BJPS

Brazilian Journal of Pharmaceutical Sciences
vol. 46, n. 1, jan./mar., 2010

Article

Evaluation of medicine package inserts: a study of two cases of *Pelargonium sidoides* D.C. phytomedicines

Tiago Duarte Linhares[1], Danilo Ribeiro de Oliveira[2,*], Michele Feitoza Silva[3]

[1]Universidade Estácio de Sá, [2]Núcleo de Pesquisa de Produtos Naturais, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, [3]Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz

In order for a phytotherapeutic drug be approved and sold in Brazil, it must be registered with the National Sanitary Surveillance Agency (ANVISA), where the quality, safety and efficacy of the product are carefully appraised. In addition, the drug must also meet a number of criteria one of which is the adequacy of the package inserts. Therefore, the aim of this study was to appraise the package inserts of all phytotherapeutic drugs produced using a standardized extract of *Pelargonium sidoides*, which were registered and available from Brazilian pharmacies. This checking was to ascertain whether these inserts fulfilled the requirements stipulated by RDC 140/03. The information required under RDC 140/03 was appraised through a previously devised standard form. Evaluation of the package inserts revealed that neither of the two brands fully met the requirements of the legislation. Manufacturer 'A' met only 37.0% of the requirements satisfactorily, while 16.0% of the information was considered unsatisfactory and 47.0% of the information was absent. Regarding manufacturer 'B', 64.2% of the analyzed requirements were considered satisfactory, while 16.0% were considered unsatisfactory and 19.8% of the information was absent. A package insert should contain information about medicine for consumers, pharmacists and doctors. However, the results obtained in this study showed that the information presented in the package insert of both medicines was unsatisfactory, and in many cases, violates the legislation.

Uniterms: Medicines/formulation of package inserts. Phytotherapeutic drugs. Package inserts/evaluation. *Pelargonium sidoides*.

Para que um medicamento fitoterápico seja comercializado no Brasil, este deve ser registrado junto à ANVISA, onde são avaliados todos os aspectos referentes à qualidade, segurança e eficácia do produto, além de verificar se estes atendem alguns requisitos, sendo um deles a adequação da bula. Por esta razão, neste estudo foram avaliadas as bulas de todos os fitoterápicos elaborados à base do extrato padronizado de *Pelargonium sidoides*, registrados e disponíveis no mercado brasileiro, com o intuito de verificar se estas atendem aos requisitos exigidos pela RDC 140/03. No presente trabalho, as informações exigidas pela RDC 140/03 foram avaliadas através de um formulário padrão previamente elaborado. Após avaliação das bulas pode ser verificado que nenhuma das duas marcas atendia por completo as exigências da legislação, sendo que o fabricante "A" atendeu apenas 37,0% dos requisitos exigidos de forma satisfatória, enquanto 16,0% das informações foram consideradas insatisfatórias e em 47,0% as informações estavam ausentes. Com relação ao fabricante "B", 64,2% dos itens analisados foram considerados satisfatórios, enquanto 16,0% foram considerados insatisfatório e em 19,8% as informações estavam ausentes. A bula deveria conter informações sobre o medicamento para consumidores, farmacêuticos e médicos, no entanto, os resultados obtidos neste estudo mostram que as informações apresentadas nas bulas foram insatisfatórias, e em muitos casos, violavam a legislação vigente.

Unitermos: Medicamentos/formulação de bulários. Fitoterápicos. Bulas/avaliação. *Pelargonium sidoides*.

***Correspondence:** D. R. Oliveira. Núcleo de Pesquisa de Produtos Naturais, Bloco H, Centro de Ciências da Saúde, Cidade Universitária, Ilha do Fundão - 21941-590 - Rio de Janeiro – RJ, Brasil. E-mail: danilopharma@gmail.com

INTRODUCTION

Initial Considerations

Up until the beginning of the twentieth century, plants and vegetal extracts were the main sources of therapeutic resources. With the impact caused by the advent of important pharmaceutical synthetic elements, natural medicines started to become relegated as a second option. Nevertheless, in the past few years, the resumption of phytotherapeutic medicine use has increased markedly (Bello *et al*., 2002). The population on the other hand, has little information concerning the use of this kind of medicine and the majority thinks that phytotherapeutic medicines offer no risks to their health and have no side effects. These beliefs can lead to their irrational use and self-medication (Amaral *et al.,* 2007).

About the medicine register

Brazilian legislation has steadily been regulating the register of phytotherapeutic medicines in Brazil, initially with SVS decree number 6 of January 31st, 1995, updated in 2000 through resolution RDC number 17, by the National Sanitary Surveillance Agency (ANVISA) and more recently with the enactment of RDC number 48 of 2004 (Virgílio, Marques, 2004). According to Carvalho *et al.* (2007), for a phytotherapeutic medicine to be commercialized in Brazil it must be registered by ANVISA. This register represents the first intervention concerning product quality, safety and efficacy.

For the industry to achieve the register of the medicine it must petition ANVISA, also known as a procedure, with a technical dossier containing information about the product concerning production, quality control, safety and efficacy assays, legally required company data, besides medicine labeling and package insert data (Carvalho *et al.*, 2007).

