



Comparative study of the pharmacopeial quality and dissolution profiles of generic and other drug forms of sodium metamizole (dipyrone) sold in Brazil

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ABSTRACT

In Brazil, in order for a pharmaceutical company to register a drug form as generic or 'similar' with the Brazilian food and drug agency (Anvisa), it must be proved bioequivalent to its innovatory branded form (reference drug). This requires comparative trials, carried out in conformity with official compendia (Brazilian Pharmacopeia or another officially recognized code). Additionally, according to the Anvisa resolution RDC 31/2010, the dissolution profile of the drug must be tested and compared with that of the branded reference, as a benchmark of quality. The aim of this study was to assess the quality of 500 mg sodium metamizole (dipyrone) tablets produced by seven different laboratories in Brazil: three generic drugs (G₁, G₂, G₃), three (branded) similar drugs (S₁, S₂, S₃) and their reference branded product (Novalgina®, Sanofi-Aventis, drug R). All tests were carried out by methods specified in the Brazilian Pharmacopeia 4th edition (Farmacopeia Brasileira IV). The following tests were performed: uniformity of mass, friability, disintegration time, hardness, assay, uniformity of dosage units, salicylic acid limit assay, dissolution and identification. The dissolution profile was also recorded, as recommended in RDC 31/2010. Whereas every sample was approved in all the Farmacopeia Brasileira IV tests, the results in the dissolution profile test showed that four of the test drugs (G₁, G₂, S₁ and S₂) were not pharmaceutically equivalent to drug R. Thus, only drugs G₃ and S₃ showed dissolution profiles similar to that of drug R and the other four drugs could not be considered equivalent to it and were not approved.

Keywords: Metamizole. Dissolution profile. Pharmaceutical equivalence. Similar drugs. Generic drugs.

INTRODUCTION

It is probable that pain generated the first human therapeutic actions. The use of *Papaver somniferum* (opium

poppy) and its opiate substitutes was already recommended to treat pain as far back as the "Great Herbarium" of the Chinese Emperor Chen Nung, more than 4700 years ago. In the nineteenth century, several substances with analgesic properties were introduced into therapy, among which was the family of pyrazolones, such as antipyrine, synthesized in 1884 in Germany, and metamizole (Figure 1), discovered years later (Anvisa, 2001).

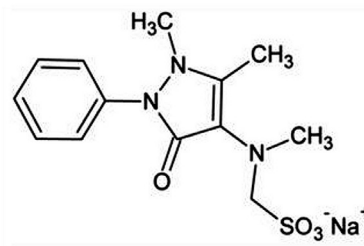


Figure 1. Chemical structure of sodium metamizole (dipyrone).

Metamizole, also known as dipyrone, is the main pyrazolone derivative indicated as an analgesic, antipyretic, anti-inflammatory and anti-spasmodic agent. It was introduced into clinical practice in 1922 and is still used in several countries, owing to its strong analgesic effect and relatively low cost (Weinert, et al., 2007). It has been banned in the USA and some European countries because of its association with cases of certain blood cell disorders, such as aplastic anemia and agranulocytosis, with an incidence of 0.2 to 2 cases per million people/day of use. However, because this rate of occurrence was considered low by the Brazilian food and drug agency (National Agency of Sanitary Vigilance: Anvisa), metamizole was maintained on the Brazilian market (Korokolvas & Burckhalter, 1988; Anvisa, 2001). Many other countries (including Germany, Spain, Portugal, Argentina, Colombia, Chile, Egypt, Israel, Italy and Switzerland) also allow the marketing of metamizole-based drugs.

In Brazil, metamizole is listed in the National Inventory of Essential Medicines (Rename), since it was set up in 1971 (Ministério da Saúde, 2010). In addition to the reference branded drug (Novalgina®, Sanofi-Aventis), recognized by Anvisa, other pharmaceutical products that contain this drug are marketed as 'similar' (branded) and generic drugs, in the form of tablets, syrups, solutions,

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injectables and combined with other active principles (Danieli & Leal, 2003).

