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A new multivariate similarity factor for *in vitro* therapeutic equivalence assessment

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Pharmaceutical equivalence is an important issue in the regulatory approval of generic and similar drug products, particularly for those that will not be tested for bioequivalence. However, there is no scientific approach that provides us an objective measure of quality and similarity of the results obtained for testing (generic or similar) and branding drug products simultaneously. This paper describes a new multivariate similarity factor for the assessment of *in vitro* therapeutic equivalence between two medicines by using pharmaceutical equivalence study. We performed pharmaceutical equivalence studies for acyclovir cream, metronidazole injection, meropenem for injection and atropine sulfate injection. All tests and assays results were standardized using an appropriate desirability function. Multivariate similarity factors for pharmaceutical studies were calculated based on individual acceptance factors and similarity deviations for brand, generic, and similar drugs. We found a perfect correlation among multivariate similarity factor and regulatory requirements. The multivariate similarity factor is a useful tool for *in vitro* therapeutic equivalence assessment, and may be used for regulatory approval of generic and similar drugs.

Key words: Therapeutic equivalency, *in vitro*, multivariate analysis.

INTRODUCTION

Drug access provision is a worldwide concern, and generic drug products play an important role in this issue. Generic drug products increase market competition, provide a more effective price control, promote national industrial development and allow physicians and patients to choose among different manufacturers (Dias and Romano-Lieber, 2006; Rumel et al., 2006). In Brazil, the generic drug products are part of the drug national policy, which obligates the government to provide drugs for Brazilian citizens (Rumel et al., 2006; Brasil, 1999). Since the introduction of generic drug products in pharmaceutical market, Brazilian's regulatory agency (Agência Nacional de Vigilância Sanitária – ANVISA) approved about 3,495 new generic drug products (Rumel et al., 2006; Brasil, 1999, 2007a). Also, similar drug products (non-generic copies of reference drug products) are important for Brazilian's drug national policy (Brasil, 2007b). Currently, ANVISA classifies drug products as: brand, generic, si-

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milar, biological, phytotherapics, specifics and new drugs. However, about 60% of drug products marketed in Brazil are generic and similar drug products.

Even though, there are some concerns about the efficacy, safety and quality of generic and similar drug products (Agudelo and Vesga, 2012; Endrenyi and Tothfalusi, 2010; Gauzit and Lakdhari, 2012; Tschabischer et al., 2008, Bialer, 2007; Kesselheim et al., 2008; Borgherini, 2003; Davit et al., 2009; Meredith, 2003; Durden and Hughes, 2010; van Wijk et al., 2006). According to ANVISA requirements, both generic and similar drug products have to confirm inter-changeability by pharmaceutical equivalence, and when appropriate, bioequivalence (Brasil, 2007a;b). About 36% of generic drug products (for example, injectable drug products, dermatological drug products, ophthalmic drug products, etc.) were tested only for pharmaceutical equivalence. On the other hand, oral drugs (for example, tables, capsules, oral suspensions, etc) were tested for pharmaceutical equivalence and bio-equivalence. Due to the biopharmaceutical classification of active pharmaceutical ingredients, some oral drug products are exempted from bioequivalence (Brasil, 2007a;b). In other words, these drug products are tested only for pharmaceutical equivalence.

Pharmaceutical equivalents drug products contain the same amount of the same active ingredient (salt or basis), are of the same dosage form, route of administration, indications and uses. Conversely, in the cases mentioned earlier, pharmaceutical equivalence may be considered as an *in vitro* therapeutic equivalence test. As a consequence, pharmaceutical equivalence assessment is an important issue on regulatory approval of generic and similar drugs. According to the requirements of most regulatory agencies, two drugs are pharmaceutically equivalent if both test (generic or similar) and brand comply with all specifications of tests and assays included in the study. However, even if both test and brand drug products were pharmaceutical equivalents, there may be a significant difference among their attributes of quality, efficacy and safety (Vesga et al., 2010; Fujimura et al., 2011; Zuluaga et al., 2010; Warren, 2012). Pharmaceutical equivalence studies need to ensure the identity, strength, quality and purity of the test (generic or similar) and brand of drug products (Brasil, 2007a;b).