In Brazil, the most important source of information for medicine users is the package inserts (Silva *et al.*, 2000; Farias *et al.*, 1985). In light of this, and assuming the medicine package inserts should effectively guide both patients and health professionals regarding the rational use of the medicine, resolution RDC number 140/03 was implemented, establishing rules for medicine package inserts for the benefit of both patients and health professionals.

In spite of the compulsory nature of the package inserts in the medicine package, they provide very little information for patients and health professionals. This is the case because of the lack of adaptation of the package inserts to meet the current legislation.

Pelargonium sidoides

The *Perlagonium sidoides* DC is a plant belonging to the family of Geraniaceae, which is found in the African continent at a height of 2.300 meters, mainly in South Africa and is popularly called *umckaloabo*. It is characterized for presenting massive dark brown roots, big round tipped leaves, an inflorescence that ranges from reddened to dark purple, with petals that vary in color. The leaves and particularly the roots are the most commonly used parts medicinally (Alonso, 2004; Bladt, Wagner, 2007).

Chemical composition

P. sidoides roots present mainly *condensed taninns* in their particular metabolism, highlighting the oligomeric proantocianidines formed by at least eight units of flavan-3-ol like monomers (afzelequine, catequine and galocatequine), and the *coumarins* escopoletine, fraxidin, isofraxedin, arteline, umckalin and its 7-*O*-methilether (5,6,7-trimethoxycoumarin) (Alonso, 2004; Kaiser, Kolodziej, 1995; Bladt, Wagner, 2007; Kolodziej, 2007b). It is also possible to find flavonoids (quercetin), terpenes (mono and sesquiterpens), phenylpropanoids, and anacardic acid (Alonso, 2004; Bladt, Wagner, 2007).

Pharmacological activities

Several authors (Alonso, 2004; Mativandlela *et al.*, 2006; Conrad *et al.*, 2007; Matthys, Heger, 2007b; Kolodziej, Kiderlen, 2007a), report that the roots of *P. sidoides* have antimicrobial activity, inhibiting Gram-positive germs (*Staphylococcus aureus, Streptococcus pneumoniae, S. beta-hemolitico* 1451), Gram-negative germs (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*), virus (*Haemophilus influenzae, Moraxella catarrhalis*), and fungus (*Aspergillus niger, Fusarium oxysporum, Rhizopus stolonifer*). Among the components that make this activity possible are the coumarins (Alonso, 2004).

The *P. sidoides* also has, according to traditional use, activity for the treatment of tuberculosis (Kolodziej *et al.*, 2003). Mantivandlela *et al.* (2006) reported antimycobacterial activity of the *P. sidoides* roots, *in vitro*, against *M. tuberculosis*.

Several studies, both *in vitro* and *in vivo*, as well as clinical assays have been performed with a standardized extract called EPs 7630, commercialized by a German company. Kolodziej and Kiderlen (2007a) verified that EPs 7630 has immunomodulating activity. The immunostimulating activity occurs due to the presence of coumarins and other polifenolic compounds which promote the

formation of cytokines that intervene defending against anaerobic microorganism infections (Alonso, 2004). According to Neugebauer *et al.* (2005), EPs 7630 present an increase in the frequency of the beating movement of the nasal epithelium. This beating movement is an important mechanism of physical defense against infections. In the *in vitro* model of fibroblasts infected with the virus of brain-miocarditis, the extract of *P. sidoides was* shown to produce alpha and beta interferons, which have recognized antiviral effect, where the umckalin and the gaelic acid are the main components responsible for these effects (Marcucci *et al.,* 1992 *apud* Alonso, 2004). The EPs 7630 extract also demonstrates action in relieving flu symptoms (Noldner, Schotz, 2007).

A study performed using extracts of roots of *P. sidoides,* involving 641 patients with infections in the oropharynx (tonsil infection, rhinopharyngitis) and breathing (bronchitis, sinusitis), demonstrated that 85% of the patients experienced significant clinical improvement after a fourteen-day course of treatment (Heil, Reitermann, 1994 *apud* Alonso, 2004). Several clinical studies (Chuchalin *et al.*, 2005; Matthys *et al*., 2003; Matthys *et al*., 2007a; Matthys, Hereg, 2007b) have also proven the efficacy of Eps 7630 for treating bronchitis.

Cumarinic derivates are among the main components of *P. sidoides*. Given this, and considering the possibility of this plant having anticlotting activity, Koch, Biber (2007) investigated the parameters of blood clotting in mice, after administration of the substance, comparing it to warfarin. After the oral administration of Eps 7630 for two weeks, no effect was observed, in contrast to warfarin, which over the same period resulted in significant changes in the clotting factor.

Adverse effects

No adverse effects have been reported in patients older than 12 years old, noting that the extract of *P. sidoides* is well tolerated in therapeutic doses (Tsyrkunov, 1989; Kolodziej *et al.*, 1997 *apud* Alonso, 2004; Correia *et al.*, 1984 *apud* Alonso, 2004; Anderson *et al.*, 1992; Edenharder *et al.*, 1995 *apud* Alonso, 2004; Heil, Reitermann, 1994 *apud* Alonso, 2004; Matthys *et al.*, 2003; Schotz *et al.*, 2007).

