



A Bioequivalence Study Analyzed in Face of the Brazilian Generic Drugs Policy

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SUMMARY. Quality and low cost drugs are available to the to the Brazilian since 1999 when the Brazilian Generic Drugs Policy was established. This report deals with the general criteria required by the Brazilian legislation for a drug to be labeled as a generic. As an example the pharmaceutical bioequivalence of a reference product (Floxacin®) and a test formulation (norfloxacin generic) is illustrated. The pharmacokinetic profiles were evaluated after oral administration to 26 healthy volunteers. The study was made through an open, crossover and one dosage randomized assay. Samples were analyzed by HPLC-UV. Pharmacokinetic parameters evaluated were AUC_{0-inf} , AUC_{0-t} , C_{max} , T_{max} , $T_{1/2}$, besides others like distribution volume, half-life for drug elimination and depuration. Three parameters, (AUC_{0-inf} , AUC_{0-t} , and C_{max}) were statistically compared to determine the bioequivalence between the two drugs. Analysis of Variance (ANOVA) showed no significant differences between the two formulations and the 90% confidence limit (80%-125%) is accepted for bioequivalence. Based on statistical analysis the test formulation is considered bioequivalent to the originator and able to be classified as generic in face of the Brazilian Generic Drugs Law.

RESUMEN. “Estudio de bioequivalencia analizado a la luz de la Política de Medicamentos Genéricos de Brasil.” Los medicamentos genéricos de calidad y bajo costo están disponibles para la población brasilera desde 1999, cuando se instituyó la Política de Medicamentos Genéricos de Brasil. Este artículo presenta los criterios generales exigidos por la legislación brasilera para que un medicamento pueda ser registrado como genérico. Como ejemplo se muestran paralelamente las etapas de un estudio de bioequivalencia farmacéutica de un producto de referencia (Floxacin®) y una fórmula ensayada (norfloxacina genérico), realizadas según la legislación vigente. Los perfiles farmacocinéticos fueron evaluados luego de ser administrados oralmente a 26 voluntarios que gozaban de buena salud. El estudio se realizó por medio de un ensayo abierto, cruzado y con una dosis aleatoria. Las muestras fueron analizadas por HPLC-UV. Los parámetros farmacocinéticos fueron evaluados por AUC_{0-inf} , AUC_{0-t} , C_{max} , T_{max} , $T_{1/2}$, aparte de otros como el volumen de distribución y vida media de eliminación y depuración. Tres parámetros (AUC_{0-inf} , AUC_{0-t} y C_{max}) fueron comparados con estadísticas para determinar la bioequivalencia entre los dos medicamentos. El análisis de varianza (ANOVA) demostró que no hay diferencias significativas entre las dos fórmulas con un límite de confianza del 90% (80%-125%), que puede ser aceptado en la bioequivalencia. Basándose en las estadísticas de los análisis, la fórmula ensayada se considera bioequivalente a la original y puede ser clasificada como genérica en relación a la ley de Medicamentos Genéricos Brasileños.

INTRODUCTION

The Brazilian Generic Drugs Policy inserted in the National Drugs Policy is the main instrument that directs the actions of the Brazilian Ministry of Health in the field of pharmaceutical products. Up to 1999, Brazil had only brand name and similar drugs but not generic. After February 10th 1999, Law 9787, known as Generics' Law, established the drugs legal basis and

attributed powers to ANVISA (National Agency for Sanitary Vigilance) to implement the rules and conditions for drugs registration and guarantees of product quality ¹.

The establishment of a generic policy involved several feeding lines and articulated actions for its complete effectiveness. To regulate actions considered fundamental to this process,

KEY WORDS: Bioequivalence, Brazilian Drugs Policy, Generic drugs.

PALABRAS CLAVE: Bioequivalencia, Medicamentos genéricos, Política de Medicamentos de Brasil.

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resolutions were implemented to insure quality, safety, dispensation and commercialization of generic drugs. For instance, control of drugs prices practiced (allowed effective market competition), selection of reference products, priorities for generics production, amplification of centers and reference systems for conducting the bioequivalence tests, and monitoring of Good Manufacturing Practices (GMP) in the pharmaceutical industry and the regular control of drugs quality ^{2,3}.