To guarantee the *in vitro* therapeutic equivalence assessment by using pharmaceutical equivalence study, it is important to have a measure of the quality and similarity of both test (generic or similar) and brand drug products results. Several methodologies are available for comparison of dissolution profiles (for example; difference and similarity factors – f1 and f2, analysis of variance, two one-sided equivalence test - TOST, multivariate methods, etc) (O'Hara et al., 1998; Shah et al., 1998). Conversely, there are a few methodologies applied to *in vitro* therapeutic equivalence of drug products tested only for pharmaceutical equivalence. Most of these methodologies are employed only to active pharmaceutical ingredient content comparison (for example; t-student tests, two one-sided equivalence tests - TOST, compliance decision based on measure-ment uncertainty) (Zuluaga et al., 2009; Lourenço and Pinto, 2012; Okamoto et al., 2013). In addition, all these methodologies cannot be employed for simultaneous comparison of all tests and assays.

An objective measure of *in vitro* therapeutic equivalence based on compliance of all tests and assays results is a promising concept for regulatory agencies. In this paper, we described a new multivariate similarity factor for *in vitro* therapeutic equivalence assessment for drug products not tested for bioequivalence. The multivariate similarity factor will also be used for *in vitro* therapeutic equivalence assessment of acyclovir cream, metronidazole injection, meropenem for injection and atropine sulfate injection, since they are tested only for pharmaceutical equivalence.

MATERIALS AND METHODS

Instruments

A high performance liquid chromatograph (Thermo, Accela) equipped with a photo-diode array detector (PDA) was used for assays and identification. A UV-visible spectrophotometer (Thermo, Evolution 201) was used for assays and identifications. An analytical balance (Shimadzu, AUY220) was used for weighting of reference standards and samples. A pH meter (Gehaka, PG 1800) was used for pH determination. A biological safety cabinet (Veco, Biosafe Class II B2) was used for sterility tests.

Chemical reference standards and drug samples

Acyclovir and meropenem reference standards were supplied by United States Pharmacopeia. Metronidazole and atropine sulfate reference standards were supplied by Brazilian pharmacopeia. Commercial samples of reference, generic and similar drugs were acquired in Brazilian market. All reagents and solvents were supplied by Carlo Erba, Merck, J.T Baker, Oxoid and Difco.

Pharmaceutical equivalence of drug products

Pharmaceutical equivalence studies of acyclovir cream drugs included identification (UV spectrophotometry (UV)), limit of guanine (thin-layer chromatography (TLC)), minimum fill, microbiological enumeration (bacterial and fungal counts), microbiological tests for specified microorganisms (*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella* sp.), and acyclovir content assay (UV) (United States Pharmacopeia, 2012; Farmacopeia Brasileira, 2010). Identification (infrared spectroscopy (IR) and high performance liquid chromatography (HPLC)), pH determination, volume, sterility test, bacterial endotoxin, and metronidazole content assay (UV and HPLC) were performed for pharmaceutical equivalence studies of metronidazole injection pharmaceutical equivalence studies (United States Pharmacopeia, 2012; Farmacopeia Brasileira, 2010). Pharmaceutical equivalence of meropenem for injection drug included identification (HPLC), loss

Table 1. Results of tests and assays performed in pharmaceutical equivalence studies among acyclovir cream brand, generic and similar drug products.