A study performed with extracts of roots of *P. sidoides* in 259 children aged up to12 years old that had acute bronchitis events, showed that it had good tolerance. However, 6 patients (2.3%) showed some adverse effects such as: exantema, light dyspnea, intestine spasms, lack of appetite, vomiting and restlessness. After suspending use of the medicine, patients' clinical pictures returned to normal (Dome, Schuster, 1996 *apud* Alonso, 2004).

Contraindication

Due to the lack of data indicating the safety of *P. sidoides* use during pregnancy, the use of the product must be avoided during gestation and breast-feeding (Alonso, 2004).

MATERIALS AND METHODS

Analysis of Package Inserts

The study was developed initially through a vast bibliographic revision, centering its source of research on scientific papers, books, laws, decrees, and resolutions, for substantiation and formation of a theoretical basis, followed by the devising of a standard form reflecting resolution RDC number 140/03 (Brasil, 2003a), transforming its articles into items on a checklist (Table I).

The purpose of the form was to confirm the presence of compulsory statement, indications for use, specific technical information and legally required content. To this end, the previously devised standard form was divided into six parts: the 1st part evaluates the size of the lettering; the 2nd part evaluates the identification of the medicine; the 3rd part, information to patients; the 4th part, technical information for health professionals; the 5th part, compulsory statement, and the 6th part, legally required content. Each aspect checked was classified into one of three possible categories: (S) Satisfactory - when the information conforms to the legislation in a complete or satisfactory way; (U) Unsatisfactory - when the information fails to fully conform to the legislation; (A) Absent - when no information is provided. All the items on the form were considered indispensable and, therefore, the weight for the evaluation fulfilled only one criterion (weight 1). All the items for the medicine package inserts were evaluated by three competent pharmaceutical professionals and the same result was presented as a whole for the interpretation of the forms.

To evaluate if the package insert information was rendered in accessible language for the patients and in accordance with the International Classification of Diseases (ICD), pursuant to RDC 140/03, both the Brazilian Center for Disease Classification (*Centro Brasileiro de Classificação de Doenças,* 2007) and the World Health Organization International Statistical Classification of Diseases (WHO, 1998) were consulted. The accessibility of language to patients was also subjectively evaluated in the authors' interpretation.

Acquisition of sample

The sample was formed by the package inserts of phytotherapeutic medicines derived from standardized extract of roots of *Pelargonium sidoide* commercialized in Brazil. Two such products were found to be registered on ANVISA's official site. The samples were acquired from drugstores in the municipalities of Campos dos Goytacazes-Rio de Janeiro State, between September and October / 2007, with the manufacturer "A" product bearing batch number 70628 while the manufacturer "B" product had a batch number of 702720.

RESULTS AND DISCUSSION

These products containing standardized extract of roots of *P. sidoides* found registered by ANVISA up to the year of 2007 were both produced by far-reaching laboratories which have strong advertising and marketing appeal in the national milieu, achieving notable success in pharmaceutical sales according to data available on the official sites of the respective companies. Manufacturer "A" is an Anonymous Society (Inc.), and therefore has to release its financial statements and results in the Official Gazette of the Federal Executive (*Diário Oficial da União)* or a prevalent newspaper with a broad coverage, every end of business year. Manufacturer "B" was a Limited Society (Ltd.) and made available on its site information concerning its annual revenues, which in 2007 was higher than R$ 500.000.000,00 (five hundred million *reais*). Concerning sanitary regulations in Brazil, the company may be rated as far-reaching (Group I) if it has a turnover which is higher than fifty million *reais* (ANVISA, 2008).

Analysis of Package Inserts

1st Part: Size of the lettering

Both medicine package inserts conformed to the legislation concerning the compulsory characteristic of the presentation of the lettering at a minimum size of 1.5 mm (Table I), allowing reading without difficulties, especially for elderly patients who often have more trouble reading.

2nd Part: Identification of the medicine

As evidenced in Table I, manufacturer "A" conformed to the legislation satisfactorily on 77.8% of the items and no items were considered unsatisfactory, although 22.2% of these were found to be absent. Manufacturer "B" conformed to the legislation on 77.8% of requirements satisfactorily and on 22.2% unsatisfactorily (Figure 1).

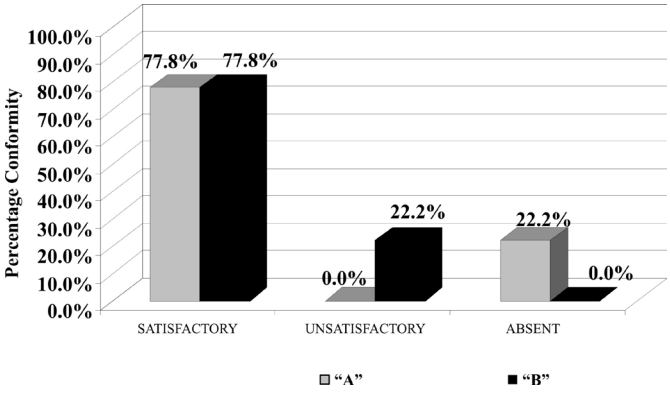

FIGURE 1 – Evaluation of the item "identification of the medicine" for the package inserts by manufacturers "A" and "B" of *P. sidoides*-based phytotherapeutics.