Several advantages were introduced: (i) cost reductions in health treatments; (ii) greater consumer awareness of existing alternative choices ⁴; (iii) regulation of clinical trials and rules/procedures for generic drugs registration; and (iv) regulation of generic drugs prescription and dispensation by pharmaceutical care services ³. As a result, the generic drugs share in the health-care market increased substantially, and consolidated the growth and strength of Brazilian Pharmaceutical Companies, as confirmed by the wide acceptance of generic drugs by the population and healthcare professionals ². Currently, generic drugs represents almost 14% of market in the Brazil, and approximately 80% are produced by national industries ¹.

The sale market for generics drugs has been steadily growing through the years. During 2001 its market share increased from 1.73% to 4.37%. In April 2003, sales reached 7.3%, with a loss of market sales of reference drugs even after a significant reduction in their prices ⁵. Sale surveys show a growth of 218% since the year 2000, and today generics are 27.68% of the Brazilian market. In relation to all pharmaceutical products its market share is 9.68%. The 27% growth in the last five years corresponds to savings of around 47% ⁶.

The generic drugs, designated by yours common definitions, may be produced after patent expiry of the reference drug or renounce of other exclusivity rights. In this case, it are equivalent pharmaceutical products that presented interchangeability with the reference. This is demonstrated by pharmaceutical equivalence and/or bioequivalence studies, that valuation and confront the efficacy, safety and quality ^{7,8}.

Pharmaceutical equivalence determines, by means in vitro tests in according to pharmacopoeias or other quality standards, if generic and reference drugs have the same drug in the same dosage and pharmaceutical form. This tests validate identity, dosage, purity, potency, uniformity of contents, disintegration times and

dissolution velocity ⁹. The Brazilian legislation allows registration of generic drug with only pharmaceutical equivalence in some cases, when the absorption process does not interfere with therapeutic activity ¹⁰. The drugs in this category contain highly soluble and permeable drugs, absolute bioavailability superior to 90% and pharmaceutical forms allowing dissolution rates of 85% in 15 min. In general they consist of aqueous parenteral formulations, oral solutions (without excipients affecting absorption), aqueous ophthalmic preparations, non-systemic topical and otological products, inhalation products and nasal sprays and drugs of oral use containing non-absorbable drugs ^{2,5}. In another cases (for instance, oral tablets and capsules), is necessary bioequivalence studies.

In the bioequivalence studies, is possible to demonstrate not only that the two formulations are therapeutically interchangeable when administered in the same dosage and way, but also determine pharmacokinetic standards related to bioavailability. This, in turn, defines the rate and extent at which the active substance is absorbed by the body and if it reached the site of action in a concentration therapeutically efficient ¹¹.

The drug is bioavailable when it is transferred unaltered from the pharmaceutical form to the systemic circulation ¹¹. Bioavailability is evaluated by data on blood concentration and based on three pharmacokinetic parameters: (i) peak plasma concentration (C_{max}), the maximal blood concentration after oral administration of the drug. It is directly related to the drug absorbed fraction; (ii) time of peak blood concentration (T_{max}), a parameter related to absorption velocity and determinant of peak concentration after oral administration; and (iii) area under the concentration-time curve (AUC), the main parameter in bioavailability determinations. It represents the fraction entering the circulation, independently of absorption velocity ¹². These data and the results of the analysis of variance (ANOVA) should be available when registering a drug as a generic ¹³. Two drugs are, thus, bioequivalent when they do not show statistically significant differences in absorption velocity and quantities absorbed, both measured in assays obeying the same standards ².

The present paper has with principal objective set a parallel between the development of a bioequivalence study and the Brazilian legislation about generic drugs, presenting its principal characteristics of to the reader. For this reason,

in the materials and methods section details of this legislation are presented.