Test and assay	Specification	Brand drug	Generic drug	Similar drug
UV identification	Positive	Positive	Positive	Positive
Limit of guanine	NMT 1%	Pass	Pass	Pass
Minimum fill (g/unit)	NLT 10	10.3	10.6	10.4
Bacterial count (CFU/g)	NMT 1000	<10	<10	<10
Fungal count (CFU/g)	NMT 100	<10	<10	<10
E. coli	Absence in 1 g	Pass	Pass	Pass
S. aureus	Absence in 1 g	Pass	Pass	Pass
P. aeruginosa	Absence in 1 g	Pass	Pass	Pass
Salmonella sp.	Absence in 1 g	Pass	Pass	Pass
UV assay (%)	90.0 -110.0	102.1±2.7*	104.8±2.7*	98.3±2.7*

NMT = not more than. NLT = not less than. *95% confidence interval obtained from 3 independent determinations.

Table 2. Results of tests and assays performed in pharmaceutical equivalence studies among metronidazole injection brand, generic and similar drug products.

Test and assay	Specification	Brand drug	Generic drug	Similar drug
IR identification	Positive	Positive	Positive	Positive
HPLC identification	Positive	Positive	Positive	Positive
pH determination	4.5-7.0	4.8	5.5	4.8
Volume (ml/unit)	NLT 100	110	102	102
Sterility test	Sterile	Pass	Pass	Pass
Bacterial endotoxin	NMT 0.35 EU/mg	Pass	Pass	Pass
HPLC assay (%)	90.0 -110.0	101.0±3.5*	101.3±3.5*	101.9±3.5*
UV assay (%)	90.0 -110.0	98.5±1.6*	90.6±1.6*	96.1±1.6

NMT = not more than. NLT = not less than. *95% confidence interval obtained from 3 independent determinations.

on drying, uniformity content, sodium content (atomic absorption spectrophotometry (AA)), sterility test, bacterial endotoxin, and meropenem content assay (HPLC) (United States Pharmacopeia, 2012; Farmacopeia Brasileira, 2010; Lourenço and Pinto, 2012). Identification (IR and TLC), pH determination, volume, sterility test, bacterial endotoxin, and atropine content assay (HPLC) were performed for pharmaceutical equivalence studies of atropine sulfate injection drugs (United States Pharmacopeia, 2012; Farmacopeia Brasileira, 2010). All tests and assays were performed according to Brazilian and United States pharmacopeia (United States Pharmacopeia, 2012; Farmacopeia Brasileira, 2010).

Multivariate similarity factor for *in vitro* therapeutic equivalence assessment

All results were standardized using an appropriate desirability function. The desirability functions were chosen based on the specification limits of each test or assay. In other words, we chose an isosceles triangle function for active pharmaceutical ingredient content. On the other hand, we chose a “0 or 1” function for sterility tests and bacterial endotoxin tests. Moreover, all desirability results were combined in individual acceptance factors. When any result is out-of-specification the individual acceptance factor is equal to 0, since it is the geometric mean of desirability functions results. Therefore, individual acceptance factor is a measure of general quality of drugs. Finally, we calculated a combined multivariate similarity factor for *in vitro* therapeutic equivalence assessment of acyclovir cream, metronidazole injection, meropenem for injection and atropine sulfate injection. These multivariate similarity factors were compared the other approaches of *in vitro* therapeutic equivalence assessment.

Statistical analysis

The two one-sided t-student tests (TOST) were employed as equivalence testing to compare the results of active pharmaceutical ingredient (API) content in brand-name, similar and generic drug products. To test equivalence, 90% confidence intervals (90% CI) were determined, using as basis the standard deviations obtained from the results of API content in drug products. In these TOST we select $\alpha = 0.05$. We assume that two drug products are pharmaceutical equivalents if the 90% CI for the difference of API content is completely contained in the equivalence range (± 10%). We considered that an appropriate range to equivalence testing should be defined based on the regulatory (or pharmacopeial) specifications for the content of API in drug products.

RESULTS

The current regulatory criteria for pharmaceutical equivalence defined that all tests and assays should

Table 3. Results of tests and assays performed in pharmaceutical equivalence studies among meropenem for injection brand, generic and similar drug products.