Studies have shown that the implementation of the national policy on the production of generic and similar drugs led to the growth of the Brazilian pharmaceutical industry and to the falling price of drugs in general (Lima & Cavalcanti Filho, 2007). Usually, a similar (or copy) drug was an off-patent pharmaceutical product for which there was no proof of bioequivalence, but which could be sold under a brand name (Homades & Ugalde, 2005). However, this scenario changed in 2007, with the Anvisa regulation RDC 17/2007 (Brasil, 2007a). From that date, a similar drug had to undergo the same tests as generic drugs, i.e., it must also be bioequivalent to its reference drug. However, it is still not legally interchangeable with the reference drug: this process remains restricted to generic drugs. Nonetheless, 'similar' drugs are the most easily found in the Brazilian public health system, according to a study by Miranda et al. (2009), which demonstrates the importance of this type of drug for the Brazilian pharmaceutical market and the need for legal registration of similar drugs as rigid as that of generics (Brasil, 2007b).

One of the stages of bioequivalence tests is the verification of pharmaceutical equivalence, a comparative assay of the *in vitro* quality of the test drug relative to its branded reference drug (Pugens et al., 2008). This must follow the official methods published in the 4th edition of the Brazilian Pharmacopeia (Farmacopeia Brasileira, 1988; 1996), or, if applicable, in other codes authorized by Anvisa, or other applicable quality standards (Anvisa, 2003). Thus, the quality of formulations may be guaranteed, ensuring the efficacy and safety of drugs consumed by the population, with supporting inspection of pharmaceutical products in actions of sanitary vigilance (Pestana et al., 2008).

Solid pharmaceutical forms for oral use are the most frequently prescribed, because of their ease of administration and greater stability. Besides, tablets tend to preserve the chemical integrity of the drug for longer and enable the prescribed dose to be taken correctly. However, these drugs can have bioavailability problems.

Bioavailability refers to the speed and extent to which a drug or its therapeutic group is absorbed from a pharmaceutical form and becomes available at the site of action (Lachman, et al., 2001; Storpirtis et al., 2004). The importance of quality control studies increases for drugs exempt from medical prescription (or "over-the-counter drugs", OTC), in solid pharmaceutical forms containing aspirin, acetaminophen, metamizole or ibuprofen; in such cases, interchangeability is determined only by comparing the dissolution profiles and *in vitro* studies are the only ones that grant bioequivalence of these drugs (Anvisa, 2003).

Deviations from the recommended quality of a drug may lead to serious consequences for patients or even an entire public health system. For instance, Petralanda (1995) reported that the low quality and great variation in the concentration of the primaquine in different drugs may have led to the selection of resistant strains of *Plasmodium vivax*. At the beginning of the 2000s, Anvisa began to adopt a series of measures to ensure the quality, safety and efficacy of medicines produced in Brazil, according to international standards (Anvisa, 2003). However, despite the current rigid legislation regarding good manufacturing practice (GMP) and quality control, it is still possible to find drugs that deviate from quality standards being marketed in Brazil. Although this situation is very sporadic, studies carried out by Brazilian researchers have shown that concern over the quality of drugs produced in Brazil must still be taken seriously. A list of articles published between 2001 and 2010, highlighting many negative results, is given in Table 1. Among these reports are OTC drugs, such as the analgesic aspirin, but there are also drugs for more serious diseases, such as the antiretroviral lamivudine and the antihypertensives captopril, amlodipine and propranolol.

Interestingly, in ten articles, seven showed negative results for the dissolution profile. This is similar to a problem indicated by Amin & Kokwaro (2007) in their review of quality deviations of antimalarial drugs manufactured in Africa: while those authors observed that most of the drugs passed the general drug quality tests, most of the unapproved samples failed in the dissolution test.

Table 1. Some negative results regarding the quality of drugs produced in Brazil (period: 2001 to 2010).