The bioequivalence study selected how example utilized norfloxacin tablets 400 mg, developed by Prati & Donaduzzi Pharmaceutical Industry, as test drug for this study. The reference drug was Floxacin® tablets 400 mg (Merck, Sharp and Dhome). Both were evaluated by comparing blood plasma pharmacokinetic parameters according to ANVISA determinations¹⁴. The analytical details about this study, included development and validation, and more complete description about the pharmacokinetic step, may be consulted in Bedor *et al.*¹⁵.

Norfloxacin is a broad spectrum antimicrobial agent chemically characterized as a fluoroquinolone, specifically 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid, C₁₆H₁₈FN₃O₃. It is a compound active against gram-positive and negative bacteria, by inhibiting bacterial DNA synthesis and it is bactericidal. It is usually utilized in the treatment of urinary, respiratory and gastrointestinal tract infections^{16,17}.

MATERIALS AND METHODS

Legislation

The list of directives shown in Table 1 are published by ANVISA and available on-line (in portuguese) in the period of the study. Actually, some are updated. This aims at regulating bioequivalence studies in Brazil and detailing the results that are necessary for the registration procedure. These rules were followed in this study and the most important ones are discussed next. The clinical protocol was approved by the Ethics Committee in Research of the Federal University of Pernambuco (UFPE) under the register 066/2005-CEP/CCS/UFPE.

Production of the test drug - pilot scale

The test drug was Norfloxacin Generic 400 mg tablets (lot "Piloto A"), produced in 09/2004, with validity date until 09/2006. The reference drug was Floxacin® 400 mg tablets, produced by Merck Sharp and Dhome (Lot: FH031) in 08/2004 with validity date until 02/2007. The production of the test drug followed standards adopted by Prati, Donaduzzi & Cia Pharmaceutical Industry, with developed the formulation and realized the production in pilot scale in conformity with the RE 2999/2006¹⁸. The productive process utilized are direct compression in conformity with the standard formulation. The stability tests (short and long duration) fol-

lowing the determinations of RE 1/2005¹⁹. After the production and approbation by the quality control department, the lot was sent by Pharmaceutical Equivalence Laboratory for realization of the studies with the reference medicine. This step need follow the resolution RE 310/2004²⁰. The reference medicine utilized need present the fabrication date with, at less, six months. The same test lot need be utilized in the bioequivalence studies. Table 1 includes ANVISA directives for studies on pharmaceutical equivalence and bioequivalence available in the period of the present study

Place of study

The study was a joint project with the *Núcleo de Desenvolvimento Farmacêutico e Cosmético* (NUDFAC) of the Federal University of Pernambuco, Pernambuco, Brazil. The clinical stage was conducted at the Clinical Center of the Childrens Hospital, Foundation Manoel Almeida, located at 95 Parnamirim Avenue, Recife, PE. The Generics' Law has specific requirements for places where bioequivalence studies are conducted. The premises should be exclusive for clinical research, forbidding joint occupation by volunteers and sick patients. The patient rooms and infirmaries should be well lighted and ventilated with beds and sanitary facilities in good hygienic conditions and in sufficient number and having a nursing station close by. A Intensive Therapy Unit (ITU), local or mobile, should be available together with emergency transportation and the materials necessary for reversal of cardiopulmonary arrest. An electric generator should be available in the venues used for the clinical studies, which should be conducted by an able professional^{13,21}.

Human subjects in the study

According to the Generics' Law, volunteers in bioequivalence studies should present the following pre-requisites: good health, corroborated by clinical evaluation and clinical laboratory tests, as well as mental health and emotional conditions to participate in the study. The volunteer should be an adult, 18 to 50 years old, weighing around $\pm 15\%$ of the ideal Body Mass Index (BMI), and sign the informed consent document²³.

