ELABORATION OF GUIDELINE FOR MONITORING IN RELATIVE BIOAVAILABILITY / PHARMACEUTICAL BIOEQUIVALENCE STUDY BY THE SPONSOR

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ABSTRACT: For registration of generic and similar drugs, it is necessary to carry out pharmaceutical equivalence (PE) tests and pharmaceutical bioequivalence (PB). To carry out these tests, duly qualified research centers are contracted, which need to be monitored by the sponsor who is legally responsible for the activities. To this end, it is the recommendation of the Document of the Americas, periodic monitoring to verify compliance with quality requirements, Standard Operating Procedures, Good Clinical Practices (GCP), Good Laboratory Practices (GLP), of the applicable regulatory framework, as well as of compliance with the study protocol. Thus, monitoring is a methodical and documented process to evaluate the degree of adhesion of the center to the planned design for the evaluation of the formulations. To this end, the implementation of a standardized and easily completed guideline is a very important tool to guarantee a consistent evaluation and maintain the organizational memory of the evaluated items by monitors designated by the sponsor, contributing to the constant improvement of the contracted centers and supporting traceability of the studies. This work provided a systemic view of the evidence process related mainly to pharmaceutical bioequivalence, with the monitoring guideline summarizing the items of greatest relevance to be verified.
KEYWORDS: Pharmaceutical bioequivalence; Good Clinical Practices; Generic drug; Drug development.

ELABORAÇÃO DE DIRETRIZ PARA MONITORAMENTO EM BIODISPONIBILIDADE RELATIVA / ESTUDO DE BIOEQUIVALÊNCIA FARMACÊUTICA PELO PATROCINADOR

RESUMO: Para registro de medicamentos genéricos e similares, é necessária a realização de testes de equivalência farmacêutica (EF) e bioequivalência farmacêutica (BF). Para a realização desses testes, são contratados centros de pesquisa devidamente habilitados, que precisam ser monitorados pelo patrocinador legalmente responsável pelas atividades. Há também a recomendação do Documento das Américas de realizar monitoramentos periódicos para verificar o cumprimento dos

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requisitos de qualidade, Procedimentos Operacionais Padrão, Boas Práticas Clínicas (BPC), Boas Práticas de Laboratório (BPL), de marco regulatório aplicável, bem como de cumprimento do protocolo do estudo. Assim, o monitoramento é um processo metódico e documentado para avaliar o grau de adesão do centro ao desenho planejado para a avaliação das formulações. Para tanto, a implantação de uma diretriz padronizada e de fácil preenchimento é uma ferramenta muito importante para garantir uma avaliação consistente e manter a memória organizacional dos itens avaliados por monitores designados pelo patrocinador, contribuindo para a melhoria constante dos centros contratados e apoiando rastreabilidade dos estudos. Este artigo forneceu uma visão sistêmica do processo de evidência relacionado principalmente à bioequivalência farmacêutica, com a diretriz de monitoramento resumindo os itens de maior relevância a serem verificados.
PALAVRAS-CHAVE: Bioequivalência Farmacêutica; Anvisa; Monitoria; Medicamentos genéricos.

ELABORACIÓN DE LA DIRECTRIZ PARA EL SEGUIMIENTO EN LA BIODISPONIBILIDAD RELATIVA / ESTUDIO DE BIOEQUIVALENCIA FARMACÉUTICA POR PARTE DEL PROMOTOR

RESUMEN: Para el registro de medicamentos genéricos y similares, es necesario realizar pruebas de equivalencia farmacéutica (EP) y de bioequivalencia farmacéutica (PB). Para llevar a cabo estas pruebas se contratan centros de investigación debidamente cualificados, que deben ser supervisados por el promotor, que es el responsable legal de las actividades. Para ello, es la recomendación del Documento de las Américas, el monitoreo periódico para verificar el cumplimiento de los requisitos de calidad, los Procedimientos Operativos Estándar, las Buenas Prácticas Clínicas (BPC), las Buenas Prácticas de Laboratorio (BPL), del marco regulatorio aplicable, así como del cumplimiento del protocolo del estudio. Así, la monitorización es un proceso metódico y documentado para evaluar el grado de adhesión del centro al diseño previsto para la evaluación de las formulaciones. Para ello, la implantación de una pauta estandarizada y de fácil cumplimentación es una herramienta muy importante para garantizar una evaluación consistente y mantener la memoria organizativa de los elementos evaluados por parte de los monitores designados por el promotor, contribuyendo a la mejora constante de los centros contratados y apoyando la trazabilidad de los estudios. Este trabajo proporcionó una visión sistémica del proceso de evidencia relacionado principalmente con la bioequivalencia farmacéutica, con la pauta de monitoreo que resume los ítems de mayor relevancia a ser verificados.
PALABRAS CLAVE: Bioequivalencia farmacéutica; Buenas Prácticas Clínicas; Medicamento genérico y Desarrollo de medicamentos