Reference	Drug	Results
Pinho & Storpirtis (2001)	Metformine 850 mg	Two industrialized drugs (not specified) failed in the hardness test and in the information to the patient
Fernandes, Campos & Pianetti (2003)	Lamivudine 150 mg	Three batches of a test drug produced by the same laboratory were not approved in the dissolution profile.
Castro et al. (2005)	Sodium diclofenac 50 mg	Three generic and two similar drugs failed in the dissolution profile.
Malesuik et al. (2006)	Amlodipine 5 mg	A compounded drug (capsules) and an industrialized drug (tablets) failed in studies of uniformity of dose and hardness, respectively.
Rodrigues et al. (2006)	Propranolol 40 mg	A similar and a generic drug failed in the dissolution profile.
Linsbinski, Musis & Machado (2008)	Captopril 25 mg	A similar drug and a generic product failed the friability test (generic), content uniformity (similar) and dissolution profile (both).
Rodrigues et al. (2008)	Metronidazole 250 mg	Two similar drugs failed in the dissolution profile.
Scandolara et al. (2008)	Piroxicam 20 mg	Two generic drugs were analyzed: both failed in the dose assay and one in the uniformity of dose.
Köhle et al. (2009)	Sodium metamizole 500 mg	One generic and three similar drugs failed in the dissolution profile.
Bunhak, Stoef & Melo (2010)	Aspirin 100 mg	Five samples failed in the free salicylic acid limit test and six in the dissolution profile.

Thus, considering the current importance of generic and similar drugs for the Brazilian health system and pharmaceutical market, the importance of drug forms containing metamizole in Brazil, and the drug quality deviations observed in recent years by several research groups, this study was performed to assess the pharmaceutical equivalence of various generic and similar brands of 500 mg tablets of sodium metamizole produced in Brazil, by determining if they satisfy the quality criteria specified in F. Bras IV and if their dissolution profiles are equivalent to the reference.

MATERIAL AND METHODS

Tablets of 500 mg sodium metamizole produced by seven different Brazilian laboratories and bought in drugstores were used in this study: a sample of the reference drug (R: Novalgina®, Sanofi-Aventis, batch 902791), three generic drugs (G_1 , G_2 , G_3) and three 'similar' brand drugs (S_1 , S_2 , S_3). All the assays were performed as stipulated in the General Methods (Farmacopeia Brasileira, 1988) and Monograph 145.1 (Farmacopeia Brasileira, 1996). The study of the dissolution profile followed the advice of the *Guide to Performance of Pharmaceutical Equivalence and Comparative Dissolution Profile Reports* (Brasil, 2010). The volumetric (VS), reagent (RS), and indicator (IS) solutions were prepared as specified in Farmacopeia Brasileira IV (1988; 1996). The following tests were performed:

Identification

Two tablets from each drug sample were pulverized and 0.5 g of the resulting powder was transferred to a test tube. Some drops of 30% (w/w) hydrogen peroxide were added.

Uniformity of mass

Twenty tablets from each sample were individually weighed on an analytical balance (precision 0.0001g).

Friability

Twenty tablets from each sample were individually weighed on an analytical balance and then placed in the drum of a friabilator. After 5 minutes of testing (100 rotations), the drum was stopped; the powder generated by the tablets was collected and again weighed.

Hardness

The test consisted of compressing a tablet across its diameter until it broke. Twenty tablets from each sample were tested in a hardness tester.

Disintegration

The immersion liquid for this test was water at $37 \pm 1^\circ\text{C}$. Six tablets of each sample were assessed

in the disintegrator in three trials. With the help of the inbuilt chronometer, the time (minutes) needed for total disintegration of the tablets was recorded.

Drug content test

Twenty tablets of each sample were weighed and pulverized. A quantity of powder equivalent to 0.25 g of sodium metamizole was weighed and transferred quantitatively to an Erlenmeyer flask, where 25 mL water and 5 mL glacial acetic acid were added and the solution was shaken until homogeneous. Active content was determined by redox titration, in triplicate, against 0.05 mol L⁻¹ iodine (VS), at a temperature below 15 °C, using 1 mL of starch indicator solution (IS). The endpoint was reached when the violet color in the solution took more than one minute to disappear. Each mL of VS is equivalent to 17.57 mg of sodium metamizole.

Uniformity of dosage units

The dose content uniformity was tested by the method of weight variation. Ten tablets were weighed, accurately and individually, in each sample. From the content test result, the active content in each unit was calculated, presuming homogeneous distribution of this component in the formulation. Results were expressed as percentage of declared quantity and its relative standard deviation (RSD%).