Test and assay	Specification	Brand drug	Generic drug	Similar drug
HPLC identification	Positive	Positive	Positive	Positive
pH determination	7.3–8.3	7.9	8.0	7.6
Loss on drying (%)	9.0–12.0	10.1	9.9	10.8
Uniformity content (%)	85.0 –115.0 (RSD ≤ 6.0)	94.0–98.1 (RSD = 1.3)	91.1–102.7 (RSD = 3.4)	94.7–100.5 (RSD = 2.2)
Sodium content (%)	80.0% - 120.0	102.5	100.7	129.9
Sterility test	Sterile	Pass	Pass	Pass
Bacterial endotoxin	NMT 0.125 EU/mg	Pass	Pass	Pass
HPLC assay (%)	90.0-110.0	96.1±3.7*	99.6±3.7*	97.5±3.7*

NMT = not more than. NLT = not less than. *95% confidence interval obtained from 3 independent determinations.

Table 4. Results of tests and assays performed in pharmaceutical equivalence studies among atropine sulfate injection brand, generic and similar drug products.

Test and assay	Specification	Brand drug	Generic drug	Similar drug
IR identification	Positive	Positive	Positive	Positive
TLC identification	Positive	Positive	Positive	Positive
pH determination	3.0 – 6.5	3.7	5.8	5.3
Volume (ml/unit)	NLT 1.1	1.1	1.1	1.1
Sterility test	Sterile	Pass	Pass	Pass
Bacterial endotoxin	NMT 55.6 EU/mg	Pass	Pass	Pass
HPLC assay (%)	90.0-110.0	102.7±4.5*	112.7±4.5*	106.9±4.5*

NMT = not more than. NLT = not less than. *95% confidence interval obtained from 3 independent determinations.

comply with the specifications for both test (generic or similar) and brand drug products. All tests and assays performed for acyclovir cream and metronidazole injection drug products comply with the specifications (Tables 1 and 3). On the other hand, out-of specification results were found for atropine injection and meropenem for injection drug products (Tables 2 and 4). Therefore, atropine generic drug and meropenem similar drug were not pharmaceutical equivalents to their brand drug products.

Although most of the tests and assays comply with the specifications, it is important to consider how close these results are to the specification target. The quality of a drug may be evaluated by the distance of their parameters to the specification target. The closer a result is from the specification target the higher is the drug products quality. In contrast, the closer a result is from the specification limit the lower is the drug products' quality. In addition, the comparison of results from different tests and assays is difficult, once they correspond to different properties of the drugs.

Therefore, each result should be converted to a standardize value using a suitable desirability function. The desirability function should be chosen according to the specification limits and specification target of the test or assay. An isosceles triangle function (Figure 1A) may be used for tests and assays that have a central target specification (for example, content of active pharmaceutical ingredient, content of sodium, minimum fill, etc). A rectangular triangle function (Figure 1B and C) may be used for tests and assays that have a lower or higher limit specification (for example, volume, loss on drying, etc). Other combined desirability function (Figures 1D and E) may also be used for these tests and assays. For 'pass/fail' tests and assays a '0 or 1' function (Figure 1F) is appropriated (for example, limit of guanine, sterility test, bacterial endotoxin, etc). The standardize results will range from 0 (no compliance or worst fit compliance) to 1 (best fit compliance).

When we standardize the results, all tests and assays will have the same weight in the evaluation of *in vitro* therapeutic equivalence. However, some tests and assays are more relevant than others. An exponential weight factor (w) may be used to attribute a weighted relevance to each test or assay. An exponential weight factor greater than 1 will fine tune the shape of the desirability function (Figure 1G), and may be used to high relevant tests and assays. On the other hand, an exponential weight factor less than 1 will expand the shape of the desirability function (Figure 1H), and may be used to low