The commercialized presentations were properly described by both manufacturers, including the pharmaceutical forms, commercial name or brand of the medicine, official botanic nomenclature, administration route, liquid volume and the part of the plant used.

Concerning the qualitative and quantitative description of the active ingredients, "A" described this incompletely in stating that the product contained 825 mg of liquid extract of the root of *P. sidoides* and a sufficient amount for 1ml of the vehicle, but omitted the information on which vehicle was being referred to. Manufacturer "B" presented glycerol as its vehicle and a wide spectrum of variation of levels of a non-specified class of active ingredient (0.08% to 0.32% of total phenols) as markers. However, the medicines should clearly state the active ingredients, such as coumarins and taninns (Alonso, 2004; Kaiser, Kolodziej, 1995; Kolodziej, 2007b), and therefore the information presented by both manufactures was considered lacking.

In addition, the two manufacturers cited here also omitted other components in the formula, such as coloring, flavoring, edulcoloring, stabilizers among other common items used in the manufacture of oral solutions for both pediatrics and adult use (Ansel *et al.*, 2000).

It is important to highlight that, according to Resolution RDC 137/2003 (Brasil, 2003b), there are substances for which it is necessary to include compulsory sentences in the package inserts where packages must highlight the danger of their use by special groups (i.e. diabetics, celiacs, phenylketonurics), or provide warnings for patients who have allergies to them (i.e. tartazine yellow). As the excipients which have been used were not described in the package inserts, in the manner stipulated by RDC 140/2003, these could not be evaluated (Brasil, 2003a).

Furthermore, the absence and total non-specification

of excipients infringes not only sanitation regulations, but also the Consumer Defense Code (Brasil, 1990).

3rd Part: Information to patients

The required items that constitute correct information for the patient are presented in Table I, which shows that manufacturer "A" conformed to the legislation satisfactorily on 41.7% of the items, unsatisfactorily on 25% whereas for 33.3% of items the information was absent. Manufacturer "B" conformed to the legislation in approximately 58.4% of items satisfactorily, in 20.8% unsatisfactorily while 20.8% of items were absent (Figure 2).

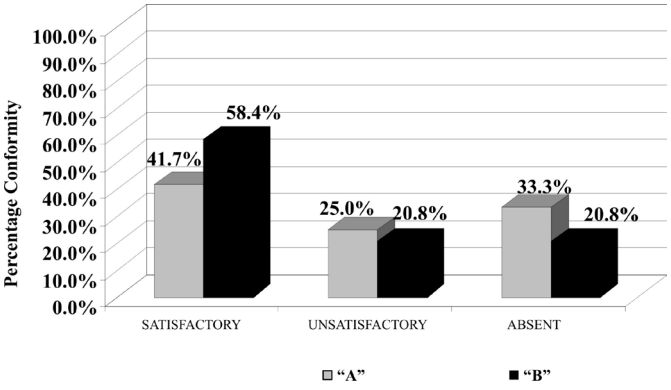

FIGURE 2 - Evaluation of item "Information to patients" in package inserts by manufacturers "A" and "B" for *P. sidoide*-based phytotherapeutics.

With regard to the "information to patients", the package inserts of both medicines satisfactorily presented physical aspects, procedures for use of the medicine, intervals of administration, dosage, in accordance with the pharmaceutical form, administration route, warnings, contraindication and precautions.

However, with regard to the "medicine action", manufacturer "A" only reported the pharmacological action of the medicine, not informing the estimated average time of action, in contrast to manufacturer "B" that reported pharmacological action, estimated average time for the action of the medicine, and the estimated time for full patient treatment.

Concerning the "medicine storage", manufacturer "A" omitted this item, not giving any information about the correct storage procedure, before or after opening. Regarding manufacturer "B", the information was also incomplete, in that it only informed the expiry date after opening, while omitting the precautions patients should take in storing the medicine before and after opening. Manufacturer "B" also reported that the medicine was made up by vegetal extracts, and for this reason may present a tendency for darkening, small variations in both color and taste, without altering the effectiveness of the product. However, these problems may be caused by the inappropriate storage of the product (Brasil, 2001; Brasil, 2006).

The inappropriate storage of the medicine may cause the growth of fungus and bacteria, or may provoke alterations in the consistency, taste, odor and color, besides the acceleration of chemical reactions which lead to decomposition of the product and alterations in its effectiveness (Brasil, 2001; Brasil, 2006).

In the part indicating use of the medicine, both manufacturers "A" and "B" proved satisfactory in reporting this information.

