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Article

Comparator product issues for biowaiver implementation: the case of Fluconazole

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The aim of this work was to assess if the commercially available Fluconazole drug products (Reference, Generic and Similar) would meet the biowaiver criteria from Food and Drug Administration (FDA) and Brazilian Agency for Health Surveillance (ANVISA) agencies. All formulations were evaluated considering the dissolution profile carried out in Simulated Gastric Fluid (SGF) pH 1.2, Acetate Buffer (AB) pH 4.5 and Simulated Intestinal Fluid (SIF) pH 6.8. The results demonstrated that all formulations fulfilled the 85% of drug dissolved at 30 min criterion in SGF pH 1.2. However, in AB pH 4.5 and SIF pH 6.8, some formulations, including the comparator, did not achieve this dissolution percentage. The discrepant dissolution profiles also failed the *f*2 similarity factor analysis, since none of the formulations showed values between 50 and 100 in the three dissolution media. Comparative dissolution profiles were not similar, considering that the main issues concerning the dissolution were evidenced for the comparator product. Hence, a revision in the regulatory norms in order to establish criteria to switch the comparator could result in an increased application of drugs based on biowaiver criteria.

Keywords: Fluconazole. Biopharmaceutics classification system. Biowaiver. Dissolution profile.

ABBREVIATIONS

AB	Acetate Buffer
ANVISA	Brazilian Health Surveillance Agency
BCS	Biopharmaceutics Classification System
BDDCS	Biopharmaceutics Drug Disposition Classification System
ECCS	Extended Clearance Classification System
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation
*f*2	Similarity factor
G	Generic formulations
IR	Immediate Release
R	Reference product
S	Similar formulations
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
WHO	The World Health Organization

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INTRODUCTION

Multisource (generic) medicines are the most affordable option for treating diseases. However,

bioequivalence has to be demonstrated to allow for interchangeability by carrying out relative bioavailability/bioequivalence studies against the reference medicine (Löbenberg *et al*., 2012). In some countries, including Brazil, there is one more possible category for medicinal products, i.e. "similar" products. The differences between similar and reference are related to some aspects such as: shelf-life period, packaging, labeling, size and shape of the product. In Brazil, generic medicines contain on their packaging the name of the active ingredient and the phrase "generic medicine - law N° 9787 of 1999". For easy identification, they have a large blue letter "G" printed on a yellow strip on the bottom of the product packages (Brasil, 1999; Brasil, 2003).

Similar medicines, in Brazil, are interchangeable with the reference product when the bioavailability/bioequivalence test is required. Differently from the generics, the similar medicines adopt a commercial "brand" name Brasil, (2014). Usually, similars are the cheapest medicines in the market. Although generic and similar medicines are more affordable than the reference drug product medicine, the bioequivalence tests (that is mandatory for both categories of products) present two major disadvantages: healthy volunteers are exposed to the drug products and the analytical costs are relatively high. To overcome this, the biowaiver studies based on the Biopharmaceutics Classification System (BCS) have been proposed by many regulatory agencies around the world (Davit *et al*., 2016; Löbenberg *et al*., 2012; Reddy, Patnala, Kanfe, 2017).

In 1995, Amidon and coworkers proposed the Biopharmaceutics Classification System (BCS) considering aspects like drug solubility and intestinal permeability in combination with the dissolution properties of immediate release (IR) oral medications. The BCS classified drugs into four groups: Class I high solubility/high permeability, Class II low solubility/high permeability, Class III high solubility/low permeability and Class IV low solubility/low permeability.

The main objectives of BCS are to improve drug development, obtain optimized formulations that allow for an *in vivo* pharmacokinetic prediction of drugs from permeability and solubility measurements (Amidon *et al*., 1995). Nowadays, the BCS is recognized as an important scientific instrument for waiving the regulatory requirements for *in vivo* assays (Amidon *et al*., 1995; Cardot *et al*., 2016; Larregieu and Benet, 2014; Reddy, Patnala, Kanfer, 2017). In fact, the BCS classification was used for waiving the requirements for *in vivo* bioavailability (BA) and bioequivalence (BE) studies of Class I and Class III immediate release (IR) solid oral dosage forms (Davit *et al.*, 2016) for drugs that do not present a significant intestinal absorption problem (FDA, 2017; Niazi, Swarbrick, 2007).

