations

and increase the number of examined package inserts. Including a step to assess owners' understanding will better assess the problem, support new solutions, and propose updates to existing standards.

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