The 26 volunteers in this study, were healthy adults with average age 22.8 years, average weight and height, 69.26 kg and 1.73 m, respectively. They were evaluated by medical consultations, anamnesis, physical exams, electrocar-

Code	Title	URL
RE 894/2003	Directive for protocol and technical reports elaboration in bioequivalence	www.anvisa.gov.br/legis/resol/2003/re/894_03re.htm
RE 895/2003	Directive for elaboration of technical reports on bioavailability / bioequivalence	www.anvisa.gov.br/legis/resol/2003/re/895_03re.htm
RE 896/2003	Directive for relative bioavailability/ bioequivalence tests for drugs	www.anvisa.gov.br/legis/resol/2003/re/896_03re.htm
RE 897/2003	Directive for exemption and substitution of bioequivalence	www.anvisa.gov.br/legis/resol/2003/re/897_03re.htm
RE 898/2003	Directive for planning and performing statistical analysis of results in relative bioavailability/bioequivalence studies	www.anvisa.gov.br/legis/resol/2003/re/898_03re.htm
RE 899/2003	Directive for validation of analytical and bioanalytical methods	www.anvisa.gov.br/legis/resol/2003/re/899_03re.htm
RE 900/2003	Directive for conducting studies on pharmaceutical equivalence and elaboration of the respective technical reports*	www.anvisa.gov.br/legis/resol/2003/re/900_03re.htm
RE 901/2003	Directive for dissolution assays of oral solid pharmaceutical forms for immediate liberation*	www.anvisa.gov.br/legis/resol/2003/re/901_03re.htm

Table 1. ANVISA directives for studies on pharmaceutical equivalence and bioequivalence available in the period of the study. * Both the directives indicated were revoked by the RE 310/2004 - Directive for realization of study and elaboration of the pharmaceutical equivalence technical report and dissolution assays, available in <http://e-legis.anvisa.gov.br/leisref/public/showAct.php?id=15466&word=%20RE%20310/2004>.

diagrams, clinical laboratory tests (hematological, biochemical, total urine, parasitological and serological) and psychological evaluation. The subjects were warned not to take any drug, four weeks prior to starting in the study.

Drugs administration and collection of samples

According to the *Manual on good administration practices in bioavailability and bioequivalence procedures*²¹, dosage administration by a nurse, pharmacist or an able professional, under medical supervision, should follow the protocol. Physicians should supervise volunteers during the hours after drug administration and sample collection following the drug pharmacokinetic characteristics. Collection times described in the protocol should be rigorously followed.

In the present report, the study was conducted as an open, crossover assay, using randomized single dosages of two formulations of norfloxacin. The volunteers were admitted to the clinic at 10 p.m. on the day prior to the drug administration. They had a regular meal and at 11 p.m., a light luncheon; after 12 p.m. they fasted until 12 a.m. in the following day. The single drug dose (400 mg tablet) was administered at 8 a.m. with 240 mL of water. Lunch was served at

12 a.m., afternoon snack at 4 p.m., supper at 7:30 p.m., night snack at 10 p.m. and breakfast at 8 a.m. the following morning. Liquids were allowed *ad libitum* after meals, excepting the ones containing xanthines (coffee, tea and colas) up to 10 a.m. and then liberated. The period of interment was 36 hours during which 16 samples were collected from each subject. The 8 mL blood samples were collected by a heparinized butterfly at times: 0 h; 0.5 h; 1.0 h; 1.25 h; 1.5 h; 1.75 h; 2.0 h; 2.5 h; 3.0 h; 4.0 h; 6.0 h; 8.0 h; 10.0 h; 14.0 h; 18.0 h; 24.0 h. Diets, established by professional nutritionists did not interfere with the pharmacokinetic study.

Blood samples were centrifuged at 5000 rpm for 5 minutes, the plasma was separated and kept frozen at -20°C until assayed. After a washout period of 7 days, the tests were repeated to complete the volunteer transitions. The samples are submitted to the liquid-liquid extraction proceeding with chloroform how extraction solvent.

Chromatography conditions

Norfloxacin serum concentrations were determined by High Efficiency Liquid Chromatography (HPLC-UV) in a Shimadzu equipment fitted with a UV-280nm detector and software Shi-

madzu/Class-VP5.32), using column and pre-column Gemini C18® 5 µm (150 x 4.6 mm) and a pre-column security guard TM C18 10 µm (4x3.0 mm). The mobile phase was acetonitrile/phosphate buffer, pH 3.5, elution at 1.2 mL/min, oven temperature, 40 °C, volume of injection 50 µL, analysis time 14 min.