Concerning the language approach, manufacturer "A" presented satisfactory language, although it did not fully meet ICD requirements, presenting terminologies that are not easy for patients to understand, such as: "immunomodulating action", "immunologic system restoration", "rhinopharyngitis". The insert for Manufacturer "B" medicine not only presented a clear text, but also reported the main symptoms for each illness. However, this also failed to fully conform to ICD requirements by using terminology such as: "tonsilar angina", "rhinopharyngitis".

None of the manufacturers fully presented the organoleptic characteristics of the medicine. In both package inserts, only the color was described while omitting the other characteristics such as the consistency and odor, making it impossible for patients to check if the medicine was within the standards for consumption or was "rotten".

Manufacturer "A" omitted information concerning the required conduct in the event of forgetting to take the medicine. The lack of this information may lead the patient to taking an overdose, due to the false notion that the skipped doses should all be taken at once. Manufacturer "B" informed the correct procedure for patients, besides explaining that the patient should not take a double dose.

Manufacturer "B" also clearly stated the duration of the treatment, and presented supplementary information on the maximum treatment period, besides recommendations against stopping the treatment immediately after symptoms disappear, explaining that the treatment should be continued for some days to avoid recurrence of the illness. Manufacturer "A" presented no information about the duration of the treatment, although it presented instructions on continuing the treatment for some days after the resolution of symptoms in order to prevent recurrence. The lack of complete information on the package inserts could lead to patients using the medicine continually.

Concerning the dosage, according to the pharmaceutical form and its respective instructions for use, both

manufacturers described them satisfactorily. Manufacturer "B" also instructed the patient about the recommended amount and dosage in case of subsequent treatment (chronic evolution of the illness or frequent recurrence), thus not limiting the information only to that required by the legislation. However, neither of the manufacturers presented the dosage for special illnesses or situations. The adverse reactions were reported by both manufacturers, although neither of them informed the adverse reactions including migraine, light dyspnea, lack of appetite and restlessness, which may occur in children aged up to 12 years old (Dome, Schuster, 1996 *apud* Alonso, 2004).

In the medicinal part, both manufacturers "A" and "B" described feeding and laboratory test interactions only with coumarin derivates owing to their increase in the anticlotting action of the medicine. As *P. sidoides* contains large amounts of coumarins in its composition, the administration of this phytotherapeutic in combination with others rich in coumarin (i.e. meliloto) and/or anticlotting (warfarin) may lead to an increase in the inhibiting effect of clotting.

A more detailed study of the possible interactions of *P. sidoides* with other medicines is recommended as well as on feeding interactions and laboratory tests (Koch, Biber, 2007).

Regarding restrictions for groups at risk, manufacturer "A" reported no restrictions concerning the use of the medicine, which may lead the patient to understanding that this medicine may be safely used by anybody, including new-borns, children, adults, elderly people, sick individuals and so on. On the other hand, manufacturer "B" advised against the use of the medicine by pregnant women or those who are breast feeding, without doctors' advice, or in infants younger than one year old, due to the lack of clinical trials.

Both manufacturers omitted the statements on the risks of use by non-recommended administration routes required by law.

Neither of the manufacturers satisfactorily described the measures to be taken by patients in the event of overdose. Manufacturer "A" reported an absence of studies on overdose, and that in the event of overdose the patient should seek medical attention immediately. In contrast, manufacturer "B" reported that this was a phytotherapeutic medicine which is well tolerated, and in case of accidental ingestion of doses much higher than those recommended, the patient should take the usual measurements for controlling vital functions. It is important to highlight that most of the population do not know what "control of vital functions" stands for, and therefore neither the procedure, nor the language is easily accessible to patients.

4th Part: Technical information for health professionals

The items required according to RDC 140/03 for the "technical information for health professional" are presented in Table I, which shows that manufacturer "A" conformed to the legislation satisfactorily on only 3.4% of the items, and unsatisfactorily for 10.3% while 86.3% of the items were absent. Manufacturer "B" met the requirements of the legislation satisfactorily in 44.8% of items, 20.7% were regarded as unsatisfactory and 34.5% of the items were absent (Figure 3).

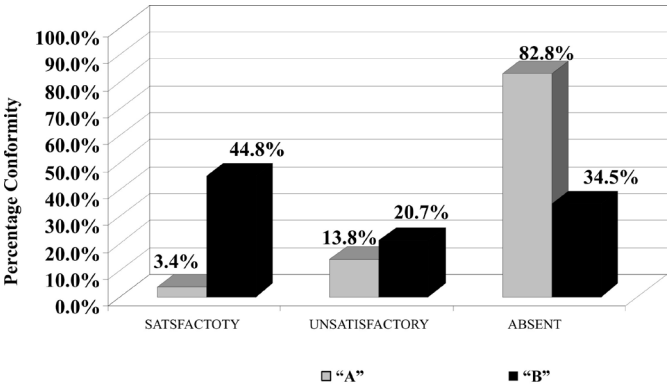

FIGURE 3 – Evaluation of the item "Technical Information for Health Professionals" for the package inserts of both manufacturers "A" and "B" of *P. sidoides*-based phytotherapeutics

In the part on technical information, manufacturer "A" was totally lacking informing this in an unsatisfactory way providing only the care with storage, pharmacological characteristics and indications of the medicine. The further information required by the legislation was not included.