New classification systems have been proposed afterwards, such as the Biopharmaceutics Drug Disposition Classification System (BDDCS), introduced by Wu and Benet (2005), where drugs are categorized in terms of the extent of metabolism and solubility and the Extended Clearance Classification System (ECCS), which can be used to predict the predominant clearance mechanism (rate-determining process) based on physicochemical properties and passive membrane permeability and can be very useful mainly during early drug development (Varma *et al*., 2017). Although these new classification systems are important for the pharmaceutical area, from a regulatory point of view, only the BCS is currently used by agencies for biowaiver purposes.

The BCS, BDDCS and ECCS are complementary, non-competitive classification systems that aim to improve, simplify and expedite the development of medicines. The complementarity of these systems can play an important role for the waiver of *in vivo* bioequivalence. However there is still no official guide authorizing the use of BDDCS and ECCS classification systems. Both the permeability and the metabolism of the BCS and BDDCS may be used as substitutes of drug absorption, thus becoming important tools for biowaiver studies (Camenisch, 2016).

Years ago, it was suggested that the BCS are not used to its full potential, since the number of biowaiver requirements in the regulatory agencies is still low, due to the probability that at that time the biowaiver regulations had not yet been globalized (Bergström *et al*., 2014). In 2015, the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and WHO harmonized the criteria for obtaining biowaivers for BCS

Class I and Class III drugs (Cardot *et al*., 2016; Davit *et al*., 2016). Usually, the comparator/reference product is the innovator and every regulatory agency from almost all countries around the world has a list of reference products. Moreover, the International Pharmaceutical Federation (FIP) has been publishing monographs of drugs that are considered to belong to BCS Class I or III (FIP, 2014).

In 2011, The Brazilian National Health Surveillance Agency (ANVISA) published a regulation for biowaiver in Brazil (Brasil, 2011). The difference of the ANVISA guideline from FDA, EMA and WHO guidelines resides in the fact that ANVISA presented a list of drugs candidates for biowaiver (Brasil, 2016). Only drugs considered as BCS Class I were included in the list. The list by ANVISA also includes the antifungal drug fluconazole.

Fluconazole is an antifungal agent used for the prophylaxis and treatment of superficial and systemic fungal infections, mainly candidiasis and cryptococcal meningitis (Zervos, Meunier, 1993). Nowadays fluconazole belongs to the WHO list of essential medicines, and is considered a basic medicine for pharmaceutical care, also important to treat HIV/AIDS related conditions (WHO, 2018).

The BCS for fluconazole is not clear in the literature. Most of the information classifies it as Class I (Bergström *et al*., 2014; Lindenberg *et al*., 2004), but some researchers regard it as Class III (Bergström *et al*., 2014; Ramirez *et al*., 2010). The discrepancy in the literature data may be a result of different criteria used early for classification by EMA and FDA (different pH ranges for solubility assessment, different limits of absorption for permeability and different maximal doses when indicated for the treatment of different diseases) and different methods used in the solubility and permeability assays (Bergström *et al*., 2014).

Considering that BCS for fluconazole is inconsistent in the literature and fluconazole is present in ANVISA and FIP lists as a possible biowaiver candidate, the aim of this study was to evaluate the dissolution profile of reference medicine (used as comparator), generic and similar commercial capsules containing fluconazole 150 mg based on the biowaiver criteria and to raise a discussion about the implications when the reference product did not meet the dissolution criteria.

MATERIAL AND METHOD

Drugs

Fluconazole 150 mg capsules were purchased from different manufacturers in the Brazilian market within their shelf-life period and were identified as G1, G2 and G3, for the generic formulations and S1, S2 and S3 for similar formulations. The reference product (R), approved by ANVISA, was the Zoltec® (Pfizer, USA) considered the innovator medicine in Brazil. The qualitative formulation of each sample was also analyzed. All formulations were manufactured in number 1 capsule.

Chemicals and Reagents

Ultrapure water was obtained by Milli-Q purification system (Merck Millipore, Darmstadt, HE, Germany), HPLC grade acetonitrile (Tedia, Fairfield, OH, USA) was used for chromatographic analysis. All other reagents were of analytical grade.