In the bioequivalence studies, is obligatory utilize too a internal standard, that can be the same therapeutic class and that pharmacokinetic profile similar of the drug in study. This need be additioned in the calibration standards and samples of know and constants, with the objective aid in the drug test ²⁴. In this case, ciprofloxacin hydrochloride USP (4.0 µg/mL) are utilized how internal standard. The method was previously validated according to the *directive for validation of analytic and bioanalytic methods* ²⁴.

Pharmacokinetic Analysis

Pharmacokinetic data in bioequivalence studies derive from drug concentration *vs* time curves obtained by quantification of the biological samples collected in predetermined times as already described ²¹. To determine drugs bioequivalence three measurements are fundamental: the area under the concentration x time curve (AUC); the observed peak concentration (C_{max}) and the time to attain this concentration (T_{max}) ²⁵.

Literature data can be utilized by analysis of the results. According to Sweetamm ²⁶, norfloxacin has an oral bioavailability of 30 to 40% and a C_{max} of 1.5 µg/mL after administration of a single dose of 400 mg in a T_{max} of 1-2 h. Korolkovas ²⁷ reports C_{max} of 1.4-1.6 µg/mL, 1-2 h after administration of 400 mg norfloxacin in a single dose.

Statistical Analysis

The *Directive on planning and performing statistical analysis of results in relative bioavailability/bioequivalence studies* ¹³ indicates that

parameters AUC and C_{max} should be analyzed using the log ratio of individual values for the test and reference drugs and T_{max} as an individual difference between the drugs tested. Both tests, parametric and non-parametric will be employed to analyze the variables. The drugs will be considered as bioequivalent, in rate and extent of absorption, if the 90% confidence interval of AUC_{inf} , AUC and C_{max} of the test geometrical mean lies entirely between the confidence intervals 80-125% of the reference drug geometrical mean.

Analysis were conducted with the help of the following softwares: WinNonLin Professional Network Edition, Version 1.5m ²⁸; Bioequivalence program for two-period Cross-over Studies-Version 3.4 ²⁹; Microsoft Excel version 7.0 ³⁰ and Graph Pad Prism Version 2.01 ³¹.

RESULTS

Table 2 shows the pharmacokinetic parameter values for the two brands (test and reference). The mean plasma concentration of norfloxacin reference *versus* test is shown in Fig. 1.

DISCUSSION

Norfloxacin was well tolerated by volunteers. Determination of the 90% confidence interval for the mean differences should be based on the least squares means of data as logs and on the residual square mean in the ANOVA analysis of variance. Antilogs of the confidence limits constitute the 90% confidence interval for the ratio of geometric means of test and reference drugs. Mean bioequivalence is considered when this confidence interval lies between 80 and 125% ¹³.

C_{max} and T_{max} are also considered in this study since they show plasma characteristics and may affect the drug therapeutic activity. The confidence interval (Table 2) for the ratio of C_{max} means was 85.36% (lower limit) and 111.69% (upper limit) through the shortest. The values for the westlake were 86.43% (lower limit)

Pharmacokinetic parameter	Floxacin (reference)	Generic Norfloxacin (test)
AUC _{0-t} (ng/mL.h)	5532.00 ± 31.7	5285.79 ± 32.7
AUC _{0-inf} (ng/mL.h)	6029.12 ± 29.3	5961.32 ± 29.6
C_{max} (ng/mL)	1072.75 ± 33.6	1047.67 ± 33.6
T_{max} (h)	1.79 ± 43.3	1.61 ± 49.5
$T_{1/2}$	5.38 ± 23.6	6.40 ± 42.4
Kel (h/h)	0.14 ± 27.3	0.12 ± 26.0
Vd (mL)	559326.42 ± 40.7	671928.81 ± 51.7
CL _F (mL/h)	72797.45 ± 34.2	74295.85 ± 36.8

Table 2. Pharmacokinetic parameters of norfloxacin 400 mg tablets (mean ± standard deviation, n = 26).