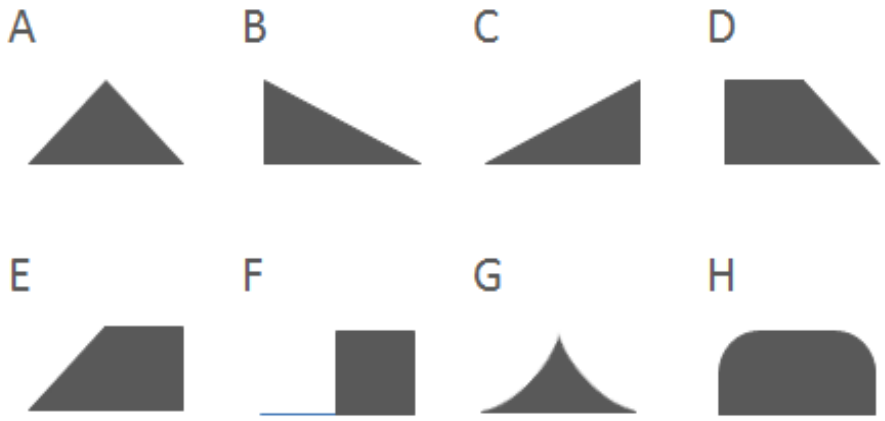

Figure 1. Desirability functions for several types of tests and assays.
(A) Isosceles triangle function; (B) and (C) rectangular triangle function; (D) and (E) combined function, (F) 'pass/fail' function, and (G) and (H) exponential weighted function.

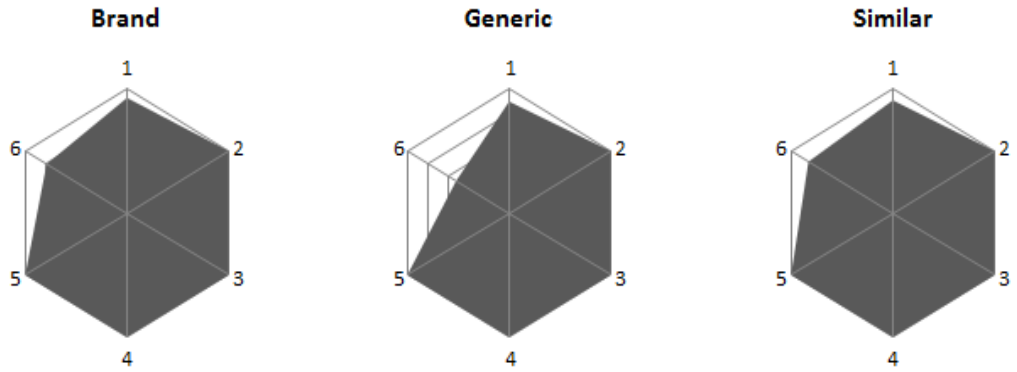

Figure 2. Star graphics for brand, generic and similar acyclovir cream drug products.
(1) weight, (2) guanine limit, (3) UV identification, (4) microbiological enumeration, (5) microbiological tests for specified microorganisms, (6) UV assay.

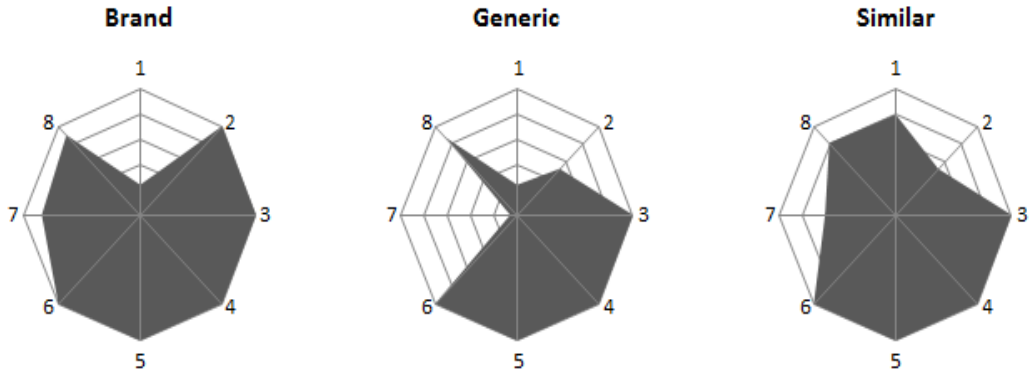

Figure 3. Star graphics for brand, generic and similar metronidazole injection drug products.
(1) pH, (2) volume, (3) IR identification, (4) HPLC identification, (5) sterility test, (6) bacterial endotoxin, (7) UV assay, and (8) HPLC assay.