Chromatographic conditions

All samples were analyzed by HPLC (Shimadzu, Kyoto, Japan) using a reverse phase chromatographic column (Phenomenex Synergy Fusion C_{18}, 150 mm x 4.60 mm, (Phenomenex, Torrance, USA) maintained at 30˚C. The mobile phase consisted of a mixture of acetonitrile:water (25:75, v/v), eluted isocratically at 1 mL min^{-1}. Detection was performed by UV spectroscopy at 260 nm. The method was previously validated. The amount of drug dissolved was calculated in relation to a linearity curve. For the preparation of each calibration curve, an amount of 10 mg of fluconazole was exactly weighted out and diluted in 10 mL volumetric flask with methanol, to obtain a final concentration of 1 mg mL^{-1}. This solution was then diluted in six levels (0.5, 1, 2, 5, 10, and 15 µg mL^{-1}) with dissolution media covering the lowest and the highest concentration that were expected for drug dissolution.

Dissolution profile studies

All dissolution studies were performed in a USP Apparatus I (basket) dissolution equipment (708 DS, Agilent Technologies) operated at 100 rpm, kept at the constant temperature of 37 ± 0.5 ˚C and containing 900 mL of media.

For the dissolution profiles, the three dissolution media recommended by FDA and ANVISA were used: Simulated Gastric Fluid without enzymes (SFG) pH 1.2, Acetate Buffer (AB) pH 4.5 and Simulated Intestinal Fluid without enzymes (SIF) pH 6.8.

Biorelevant dissolution media were prepared as detailed below: Simulated gastric fluid without enzymes (pH 1.2): 2.0 g of sodium chloride was dissolved in 7.0 ml of hydrochloric acid (37%) and the volume was completed with enough distilled water to make 1000 mL of solution. Acetate buffer solution pH 4.5: 2.99 g of sodium acetate trihydrate was dissolved in 500 mL of distilled water and 14 mL of the 2 N acetic acid solution was added. The volume was completed with enough distilled water to make 1000 mL of solution. Simulated intestinal fluid without enzymes (pH 6.8): 6.8 g of monobasic potassium phosphate was dissolved in 250 ml of distilled water and mixed. 77 mL of a 0.2 M sodium hydroxide was added and the volume was completed with enough or distilled water to make 1000 mL of solution. The pH of the solutions was adjusted with 0.2 M sodium hydroxide solutions or 0.2 M hydrochloric acid to the correct value before the volume was completed for all dissolution media.

All dissolution media were filtered and degassed before use. The dissolution sampling times were 2, 2.5, 3, 4, 5, 6, 8, 10, 15, 20, and 30 minutes. For each time point, 5 mL of sample were withdrawn and immediately replaced with pre-heated fresh medium. The samples were immediately filtered using syringe filter (Allcrom, nylon 13 mm, 0.45 µm, São Paulo, Brazil) and submitted to HPLC analysis.

Considering the FDA and ANVISA biowaiver guidelines for BCS class I, the percentage of fluconazole dissolved at 30 min was evaluated.

Statistics

The dissolution profiles of generic and similar products were compared to the reference product by statistical analysis using the $f2$ (similarity factor, Eq. 1).

$$f2 = 50.log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} |R_t - T_t|^2\right]^{-0.5}.100\right\}$$

Equation (1)

Where Rt and Tt are the percentages released at each time point for the reference and the test product, respectively.

The dissolution profiles can be considered similar if the values of $f2$ are between 50 and 100 (Brasil, 2010; Davit *et al*., 2016; FDA, 2017; Suarez-Sharp *et al*., 2016).

RESULTS AND DISCUSSIONS

The most important reasons to waive *in vivo* bioequivalence/bioavailability studies is the reduction of exposition of volunteers to drug products and reduction of costs (Polli, 2008). Drugs candidates to biowaiver are the right way to reach these goals mainly for immediate oral release products. According to the FDA and ANVISA biowaiver guidelines for BCS Class I drugs, the criteria that must be considered for the approval are:

1. The $f2$ similarity factor value between test and reference dissolution profiles is between 50 and 100;
2. The amount drug dissolved at 30 min is higher than 85% in all dissolution media: SGF pH 1.2, AB pH 4.5 and SIF pH 6.8;
3. If the amount of drug dissolved at 15 min is higher than 85% in all three media, the $f2$ statistical analysis is unnecessary.

The dissolution profile was carried out in 900 mL of dissolution media following the Brazilian ANVISA guideline Brasil, (2011). The FDA guidance for industry recommends a volume of 500 mL (FDA, 2017).

For the dissolution profiles carried out in SGF pH 1.2 (Figure 1) all formulations dissolved more than 85% of the drug dose in 30 min (Table I). However, while G1, G2, S2

and S3 formulations presented a fast fluconazole release, with dissolved drug values higher than 85% in 15 minutes, the reference product, R and S1 and G3 formulation presented a distinct and slower drug dissolution profiles, with values between 59.76 and 73.73%.