Dissolution profile

The dissolution profiles were defined by the quantity of substance dissolved in each interval of time. Four tablets from each sample were tested, with a DT80 dissolution tester (Erweka, Germany), under the following experimental conditions (apparatus 2): 500 mL of 0.1 mol L⁻¹ HCl as dissolution medium, maintained at $37 \pm 0.5^\circ\text{C}$ and stirred by paddle at 50rpm; at determined intervals (5, 10, 15, 30 and 45 min), aliquots of 10 mL of the solution were collected and replaced by 10mL dissolution medium. These aliquots were filtered, diluted and analyzed by UV spectrophotometer (Shimadzu 1601) at 258 nm, with the 0.1 mol L⁻¹ HCl solution as blank. For calibration purposes, we used a secondary standard of known content (95.15%) and the quantity of sodium metamizole dissolved in the medium was calculated as:

$$\text{dissolved \%} = (A_a \cdot C_p \cdot T_p) / (A_p \cdot C_a) \quad \text{Eq. 1}$$

where A_a and A_p are, respectively, the absorbance of sample and standard, C_a and C_p their concentrations in mg/mL and T_p the % content of sodium metamizole in the standard.

The dissolution profiles of similar and generic drugs were compared with that of the reference drug by comparing the average dissolution concentrations at each collection time. The results were expressed as the factor of similarity (f_2 , Equation 2), as in the *Guide to the Study and Reporting of Pharmaceutical Equivalence and Comparative Dissolution Profiles* (Brasil, 2010):

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{\sum_{t=1}^n (R_t T_t)}{n} \right]^{-0.5} \right\} \times 100 \quad \text{Eq. 2}$$

where: n = number of collection times; R_t and T_t = percentages of reference brand and test drug dissolved at time t . All values were rounded to two significant figures.

RESULTS

In the identification test, it was expected that, after adding 30% hydrogen peroxide, a blue color would develop and quickly disappear, turning an intense red. This phenomenon was observed for all the drugs. For the assay of average weight, since the values found were higher than 250 mg, ranging from 530 to 630 mg, each unit could vary by $\pm 5\%$ around the average, with a tolerance of two tablets outside this limit, and none could deviate more than 10% from the nominal value. Just one tablet of sample S_2 had an individual weight more than 5% higher than average and

thus all drugs were approved. The friability test resulted in a small loss of mass, well below the limit recommended by Farmacopeia Brasileira IV (1.5%), for all the tablets analyzed (Table 2). All drugs were approved with regard to hardness, since this parameter was found to be above 30N for all samples. The disintegration time of all samples also proved satisfactory, as all tablets had completely disintegrated within less than 30 minutes. The results of these tests are presented in Table 2.

Table 3 presents the results for dosage unit content and uniformity. All seven of the analyzed samples had contents compatible with that required by Farmacopeia Brasileira IV: mean content ranging from 90 to 110% and uniformity of dosage units between 85 and 115%, with $RSD \leq 6\%$.

Figure 2 shows the dissolution profiles of the six drugs being tested against the reference drug (R). Since all the drugs showed more than 85% of the active principle dissolved within 15 minutes (Brasil, 2010), the similarity factor f_2 maintained its power of discrimination among the profiles and thus was calculated. In this assay, only drugs G_3 and S_3 achieved f_2 between 50 and 100 (Brasil, 2010) and therefore were approved. These results are presented in Table 4.

Table 2. Results of identification test and physical assays.

Assays	Samples						
	R	G1	G2	G3	S1	S2	S3
Identification	Ap	Ap	Ap	Ap	Ap	Ap	Ap
Uniformity of mass (mg \pm RSD%)	530 \pm 0.8	620 \pm 0.7	620 \pm 1.4	600 \pm 2.2	570 \pm 0.8	630 \pm 2.5	610 \pm 1.7
Friability (%)	0.41	0.24	0.41	0.52	0.41	0.18	0.09
Hardness (N \pm RSD%)	80 \pm 13.5	130 \pm 10.7	104 \pm 20.5	71 \pm 17.2	77 \pm 22.3	144 \pm 15.1	159 \pm 9.0
Disintegration time (minutes)	3.98	7.27	6.62	5.6	7.34	4.78	4.64

Ap: approved.

Table 3. Results of dosage unit assays.