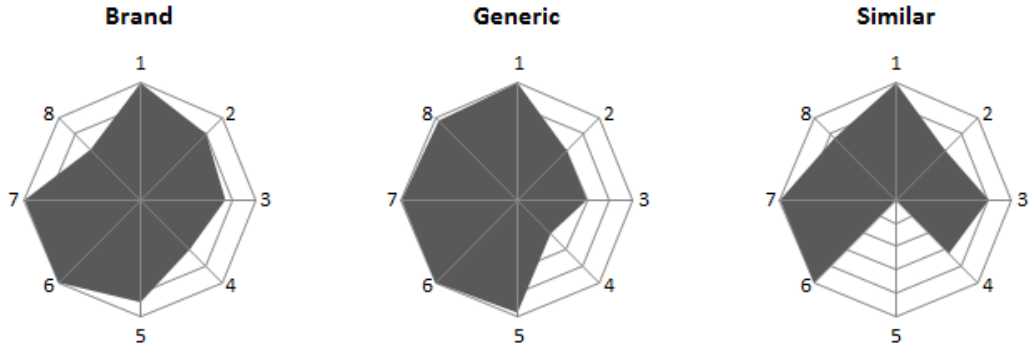

Figure 4. Star graphics for brand, generic and similar meropenem for injection drug products.
(1) HPLC identification, (2) pH, (3) loss on drying, (4) uniformity content, (5) sodium content, (6) sterility test, (7) bacterial endotoxin, and (8) HPLC assay.

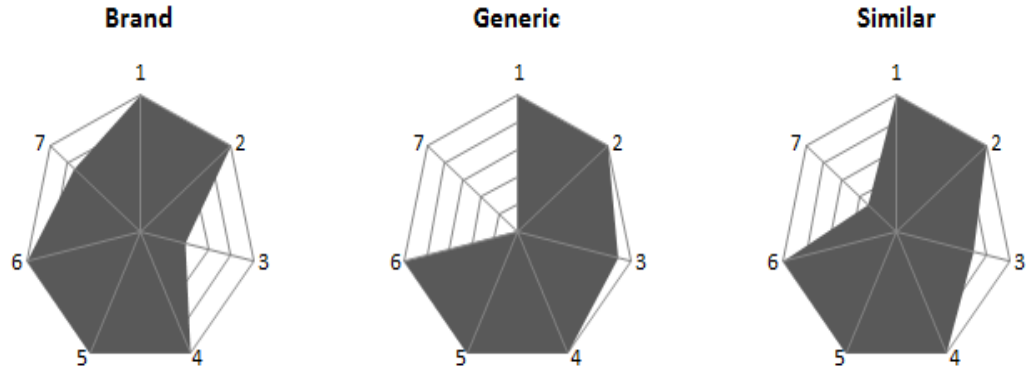

Figure 5. Star graphics for brand, generic and similar atropine sulfate injection drug products.
(1) IR identification, (2) TLC identification, (3) pH, (4) volume, (5) sterility test, (6) bacterial endotoxin, and (7) HPLC assay.

relevant tests and assays. In this work, we adopted an exponential weight factor of 1 for all tests and assays.
The desirability function allows us to standardize the results, as a consequence it is possible to compare the results among different tests and assays. The standardized results of brand, generic and similar drugs are presented as 'star' graphic (Figures 2 to 5). We can evaluate similarities and differences among the drugs, since the shape of 'star' graphic changes as the desirability results change. However, these comparisons are subjective. An individual acceptance factor for each drug was calculated as the geometric mean (Equation 1) of the desirability function results of all tests and assays.

$$a = (\prod_{i=1}^{n}(p_i{}^{w}))^{1/n} \qquad \text{Equation 1}$$

Where, a is the individual acceptance factor, p is the desirability function results for each i test or assay, w is the exponential weight factor, and n is the number of tests and assays performed.