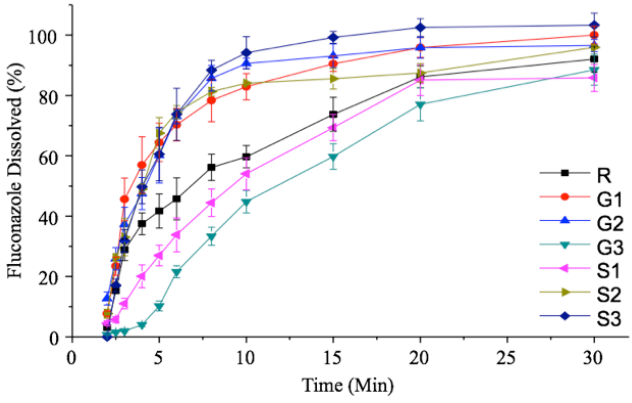

FIGURE 1 - Dissolution profile of fluconazole 150 mg capsules in simulated gastric fluid, pH 1.2 (± standard deviation).

TABLE I - Mean percentage of Fluconazole dissolved after 30 minutes of dissolution

Dissolution media	Formulations						
	R	G1	G2	G3	S1	S2	S3
SGF pH 1.2	92.07	100.02	96.58	88.52	85.84	95.95	103.31
AB pH 4.5	70.66	103.80	96.60	95.71	65.05	84.15	103.42
SIF pH 6.8	64.44	89.14	88.92	74.92	71.34	74.24	103.58

In acetate buffer pH 4.5 (Figure 2) the S3 formulation presented the highest dissolution percentage, with approximately 100 % in 15 min. On the other hand, the reference formulation R presented the lowest percentage of fluconazole dissolved with only 50.94%. Considering the dissolution rate at 30 min, G1, G2, G3 and S3 formulations were dissolved more than 85% of the labeled fluconazole dose (Table I). Conversely, the reference product dissolved only 65% of the drug at 30 minutes.

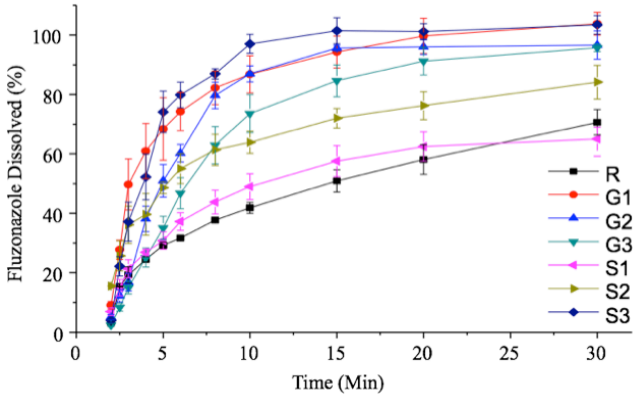

FIGURE 2 - Dissolution profile of fluconazole 150 mg capsules in acetate buffer, pH 4.5 (± standard deviation).

The dissolution in SIF pH 6.8 (Figure 3) presented the most discrepant results compared to the other dissolution media. The G3 formulation had the lowest percent of fluconazole dissolution, with approximately 35% dissolved in 15 min. At the same time, the formulation S3 presented the highest percentage, with 100.10% of drug dissolved.

From all data presented, only the formulations G1, G2 and S3 complied with the biowaiver legislation, presenting satisfactory results with percentage of dissolved drug above 85% in 30 min (Table I).

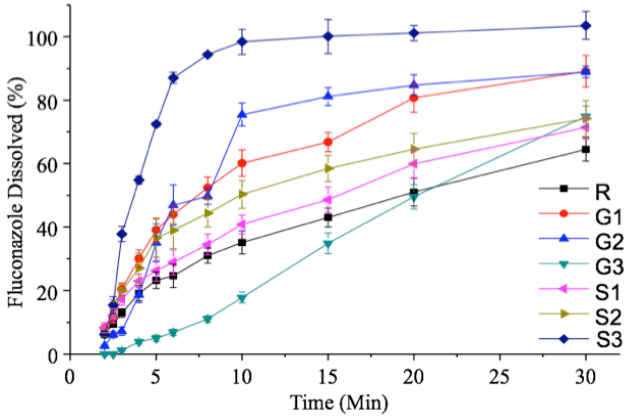

FIGURE 3 - Dissolution profile of fluconazole 150 mg capsules in simulated intestinal fluid, pH 6.8 (± standard deviation).