	Samples						
	R	G1	G2	G3	S1	S2	S3
Content (% \pm RSD%)	98.8 \pm 1.46	98.9 \pm 0.32	105 \pm 1.28	100 \pm 2.98	93.7 \pm 1.16	102 \pm 0.6	99.9 \pm 0.98
Uniformity (% \pm RSD%)	98 – 99.7 \pm 0.64	97.9 – 99.8 \pm 0.63	104 – 106 \pm 0.74	95.4- 102.6 \pm 2.07	92.6 – 94.5 \pm 0.78	97.3 - 107 \pm 2.77	97.3 - 101 \pm 1.14

Table 4. Similarity factor (f_2) of generic (G1, G2 and G3) and similar (S1, S2 e S3) tablets of sodium metamizole in relation to the reference drug (R).

GROUPS	f_2
R x G_1	29
R x G_2	28
R x G_3	52
R x S_1	36
R x S_2	39
R x S_3	50

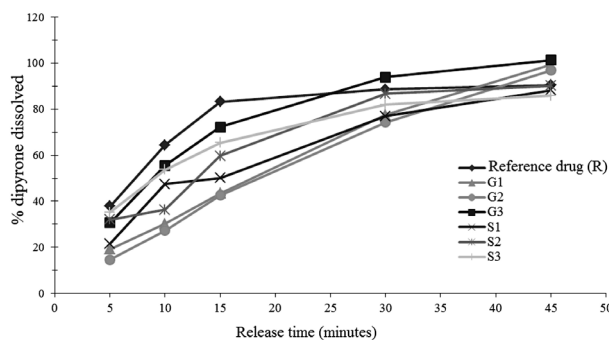


Figure 2. Dissolution of sodium metamizole over time.

DISCUSSION

The results presented in Tables 2 and 3 indicate that all the analyzed drugs attain standards of quality recommended by Farmacopeia Brasileira IV (1988; 1996). Since it is common for drug tablets to vary in weight, mechanical resistance and disintegration characteristics (besides the design, thickness, diameter and size specific to each drug), these properties must be controlled during manufacturing, to ensure the expected appearance and therapeutic efficacy of the product (Wong, 2009).

Since formulations are generally based on the weight of the pharmaceutical form, this parameter will affect the quality of the final product. Thus, the assay of uniformity of mass is used to check homogeneity among the units of the sampled batch. Tablets of different weights may differ in quality parameters, including the content of active principle (Peixoto et al., 2005; Ansel et al., 2000). Among all the tablets analyzed in this study, only one unit of drug S₂ fell outside the limits of ± 5.0 % defined for tablets of more than 250 mg. However, Farmacopeia Brasileira IV (1988) allows two units to be outside this range. Therefore, it may be concluded that the distribution of raw material during tablet production was sufficiently homogeneous.

Tablets are also subject to mechanical shocks during production, packing, storage, transportation, distribution and handling. For this reason, they should possess a certain level of mechanical resistance. High friability (*i.e.*, low capacity to withstand friction) means that the drug is more likely to suffer mechanical erosion, which may cause loss of the active principle and thus compromise its efficacy. Hardness is related to friability, but also to disintegration and dissolution speed. A very hard tablet may exhibit an increased dissolution time (Lachman et al., 2001; Peixoto et al., 2005; Aulton, 2006). As shown in Table 2, all drugs were approved in respect of their friability and hardness.

The physical assay on disintegration is related to the capacity of solid pharmaceutical forms to release their active principles, because before their solubilization the tablets must disintegrate into small particles, increasing the contact surface with the dissolution medium and favoring absorption and bioavailability of the drug (Storpiertis et al., 2009; Linsbinski et al., 2008). All drugs were approved with regard to their disintegration time (Table 2).

The results of dosage assays presented in Table 3 showed that the average content of metamizole among the analyzed drugs ranged from 93.70% to 105%. Sample G₃ showed the highest RSD% (3%), but, since its average content was 100%, this deviation still maintained the drug content within the interval 90 – 110% (Farmacopeia Brasileira, 1996). The results for uniformity of dose showed that, even with a limit higher than that allowed by Farmacopeia Brasileira IV (85 – 115%), the results were close to the average content. Therefore, all drugs were approved in the assays related to metamizole content.