A multivariate similarity factor is an objective way to assess *in vitro* therapeutic equivalence. We calculated the multivariate similarity factors for *in vitro* therapeutic equivalence according to Equation 2. Multivariate similarity factor includes two terms: (1) Quantification of combined multivariate acceptance factors, and (2) quantification of deviations between test (generic or similar) and brand drug products results. The first term indicates how tests and assays results are closed to the specifications targets. The second term is a measure of similarity between test (generic or similar) and brand drug products results.

$$f_{ms} = (\prod_{i=1}^{n}(\sqrt{|p_{T^w}| \times |p_{R^w}|} \times \left(\frac{2-|pT^w - pR^w|}{2}\right)))^{1/2n} \qquad \text{Equation 2}$$

Where, f_{ms} is the multivariate similarity factor, p_T desirability function results (for each *i* test or assay) of generic or similar drug product, p_R desirability function results (for each *i* test or assay) of brand drug product,

Table 5. Individual acceptance factors for brand, generic and similar drug products.

Drug	Branddrug product	Generic drug product	Similar drug product
Acyclovir*[1]	0.95	0.88	0.95
Metronidazole*[2]	0.81	0.53	0.82
Meropenem*[3]	0.81	0.78	0.00
Atropine sulfate*[4]	0.84	0.00	0.80

*[1]Individual acceptance factor, including: IR identification, HPLC identification, pH, volume, sterility test, bacterial endotoxin, UV assay, and HPLC assay.
*[2]Individual acceptance factor, including: UV identification, weight, guanine limit, microbiological enumeration, microbiological tests for specified microorganisms, and UV assay.
*[3]Individual acceptance factor, including: HPLC identification, pH, loss on drying, uniformity content, sodium content, sterility test, bacterial endotoxin, and HPLC assay.
*[4]Individual acceptance factor, including: IR identification, TLC identification, pH, volume, sterility test, bacterial endotoxin, and HPLC assay.

Table 6. Summary of conclusions of pharmaceutical equivalence studies and *in vitro* therapeutic equivalence assessment among brand, generic and similar drug products.

Drug		PE *[1]	TOST*[2]	f_{ms}*[5]
Acyclovir	Generic × Brand	Equivalent	Equivalent*[3]	0.51
	Similar × Brand			0.72
Metronidazole	Generic × Brand	Equivalent	Equivalent*[3]	0.60
	Similar × Brand			0.74
Meropenem	Generic × Brand	Equivalent	Not equivalent*[4]	0.75
	Similar × Brand	Not equivalent	Equivalent*[3]	0.00
Atropine sulfate	Generic × Brand	Not equivalent	Not equivalent*[4]	0.00
	Similar × Brand	Equivalent	Equivalent*[3]	0.71

*[1] Pharmaceutical equivalence among test (generic or similar) and brand drug products.
*[2] Two one-sided test (TOST), employed for active pharmaceutical ingredient content only
*[3]equivalent indicates p-value < 0.05 and *[4]not equivalent indicates p-value ≥ 0.05.
*[5] Multivariate similarity factor for *in vitro* therapeutic equivalence assessment.

w is the exponential weight factor, and *n* is the number of tests and assays performed.