On the other hand, manufacturer "B" satisfactorily informed the warning concerning the use of the medicine by children and adults, administration route, besides the advice against taking the medicine without a doctor or surgeon dentist's recommendation in case of pregnancy or breast feeding. Both manufacturers "A" and "B" unsatisfactorily described the steps for storing the medicine, since it was only reported that the medicine must be kept at ambient temperature, ranging from 15 ºC to 30 ºC, not specifying that the medicine must not be stored in damp places or those exposed to sun. Both manufacturers also omitted the product care concerning the keeping of the medicine after opening. Manufacturer "B" however, presented the expiry date after the flask was opened.

Improper medicine storage may cause the growth of fungi and bacteria, and may lead to alterations in its consistency, taste, odor and color, besides alterations and

deterioration of the medicine, accelerating chemical reactions causing rotting of the products and alteration in their effectiveness (Brasil, 2001; Brasil, 2006).

Manufacturer "B" presented incomplete information regarding its storage and reported on the package inserts that the medicine is made up of vegetal extracts and that for this reason, it may present darkening, small variations of color and taste, which do not alter the efficacy of the product. However, as was reported above, the inappropriate storage of the product may also cause alteration in taste, color and efficacy.

Regarding pharmacological characteristics, manufacturer "A" informed them in an unsatisfactory way, in that it presented the medicine indications while not informing either its pharmacodynamics or pharmacokinetic action, and justifying it with the statement: "no pharmacokinetic studies are available". The same occurred with manufacturer "B", in that it also presented only the indications of the medicine, omitting its pharmacodynamics and pharmacokinetic action, and justifying this with the statement "the pharmacokinetic data about the individual substances present in the vegetal extracts of *P. sidoides* (EPs 7630) are not yet available".

Manufacturer "A" informed the indications of the medicine in a confusing manner, whereas manufacturer "B", besides informing the indications in a very clear manner, also described the main symptoms of each illness and the mechanism of action of the indications of the medicine, in the part on pharmacological characteristics, facilitating understanding for health professionals. Regarding medicinal and feeding interactions and laboratory tests, manufacturer "A" reported no information about the possible interactions. In contrast, manufacturer "B" reported interaction with coumarin derivates, because it may have anti clotting effect (Koch, Biber, 2007). As the *P. sidoides* contains large amounts of coumarins in its composition, the administration of this phytotherapeutic in combination with others rich in coumarin (i.e. *Melilotus officinalis*) and/or anti clotting (warfarin) agents may lead to an increase in clotting inhibiting effects.

Concerning the language used, manufacturer "A" presented information using simple and easy to understand language. Manufacturer "B", besides presenting very understandable text, reported the main symptoms for each illness.

Manufacturer "B" reported by means of statements and illustrations, the correct handling of the medicine, besides the correct way of preparing and applying the medicine, thereby easing understanding. Manufacturer "A" omitted this information.

Regarding the dose and duration of the treatment, manufacturer "B", besides describing this in a satisfactory way, advised which dose was recommended in cases of subsequent treatments, thereby not limiting information to that stipulated by the legislation. However, information on the maximum daily dose was not given. Manufacturer "A" did not report any information about the dose, duration of the treatment or maximum daily dose.

According to the current regulation, it is compulsory to express quantitatively the active components present in the standardized extracts per dose, data which was not found in either of the analyzed package inserts.

Although both of the inserts indicated proportions regarding the amount of liquid extract, they did not cite the percentage or amount of their constituent active chemicals (coumarins and taninns).

Manufacturer "A" did not report any adverse reactions of the medicine, omitting therefore the several reactions that the medicine may cause.

Manufacturer "B" on the other hand reported the due adverse reaction, but did not inform some reactions such as: migraine, light dyspnea, lack of appetite and restlessness, which may manifest in children aged up to 12 years old (Dome, Schuster, 1996 *apud* Alonso, 2004).

Concerning the results on efficacy, manufacturer "B" reported the results incompletely, with the due sources incorrectly citing the author, title of the article, journal page and date of publication. Manufacturer "A" omitted all the data, raising a doubt concerning the truth of the information described in directions. Moreover, manufacturer "A" did not report clinical assays in humans, which may suggest that the medicine has no truly proven efficacy or safety.

In the case of information on overdose, manufacturer "A" did not report anything about measures that should be taken. Manufacturer "B" on the other hand, reported that this is a phytotherapeutic medicine which is well tolerated and that in case of accidental ingestion of doses which are much higher than those recommended, patients must take the usual actions to ensure control of vital functions.

However, manufacturer "B" failed to provide 34.5% of the technical information required namely: adjustment of the dose for elderly patients and other groups at risk and restrictions regarding the use of the medicine, risks of use via administration routes that are not recommended, feeding interactions and interactions with laboratory exams, necessary procedures in cases of forgetting to administer, maximum daily dose, dose for specific illnesses and special situations, use in groups at risk and elderly people, describing the warnings and the recommendations about suitable use.