However, the positive results obtained in the above tests were not reflected in the dissolution profiles (Figure 2 and Table 4). This assay can be used to determine the speed of availability and amount of the drug available, relative to its reference drug. This is an important assay for determining the pharmaceutical equivalence between drugs, and it must be performed to ensure bioequivalence of sodium metamizole tablets (Brasil, 2003; Storpiertis

et al., 2009). In order to obtain the dissolution profile, several collections of the dissolution medium were made, at suitable times, the number of replicate samples being sufficient to determine the significance of each batch and the percentage of the drug dissolved in each time interval (Porta et al., 2002). This method allows us to determine whether the cessation times of the active principle in two drugs are similar. Factor f_2 (Equation 2) is a measure of similarity between the percentages dissolved at each time during the dissolution test, and results ranging from 50 to 100 ensure equivalence between the dissolution curves (Storpiertis et al., 2009; Brasil, 2010). Table 4 shows that only two drugs (G₃ and S₃) can actually be considered equivalent to drug R.

Since the comparison of dissolution profiles is not an obligatory assay in routine quality control, this is a worrying result. According to Farmacopeia Brasileira IV (1988), the dissolution study may be performed by collecting only one aliquot from the bath after 45 minutes, in which case 70% of the metamizole must be dissolved in the dissolution medium after this interval. Figure 2 shows that all the drugs would be approved if only this one collection point were used in the analysis. In fact, this may actually have occurred during the production of each of these drugs, justifying the release of these batches on the market by their respective manufacturing companies.

These results agree with an equivalent study published by Köhle et al. (2009), who tested 500mg metamizole tablets. The authors assessed the quality of samples of the reference drug, two generic and two similar drugs. All of these were approved with respect to uniformity of mass, friability and disintegration (no hardness assay was performed). The drugs were also approved for their uniformity of content (no dosage was performed) and more than 70% of the drug dissolved within 45 minutes. However, none of the four tested drugs exhibited f_2 inside the established limits and the authors thus concluded that all four were inequivalent to the reference drug. This is the same test that revealed some inequivalent drugs in this study.

In light of these results, it may be concluded that only G₃ and S₃ can be considered as pharmaceutically equivalent to the reference drug. Moreover, the performance of a dissolution assay by the withdrawal of a single aliquot at the time stipulated in Farmacopeia Brasileira IV, or in other compendia, is not enough to determine the capacity of a drug to release the active principle into the surrounding medium. This reinforces the importance of assessing whole dissolution profiles in order to determine pharmaceutical equivalence, as well as in routine quality control. Despite the great advances in the last decade, these results confirm the need for tighter legislation and inspection regarding the quality of similar and generic drugs already on the market, which when implemented will further enhance the quality of drugs available to the Brazilian population, besides increasing the competitiveness of Brazilian manufacturers of generic and similar drugs.

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RESUMO

Comparação entre a qualidade farmacopéica e perfis de dissolução de medicamentos genéricos e similares de metamizol sódico (dipirona) comercializados no Brasil

No Brasil, para que uma indústria farmacêutica registre um produto como genérico ou similar, o medicamento deve ser bioequivalente a seu medicamento de referência. Isto requer a realização de estudos comparativos, seguindo um compêndio oficial (Farmacopeia Brasileira ou outra reconhecida oficialmente). Além disso, de acordo com a RDC 31/2010, também deve ser realizado o estudo do perfil de dissolução em relação ao seu medicamento de referência. Este estudo teve como objetivo avaliar a qualidade de comprimidos de metamizol sódico (ou dipirona) com teor de 500mg produzidos por sete diferentes laboratórios brasileiros: três medicamentos genéricos (G₁, G₂, G₃), três similares (S₁, S₂, S₃) e o medicamento de referência (Novalgina®, Sanofi-Aventis, R). Todos os testes seguiram os métodos descritos na Farmacopeia Brasileira IV. Os seguintes ensaios foram realizados: uniformidade de massa, friabilidade, tempo de desintegração, dureza, doseamento, uniformidade de doses unitárias, ensaio limite de ácido salicílico e identificação. O perfil de dissolução foi realizado como recomendado pela RDC 31/2010. Apesar das amostras terem sido aprovadas em todos os ensaios farmacopéicos, os resultados do perfil de dissolução indicaram que quatro medicamentos (G₁, G₂, S₁ e S₂) não são equivalentes farmacêuticos de R. Apenas G₃ e S₃ mostraram perfis similares a R. Assim, quatro medicamentos foram reprovados.

Palavras-chave: Metamizol. Perfil de dissolução. Equivalência farmacêutica. Medicamento genérico. Medicamento similar.

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