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1. INTRODUCTION

Pharmaceutical Bioequivalence (PB) trails correspond to tests that make it possible to conclude statistically about a comparative bioavailability assessment of two drugs. Relative bioavailability (RB) is referred to as the rate and extent of drug absorption, which involves "*in vivo*" behavior after administration of a pharmaceutical form, which becomes available to perform the intended pharmacological effect. Usually in these studies, T stands for the test drug and R is the reference drug.[1)]

Reference drug is characterized as an innovative drug, which has a registered trademark and whose quality, efficacy and safety are proven by clinical studies with the competent federal regulatory body. On the other hand, the test drug is used to designate both generic and similar drugs. The product

is equivalent to the reference product, since it presents the same active principle, same dose, pharmaceutical form, route of administration and therapeutic indication as the innovative medicine. A similar medicinal product has the same characteristics as the generic medicine and may differ only in characteristics related to the size and shape of the product, shelf-life, packaging, labeling, excipients and carriers and must be always identified by trade name or brand.[2)]

Initially, only the generic drug could be considered interchangeable with the reference drug, however, through RDC 134/2003 and 58/2014, the Brazilian legislation required PB tests for all similar drugs in Brazil, except for biowaivers, to become interchangeable.[3,4)]

Over the years, PB studies have been conducted through regulatory agencies, such as the *Canadian Federal Department of Health and Welfare* and the *Food and Drug Administration* (FDA), which required verifiable information for registration of generic / similar drugs in order to ensure the quality, safety and efficacy of the drugs to be marketed.[5)]

The generic / similar drug has its interchangeability regarding the reference drug, scientifically proven through pharmaceutical equivalence (PE) and RB / PB studies.[1)] Two pharmaceutical forms are said to be bioequivalent when administering to the same individual, under the same experimental conditions and at the same molar dose, they do not present significant differences in relation to drug RB.[2,5,6)]

The PB between the reference drug and the generic/similar drug is evaluated by comparing pharmacokinetic parameters related to the extent of absorption of the active principle(s) contained therein and the rate at which this absorption occurs. To do so, tests are usually performed on healthy volunteers, in order to evaluate comparatively the RB of the two products, promoting the safety and effectiveness of the substitution.[5)]

In order to conduct a PB study between test and reference formulations, it is extremely important to draw up an experimental protocol containing the description of the items for the research, considering the information related to the subject of the research, the qualification of the researchers and all instances responsible. The document that establishes the objectives, design, history for the study and its justification, methodology and statistical analyzes to be executed during a RB / PB study is called a clinical protocol.[7)]

Members of the independent research ethics committee should review the study protocols, which assess the rights, safety and well-being of all subjects in the study population. These interdisciplinary boards aim to ensure the interests of the study participants, their integrity and dignity, in order to preserve the study in accordance with the recommended ethical standards.[8,9)]

Thus, in addition to the guidelines attributed to regulatory bodies regarding the evaluation of PE and PB trials for the registration of generic / similar drugs, there is also the ethical evaluation in

research involving human beings. In this regard, the study should be in line with the requirements involving human beings under an ethical connotation, whose premise is the guarantee of the free and informed consent (FICT) of the participant and the confidentiality of the information. These items are listed in the Universal Declaration on Bioethics and Human Rights.[10)]

RB / PB studies are performed through the clinical, analytical and statistical steps by research centers and need to be monitored by the study sponsor, which is usually the pharmaceutical industry with a view to obtaining registration of the generic or similar candidate.[11)]

Monitoring is a methodical, independent and documented process to assess the degree of adherence to the ethical, regulatory and quality requirements required, in which it aims to examine quality standards, adherence to the protocol, traceability of information and established criteria in protocol. It aims, through guidelines, technical and scientific standards, ethical and regulatory framework, to ensure the preparation, development and execution of studies in centers of PB with high quality standards.[12,13)]

The monitoring carried out by the study sponsor allows the monitoring of the accomplishment of the activities by the authorized center during the completion of a study protocol. It is an activity that monitors the progress of a study which aims to detect deviations and evaluate them critically.[12)]

Quality deviations in the clinical study, failures in the clinical record of the volunteers or absence of information can affect the traceability of the collected data resulting in discrepant and incongruent clinical studies. This may imply sanitary infractions to the centers and the rejection of the registration process of the generic or similar candidate product. For this reason, in order to minimize protocol deviations, study monitoring is essential so that corrective actions are implemented immediately and the impact of deviations is evaluated.