The results from the dissolution studies showed (Table I) that the reference drug product did not meet the specification, dissolving 70.66% and 64.44% in phosphate buffer pH 4.5 and SIF pH 6.8, respectively. Of course, this fact is not a concern for the patient, since the reference formulation is the innovator product where its *in vivo* efficacy and safety are well established. The G1, G2 and S3 formulations showed drug dissolution higher than 85% in 30 minutes in all dissolution media. It can be observed that in SGF pH 1.2 all fluconazole formulations were dissolved more than 85% at 30 minutes. These results could be related to the chemical nature of fluconazole, which is a weak base with a pKa of 1.76 at 24°C in solution, showing that its solubility will be higher at pHs lower than its pKa.

If fluconazole belonged to BCS Class III, the drug product (test and reference) should dissolve very rapidly (> 85% in 15 min) (FDA, 2017). The dissolution profile results demonstrate that it was not achieved for fluconazole formulations.

After analyzing the percentage of drug dissolved, the *f2* factor was calculated. The dissolution profiles can be considered similar if the values of *f2* are between 50 and 100, following the FDA and ANVISA guidelines and the reference product was used as comparator.

In SGF pH 1.2 all formulations presented *f*2 values lower than 50 (Table II), demonstrating that the dissolution profiles were not similar. When the AB pH 4.5 and SIF pH 6.8 media were considered, only the S1 formulation was found to satisfy the similarity criterion, with *f*2 values of 66.02 and 64.62, respectively. Although the *f*2 criterion was satisfied, it is clear (Figure 2 and Figure 3) that there is an issue with the comparator (reference) product, since it presented a slow drug dissolution profile. So, considering the request from the guidelines to compare the dissolution of a test product with the reference product, it will be impossible to fulfill both criteria necessary for obtaining a biowaiver (*f*2 similarity factor above 50 and dissolution at 30 higher than 80% of the labeled dose). As a consequence, it appears that *in vivo* bioavailability/bioequivalence studies for generic fluconazole are necessary.

TABLE II - Analysis of the similarity factor (*f*2) in different dissolution media

Dissolution media	Formulations					
	G1	G2	G3	S1	S2	S3
SGF pH 1.2	37.09	35.60	34.34	47.39	37.50	33.75
AB pH 4.5	21.98	26.69	33.89	66.02	36.80	20.63
SIF pH 6.8	36.11	31.82	43.31	64.62	46.96	16.72

The difference in the dissolution profiles of the fluconazole may be explained by difference in the excipient composition. The use of the excipients is strictly regulated by the regulatory agencies and qualitative and quantitative differences could be reason for not granting the authorization of biowaiver (Kubbinga, Langguth, Barends, 2013). The excipients may have a great pharmacokinetics influence behavior on oral immediate release formulations. For that reason, the guidelines recommend caution, mainly when critical excipients known as dissolution modulators are employed (Elder, Kuentz, Holm, 2016; García-Arieta, 2014; Zhang *et al*., 2016). These critical excipients (e.g. sorbitol, mannitol, sodium lauryl sulfate, or other surfactants) can affect the bioavailability and should be identified along with their possible impact on the gastrointestinal motility, susceptibility of interactions with the drug substance, drug permeability, and interaction with membrane transporters (Cardot *et al*., 2016; Charoo *et al*., 2014; Suarez-Sharp *et al*., 2016; Yu *et al*., 2002). In general, for BCS class I drug (high soluble) it should not be a concern for the product *in vitro* and *in vivo* performance, since the use of critical excipients is usually not necessary (FDA, 2017; Vaithianathan *et al*., 2016; Zhang *et al*., 2016).

For better comprehension of the observed *in vitro* differences, the qualitative formula of each fluconazole formulation was taken into account (Table 3). Concerning fluconazole, even though it is often considered as a BCS Class I, the analysis of the capsule composition showed the presence of sodium lauryl sulfate (SLS) in all formulations, with the exception of G3. SLS is considered a potential dissolution modulator and one of the main purposes of its use in pharmaceutical formulations is to accelerate the dissolution process (Rowe, Sheskey, Quinn, 2009). It is typically used in the formulations containing BCS Class II and IV drugs (Aljaberi *et al*., 2012; García-Arieta, 2014). In this way, the amount of SLS, when this excipient is present in the formulations, could be a factor to explain the dissolution differences.