5th Part: Compulsory statements

The required items for compulsory statements, according to the legislation, are presented in Table I, which shows that manufacturer "A" complied with the legislation satisfactorily on 50% of items, but on 25% was considered unsatisfactory and failed to present 25% of the items. Manufacturer "B" satisfactorily conformed to the legislation on 91.7% of items while 8.3% of the items were absent (Figure 4).

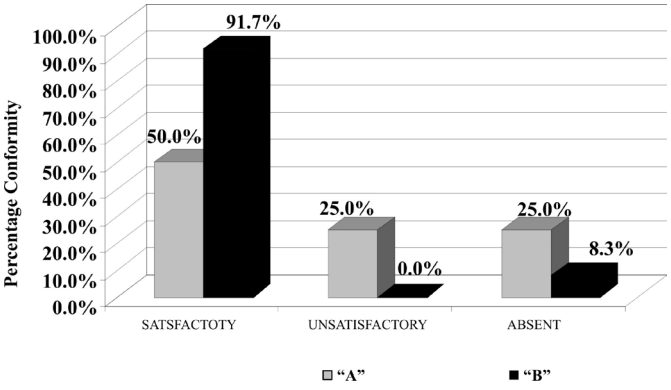

FIGURE 4 – Evaluation of the item "Compulsory Statements" for manufacturer "A" and "B" of *P. sidoides* –based phytotherapeutics

In the part on compulsory statements, manufacturer "A" did not include 25% of these, which were: warning to pregnant women; statement indicating contra-indication in specific age ranges or that there was no contra-indication regarding age range; and the statement "Sale under medical prescription". The lack of these statements is regarded as extremely serious in nature in failing to warn patients about the necessary care when using the medicine.

Concerning the statement "Inform the physician or the surgeon-dentist upon the appearance of uncomfortable reactions", Manufacturer "A" did not cite the surgeon-dentist, although this is understandable given that this medicine is not commonly prescribed by dentists. Also, the statement "All medications must be kept far from children's reach" was located incorrectly, placed in the section addressing health professionals.

Regarding manufacturer "B", it presented most of the compulsory statements (91.67%), however, it failed to mention the statement "This medicine is contra-indicated in the _____ age range." or "There are no contra-indications concerning age range".

6th Part: Legally required content

Concerning the legal statements, both manufacturers presented them all in a satisfactory way, however, manufacturer "A" did not cite which Federal unit the technical pharmacist responsible for it belonged to (Table I).

The legal content allows verification that the company is properly regulated, as well as the product it manufactures. It is important to remember that the inclusion of a pharmacist who is technically responsible for the manufacture of the medicine is essential.

TABLE I – Standard form for evaluation of package inserts according to RDC 140/2003, employed in the verification of package inserts of *P. sidoides* medicines produced by manufacturers "A" and "B"

SIZE OF LETTERING		"A"	"B"
Letters a minimum size of 1.5 millimeters		S	S
IDENTIFICATION OF THE MEDICINE		"A"	"B"
Commercialized presentations		S	S
Qualitative and Quantitative description of active compounds		A	U
Qualitative Description for the other components of the formulation		A	U
Pharmaceutic Form		S	S
Commercial name or Brand of the medicine		S	S
Official botanic nomenclature		S	S
Part of the plant being used		S	S
Route of administration		S	S
Liquid Volume		S	S
INFORMATION TO PATIENTS		"A"	"B"
Action of the medicine	Action of the medicine after an average time estimated from the onset of pharmacological action	U	S
Storage of the medicine	Specific care for keeping the medicine before and after opening it	A	U
Indication of the medicine	Indications for the use of the medicine	S	S

TABLE I – Standard form for evaluation of package inserts according to RDC 140/2003, employed in the verification of package inserts of *P. sidoides* medicines produced by manufacturers "A" and "B" (cont.)

	INFORMATION TO PATIENTS	"A"	"B"
Language Approach	Information in accessible language, according to ICD, when referring to signs, symptoms and illnesses	U	U
	Easy-to-understanding text	S	S
Method of Use	Physical aspect	S	S
	Organoleptic characteristics of the product	A	A
	How to use the medicine	S	S
	Necessary procedure in case of omitting to administrate	A	S
	Duration of the treatment	U	S
	Interval of administration	S	S
	Dosage according to each pharmaceutical form and their respective instructions of use	S	S
	Dosage for specific illnesses and special situations	A	A
	Route of administration	S	S
Adverse Reactions	Most important adverse reactions	U	U
	Warnings	S	S
	Contraindications	S	S
	Precautions	S	S
	Main feeding interactions	A	A
Risks of the medicine	Main interactions with laboratory tests	A	A
	Main medicinal interactions	U	U
	Restrictions for groups at risk	A	S
	Risks of using a route of administration that is not recommended	A	A
Overdose	Procedure in case of overdose, describing the symptoms and measures before seeking medical attention	U	U
	TECHNICAL INFORMATION FOR HEALTH PROFESSIONALS	"A"	"B"
Warnings	Warnings about the medicine	A	S
	Adjustment of dose for elderly patients or groups at risk	A	A
	Categories of risk during pregnancy	A	S
	Recommendations concerning the appropriate use of the medicine	A	S
	Restrictions concerning the use of the medicine	A	A
	Risks of use via a route of administration that is not recommended	A	A
Storage	Care needed for storing	U	U
	Care needed for storing after opening	A	U
Pharmacological Characteristics	Pharmacological characteristics (pharmacodynamics and pharmacotechnical)	U	U
Contraindication	Description of contraindications	A	S
Indications	Indications of the medicine	U	S
Interactions	Feeding interactions	A	A
	Interactions with laboratory exams	A	A
	Medicinal interactions	A	S
Language Approach	According to the recommended terminologies by the ICD 10, when referring to symptoms and sicknesses	S	S
Way of use	Handling and Application	A	S
	Correct method of preparing	A	S
	Correct administration route	A	S
	Necessary procedure in case of omitting to administrate.	A	A