Thus, this paper aimed to elaborate a monitoring guideline for the sponsor to apply in the conduction of PB study in order to check the flow of studies conducted by the authorized center, and to standardize the critical analysis carried out, ensuring traceability and management of documents and information.

2. METHODOLOGY

For the accomplishment of this work, an applied, qualitative, exploratory and documentary methodology was developed, in which sequenced steps were followed. It is relevant to clarify that the developed guideline has application in PB studies because it is a stage of great relevance for the development of medicines. The used method consisted of four stages:

STAGE 1: A survey about the ethical and regulatory framework applicable to the approved centers was carried out, aiming to assess the degree of adherence of these guidelines during the

conduction of a PB study.

STAGE 2: Immersion in a center contracted by the sponsor of the study was carried out in order to explore the routine of the clinical, analytical and statistical stages, besides knowing the quality system of the center. Two PB studies were followed from recruiting the volunteers to issuing clinical, analytical and statistical reports to the sponsor.

The clinical stage comprised from the recruitment and selection of the volunteers to the administration of the medication and collection of blood samples. A Research Ethics Committee (REC) duly accredited to the National Research Ethics Committee (NREC) initiated this stage after approval of the experimental protocol. Therefore, healthy volunteers were selected through clinical history, electrocardiogram, laboratory and clinical examinations, aged between 18 and 50 years and able to grant their free and informed consent. The volunteers were submitted to hospitalization and received a standard diet. Drugs were administered and, from time to time, biological samples were collected. Due to the variability of the drug according to the physiological characteristics, gender, age, race / ethnicity of each volunteer, the inclusion criteria established in protocol were extremely important, since the need to obtain plasma concentration values within extremely standardized criteria, avoiding the discrepancy of results due to the lack of parameterization of the intrinsic characteristics of each participant.

In the analytical stage, the drug was quantified by using biological samples of the volunteers through validated bioanalytical methods, developed in the laboratory or obtained from compendiums and appropriate literature, according to the current legislation and regulations.

The statistical stage comprised the analysis of the data obtained in the analytical stage with the calculation of the pharmacokinetic parameters, such as the time to reach the $C_{máx}$ ($T_{máx}$), maximum observed concentration for the drug ($C_{máx}$), area on the curve from zero time to last collection point (AUC_{0-t}) and area on the curve from zero time extrapolated to infinity (AUC_{0-inf}). In these studies, PB among the formulations analyzed was established in cases where the mean plasma concentrations were within the bioequivalence range, which is usually between 80 and 125% for the AUC_{0-t} and $C_{máx}$ parameters, that is, when the rates of absorption and rate of extension between the drugs were similar.[7)]

STAGE 3: During the follow-up of these stages, the guideline for monitoring the study sponsor was elaborated and applied, contemplating objective and easily understandable items, in order to evaluate the execution of the activities of each stages separately, allowing individual application, as routine to be monitored.

The monitoring consisted of the evaluation of pre-selection documents, including the recruitment term, FICT, hematological laboratory tests, biochemical, serological and urinalysis

results, clinical evaluation records of volunteers, as well as the results of alcohol and drug abuse test. We also monitored the hospitalization of the volunteers, the standardized diet provided, vital signs, adverse events, the administration of the drugs being studied, the bioanalytical method validation, quantification of the volunteers samples, and finally, partial inspection of each stage reports.

STAGE 4: Following the guideline validation, we developed a standard operating procedure, which aims to maintain the organizational memory of the findings obtained in each study, allowing easy interpretation of the data, as well as traceability, confidentiality and standardization.

3. RESULTS AND DISCUSSION

According to the following-up of PB studies carried out in an authorized center, extremely relevant items to be evaluated were listed for the monitoring plan of the study sponsor, which correlate with the quality of the studies conducted. The elaboration of this guideline is very relevant because there are few data in the literature that classify by relevance the criteria to be evaluated by the industries during these test following-up. This document is very important in conducting a study of RB / PB, as it is representative of the methodology used in conducting the study, as well as documenting the observations made by the sponsor to the research centers, providing a continuous improvement flow.