TABLE III - Qualitative formulation of fluconazole 150 mg capsules

Excipients	Formulations						
	R	**G1**	**G2**	**G3**	**S1**	**S2**	**S3**
Calcium hydrogen phosphate dihydrate						X	
Croscarmellose sodium		X				X	
Ethyl alcohol				X			
Lactose anhydrous							X
Lactose monohydratade	X	X	X		X		
Magnesium stearate	X	X	X	X	X	X	X
Mannitol				X			
Microcrystalline cellulose				X		X	
Polyvinylpyrrolidone				X		X	X
Silicon Dioxide	X	X	X		X	X	X
Sodium Lauril Sulfate	X	X	X		X	X	X
Starch	X		X		X		

The difference in the dissolution profile could be due to the presence of different disintegrants used by the different industries, such as croscarmellose sodium, microcrystalline cellulose, polyvinylpyrrolidone, and starch. This qualitative difference is clear. Additionally, the quantitative difference should be considered but, unfortunately, this information is not available. The manufacturing process may also result in different dissolution profiles. It is evident that G3 formulation was prepared by wet granulation. However, the other products did not includ this information in the product leaflet. If fluconazole is considered as BCS Class III the influence of excipients is a major concern since, besides the dissolution difference, they may modify negatively the permeability of the drug (Kubbinga, Moghani, Langguth, 2014; Ono and Sugano, 2014; Parr *et al*., 2016; Teleginski *et al*., 2015).

Considering that the BCS classification of fluconazole is not clear in the literature and that the dissolution profile of the comparator (reference) drug product did not meet the regulatory requirements, it could be concluded that the use of a list of drugs candidates for biowaiver should be avoided. The legislation should be clear regarding the BCS classes allowed to be candidates for biowaiver. However, it should be the responsibility of the industry to demonstrate that a determined drug belongs to those specific BCS class (with either literature and/or experimental data) (Kubbinga, Langguth, Barends, 2013; WHO, 2018). Alternatively, if a list of drug candidates is provided but a comparator does not meet the regulatory criteria, the switch for another comparator should be allowed by the guidelines.

The manufacture of fluconazole tablets were approved by FDA in 1990, when the biowaiver criteria did not exist yet, consequently, the development of fluconazole reference product was carried out only in SGF for dissolution test as evidenced in its patent (Fekete *et al*., 2005). Recently, Marcelo Dutra and co-workers showed that the dissolution profile of two comparator products batches assessed in SGF did not have similar dissolution profiles (Duque *et al*., 2019). Another study carried out in Peru using the fluconazole Brazilian reference product showed that no formulation met the criteria for f2 calculation. Also, it was demonstrated that the dissolution profile of fluconazole comparator dropped down in AB pH 4.5 and FIS pH 6.8 (Grande-Ortiz *et al*., 2019), confirming that the comparator formulation must be reevaluated in order to be used in biowaiver studies.

In this scenario, both Anvisa´s and the FIP´s still include in their lists the fluconazole as a candidate for biowaiver based on BCS, although there is evidence that the reference comparator product does not comply with the in vitro dissolution test.

Many of the innovator medicines that are currently used as a reference in biowaiver studies were developed before the first biowaiver guides were published. This means that in the development of the product the criteria of biowaiver were not taken into account. Clearly this does not affect its safety and efficacy, facts that were proven in their *in vivo* studies, in that sense the specific case of fluconazole calls for the reference medicine in Brazil to be reassessed and that the biowaiver guidelines establish rigorous procedures for the selection of new medicines that can be use as a comparators for biowaiver purposes.

For such cases, the guidelines should allow for changing the comparator from the reference product for another commercially available medicine. This possibility could be a factor for increasing the number of biowaiver and reducing *in vivo* bioavailability/bioequivalence tests. Also, the combination of the BCS with BDDCS, ECCS or other classification systems would be valuable.

CONCLUSION

The biowaiver of *in vivo* bioavailability/bioequivalence studies has acquired importance in the pharmaceutical industry. However, this exemption is not used in its full potential. In the present study, the fluconazole comparator (reference) product was not in compliance with the regulatory requirements concerning the dissolution of the drug within 30 minutes. For this reason, the formulations candidates for biowaiver, that must have similar dissolution profile to the reference product, are never going to be able to fulfill the regulatory criteria for obtaining a biowaiver. Considering this paradigmatic case, the regulatory agencies could establish criteria for changing the comparator product when the innovator does not fulfill the biowaiver criteria.

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This article represents the author's view and there is no conflict of interest.

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