it) and 113.57% (upper limit). Mean C_{\max} calculated by the method of least squares for the reference drug was 89.60 and 89.29 for the test, resulting in a ratio ($C_{\max\text{test}}/C_{\max\text{ref}}$) of 97.64 and a test power (%) for C_{\max} of 86.50. The reference has a mean C_{\max} of 1.07 $\mu\text{g/mL}$ and the test 1.05 $\mu\text{g/mL}$ and T_{\max} values of 1.79 for the reference drug and 1.61 for the test. According to literature ^{25,26}, Norfloxacin had a C_{\max} of 1.4-1.6 $\mu\text{g/mL}$ after 1-2 h administration. The difference of the mean values in relation to the literature may be at specific genetic variations between some volunteers. But it is acceptable, to take into consideration that the C_{\max} and standard deviations of reference and test drugs are practically the same, and the interval of standard deviation include the literature values. This is demonstrated too by the mean concentration-time profile for Norfloxacin for the two formulations (Fig. 1), with indicate that the mean plasma concentration profiles of the two brands were closely similar and superimposable.

The area under the concentration-time curve (AUC) is an important parameter in bioequivalence evaluating studies. The AUC from zero time (0) to the time of the last sample collection (t), $AUC_{(0-t)}$ had lower and upper confidence limits of 85.02 and 106.50, respectively, by the shortest and by the westlake the values were respectively, 86.98 and 113.02. The $AUC_{(0-t)}$ means calculated by the least squares were 123.425 for the reference drug and 122.709 for the test resulting in a ratio (test/ref) of 95.15 and a test power (%) for $AUC_{(0-t)}$ of 94.69.

When the area under the concentration-time curve was calculated from time zero (0) to infinite (inf), $AUC_{(0-\text{inf})}$ the upper and lower confidence limits by the shortest were 88.62 and

109.60, respectively, and 89.32 and 110.68 by the westlake. The mean $AUC_{(0-\text{inf})}$ calculated for the reference and test drugs by the least squares, were 137.182 and 136.950 resulting in a ratio (test/ref) of 98.55 and a power of test (%) for $AUC_{(0-\text{inf})}$ of 94.41.

The form as the study was lead, as presented in materials and methods, show that the studies had been carried through obeying the ANVISA's regulatory norms. The results obtained in the analytical phase demonstrates that the test product were bioequivalent to the reference product and, therefore, can be used in the substitution of the first one. Considered both analytical phase and the regulatory requirements of the Brazilian Generic Drugs Police, the test drug can be considered a generic drug.

CONCLUSION

The implementation of the Generic Drugs Policy was a landmark in the growth of the Brazilian drug market. The generic drugs segment intensified regulation by agencies like the ANVISA, mainly by enforcing the Good Manufacturing Practices ³². As a result the population could get safe and efficient products at a lower cost and concepts as pharmaceutical equivalence, bioavailability and bioequivalence were introduced. The most important objectives in the bioequivalence tests is to assure the safety and efficacy of the generic drugs ³³. It can be demonstrated by these studies that generic drugs (in this case, Norfloxacin Generic) and reference (Floxacin®) ones are bioequivalent, as it was statistically demonstrated by analysis of variance (ANOVA) and by confidence intervals (80%-125%) for C_{\max} , $AUC_{(0-\text{inf})}$ and $AUC_{(0-t)}$.

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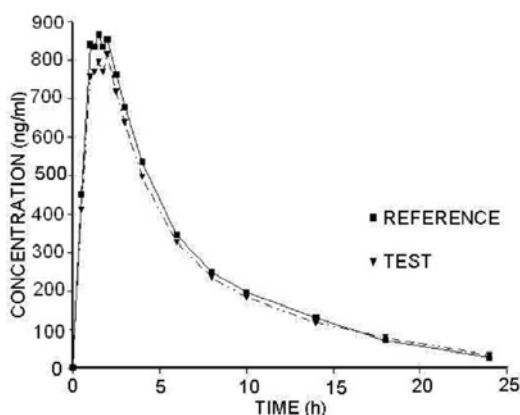


Figure 1. Mean plasma concentration of Norfloxacin after oral administration of a single dose of two brands to 26 healthy human volunteers.

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