The multivariate similarity factors for acyclovir cream, metronidazole injection, meropenem for injection and atropine sulfate injection are presented in Table 5. Acyclovir cream studies presented higher multivariate similarity factors (close to 1), because most of the tests and assays were found to be close to the specification target (Figures 2 and 3 and Tables 1 and 2). In contrast, multivariate similarity factors for generic and brand of both meropenem and atropine sulfate drugs were found to be 0, due to the out-of specification results (Figures 4 and 5 and Tables 3 and 4). In addition, the multivariate similarity factors showed perfect correlation to the regulatory requirements for pharmaceutical equivalence (Table 6). Besides, the multivariate similarity factor provides a degree of combined quality and similarity for both test (generic or similar) and brand drugs. The multivariate similarity factor also showed a good correlation to two one sided equivalence test (TOST) (Table 6) (Lourenço and Pinto, 2012). However, we found differences in meropenem for injection studies, because TOST is used for evaluation of active pharmaceutical ingredient content only. In contrast, multivariate similarity factor allows us to evaluate all tests and assays results simultaneously.

DISCUSSION

In this paper, we described a new multivariate similarity factor to assess *in vitro* therapeutic equivalence based on pharmaceutical equivalence studies. Ours results indicate that the higher the multivariate similarity factor the higher the level of similarity between tested drug products. In other words, the multivariate similarity factor is not only an indication of compliance for pharmaceutical equiva-

lence, but it also indicates the level of similarity between test (generic or similar) and brand drug products. The multivariate similarity factor can be used for any kind of research work on pharmaceutical equivalents, since both test (generic or similar) and brand drug product had been submitted to the same assays and tests, including their specifications.

Several drug products, such as injectable, dermatological and ophthalmic dosage forms, have been tested only for pharmaceutical equivalence. Moreover, some oral drug products are exempted from bioequivalence, due to biopharmaceutical classification of active pharmaceutical ingredients. As a consequence, confirmation of *in vitro* therapeutic equivalence is an important issue to regulatory agencies around the world. Despite of its importance, we found in literature a few methodologies applied to *in vitro* therapeutic equivalence of drug products tested. Most of these methodologies are employed only to active pharmaceutical ingredient content comparison (for example; t-Student tests, two one-sided equivalence tests - TOST, compliance decision based on measurement uncertainty) (Zuluaga et al., 2009; Lourenço and Pinto, 2012; Okamoto et al., 2013). In addition, all these methodologies cannot be employed for simultaneous comparison of all tests and assays.

According to ours results, multivariate similarity factor showed perfect correlation to the regulatory requirements for pharmaceutical equivalence and a good correlation to two one sided equivalence test (TOST) (Lourenço and Pinto, 2012). Differences among multivariate similarity factor and two one-sided equivalence test was due to limitations of TOST. TOST does not allow us to compare several tests and assays results simultaneously. On the other hand, multivariate similarity factor provides a simultaneous evaluation of all tests and assays results for both test (generic or similar) and brand drugs.

The multivariate similarity factor will be affected using different exponential weight factors (w) for each test or assay, but it could be useful to give more ($w > 1$) or less ($w < 1$) importance for a single test or assay in an *in vitro* therapeutic equivalency study. This approach could be used to reduce the weight of “pass/fail” tests and assays results in the quantification of deviation term. Alternatively, “pass/fail” tests and assays could not be consider using multivariate similarity factor, which will result in a more rigorous evaluation of *in vitro* therapeutic equivalence. In this case, both test (generic or similar) and brand drug products should comply with all “pass/fail” tests and assays, such as identification, sterility test and others.

The multivariate similarity factor is a measure of the general quality and similarity of both test (generic or similar) and brand drug products. As a consequence, it can be used to assess *in vitro* therapeutic equivalence of drug products that will not be tested for bioequivalence. Also, it can be used as a preliminary analysis for those drugs that will be tested for bioequivalence or bioavailability. In conclusion, the multivariate similarity factor is a useful tool for *in vitro* therapeutic equivalence assessment, and it can be used for regulatory approval of generic and similar drug products.

Conflict of Interests

The author(s) have not declared any conflict of interests.

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