TABLE I – Standard form for evaluation of package inserts according to RDC 140/2003, employed in the verification of package inserts of *P. sidoides* medicines produced by manufacturers "A" and "B" (cont.)

TECHNICAL INFORMATION FOR HEALTH PROFESSIONALS		"A"	"B"
Dosage	Dose and duration of the treatment	A	S
	Maximum daily dose	A	A
	Equivalence in weight of the chemical components in the pharmaceutical presentation with active substance	U	U
	Dosage for specific illnesses and special situations	A	A
Adverse reactions	Description of adverse reactions	A	U
Results of efficacy	Results of efficacy based on the percentage of healing or prevention in group intervention or group comparison, when available, citing bibliographic reference.	A	S
Overdose	General and specific procedures in event of overdose	A	U
Use of the medicine in groups at risk	Use in children, describing the warnings and recommendations about appropriate use	A	S
	Use in groups at risk, describing the warnings and recommendations about appropriate use	A	A
	Use in the elderly, describing the warnings and recommendations about appropriate use	A	A
COMPULSORY STATEMENTS		"A"	"B"
Warning addressed to pregnant women		A	S
"Attention: this is a new medicine, and although studies have shown acceptable efficacy and safety for sale, uncomfortable and unknown effects may occur. In the event of problems inform your physician"		S	S
"Attention: this medicine is a similar that has undergone tests and studies that prove its efficacy, quality and safety, according to current legislation"		--	--
"This medicine is contraindicated for the ____ age range" or "There is no contra-indication concerning age range"		A	A
"Inform your physician or surgeon-dentist upon the appearance of uncomfortable reactions"		U	S
"Inform your physician or surgeon-dentist if you have been taking any other medicine"		U	S
"Do not discontinue treatment without consulting your physician"		S	S
"Do not use any medicines without first notifying your physician. They may be harmful for your health"		S	S
"Do not use the medicine if the expiry date has elapsed. Before you use the medicine check the condition of the medicine"		S	S
"Adhere to your physician's instructions respecting the times, doses and duration of the treatment"		S	S
"All medicines must be kept out of the reach of children"		U	S
"Pediatric and /or Adult use"		S	S
"Sale by doctor's prescription"		A	S
LEGALLY REQUIRED CONTENT		"A"	"B"
Cadastro Nacional de Pessoa Jurídica (*CNPJ*)		S	S
Manufacturer's name		S	S
Pharmacist in charge with respective registration number and federal unit		U	S
Manufacturer's full name		S	S
Registration number with ANVISA		S	S
Work telephone number and consumer hotline		S	S

A = Absent, U = Unsatisfactory, S = Satisfactory

CONCLUSIONS

Analysis of "A" and "B" manufacturers' package inserts revealed that neither fully conformed to the current legislation, either omitting or presenting information necessary for both patients and health professionals, in an unsatisfactory manner, even almost five years after normative publication (RDC 140/03).

Concerning manufacturer "A", it met the requirements of the legislation satisfactorily on only 37.04% of

items, whereas 16.05% of the information was regarded as unsatisfactory and 46.91% of items were absent. The technical information was of extremely poor quality, describing only 3.45% of the items satisfactorily, 10.34% unsatisfactorily while omitting 86.21% of the legally required information.

Moreover, manufacturer "B" conformed to the legislatory requirements satisfactorily on 64.20% of items, whereas 16.05% were considered unsatisfactory and 19.75% absent. This manufacturer attempted to meet requirements in a simple and clear fashion, besides fully outlining the sources used for its production and provided evidence for these claims.

According to the Consumer Defense Code, all citizens have the fundamental right to access appropriate and clear information about products and services (Brasil, 1990). However, this right was not fully respected by either manufacturer, particularly in the case of manufacturer "A".

The directions provided by manufacturer "A" do provide sufficient instructions for patients or health professionals.

A medicine package insert is expected to present quality information for both user and health professional. However, the results obtained in this study indicated that the information presented in the package inserts for both medicines were incomplete and in many cases breached the current legislation.

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Received for publication on 10th july 2008
Accepted for publication on 27th july 2009