The adherence of the protocol by the center is essential, since it ensures the quality of management of the financial resources, minimizes the volunteers' exposure to the inherent risks of the study, and reduces the chances of deviations occurring in the center interfering in the results of the experiments, considering that these factors are evidenced when there is operational inefficiency, infrastructure problems, information not provided in protocol or even noncompliance with it. [14] Thus, the proper execution of an experimental protocol ensures that the objectives proposed in the study are achieved and supports the practice of good practices in the various sequenced activities that aim to provide solid and accurate conclusions of their studies.[15]

According to data on RB / PB studies conducted in Brazil, 46% of them are rejected and this high rate of failures is correlated with undue procedures, and could be avoided through correct adherence to the protocol and GCP, where on-site evaluations and monitoring would contribute to ensure the implementation of clinical, analytical and statistical stages in accordance with these guidelines.[16]

Some actions may affect the quality of the PB study, among them, inefficiency in the collection schedule, collection delays, lack of data and occurrence of atypical observations. Regulatory bodies such as the FDA and the European Medicines Agency (EMA) have established a risk-based approach to clinical studies by conducting Risk Based Monitoring (RBM).[11,17]

RBM aims to identify the risks inherent to the study in order to ensure the monitoring of the areas of greatest risk.[18)] The RBM / 2013 Guide was presented by the FDA under the premise of demonstrating the processes identified as critical, among them, verification of the completion and signature of the FICT; the evaluation of the inclusion and exclusion parameters of study participants; the registration procedures for proper administration of the product under investigation (ensuring the integrity of the randomization); the assessment of the responsibilities of each member of the center; the conduct and management of procedures related to the outcome (s) of the study; required security analyzes described in the protocol; documentation and recording of adverse events; early termination of the study, especially when it is related to an adverse event and essential activities to assure the integrity of the trials.[11)]

According to FDA determinations, each sponsor shall develop a monitoring plan that is adapted for individual protection. This plan shall identify the various methods and tools that will be used in the study, as well as the reasons for its use.[11)]

Although all activities are important when considering quality and safety, the items explained in the guideline that shall be evaluated with greater criticality at the clinical stage are reported in Table 1.

Table 1 - Data evaluated in the clinical stage.

Substages	Evaluated Items	Degree of impact for the study (1 to 3)
Product under investigation (test drug)	Traceability of receipt and use of medications.	3
	Certificate of pharmaceutical equivalence.	3
	Pre-medication preparation.	3
Pre-selection	Completion and signature of the Term of Recruitment and Term of Free and Informed Consent by the volunteer.	3
	Adhesion of the center to the recruitment criteria (clinical history, weight, height, body mass index, blood pressure, heart rate, pulse, body temperature and rapid hemoglobin test (when applicable).	2
	Electrocardiogram and laboratory tests performed in the volunteers and deadlines.	3
	Testing for pregnancy, drugs of abuse and alcohol (when applicable).	3
Hospitalization	Master List according to protocol.	3
	Administration of drugs according to master list.	3
	Breakfast administered entirely to all volunteers and provided as per protocol (when applicable).	3
	Collection schedule executed according to the protocol.	3
	Assessment of vital signs, performed according to protocol.	2
	Absence of more than 10% of the blood concentrations obtained from the administration of each drug per volunteer.	3
	Meals provided according to protocol	1
	Records of adverse events, concomitant medications and intercurrent illnesses presented by volunteers.	3
	Traceability of transfer of blood samples to the analytical stage.	3

Legend: 1- low criticality; 2- moderate criticality; 3- high criticality.

* Both items categorized as 1 or 2 may become 3 if there is recurrence, or there are a large number of items that are recurrent.

In accordance with the data presented in table 1, we can report that PB studies shall be performed by considering the pharmaceutical form, via of administration, active ingredient, dose and

therapeutic indication of the test and reference formulations, therefore it is necessary the certification of PE prior to the study conduction and involve the quantification of the drug in the blood circulation from a schedule of collections. It is essentially important to fill up all the registration forms, especially the adverse events form, the administration of the drug and the chain of drug custody in order to maintain the traceability of the information, once the information has not been registered, it is understood that the procedure related to it has not been carried out or there is a lack of traceability in the process.

Ethical evaluation bodies shall submit and approve the experimental protocol and the FICT. The FICT application shall be performed for all volunteers so that all questions related to the study are clarified prior to their participation in the study. The center shall have an appropriate place, where the participants need confinement, under the responsibility of a physician and if appropriate, the report and justification of all protocol deviations.[7)]

Because the volume of blood samples collected per participant is limited, due to ethical and regulatory issues, the schedule for collection shall ensure that the values of the concentration curve can assertively provide pharmacokinetic parameters. According to the regulatory guidelines, sample collections shall cover a time equal to or greater than 3-5 times the elimination half-life of the active drug or metabolite, considering the interval between washout periods of at least seven half-lives in order to enable complete clearance of the drug or metabolite prior to re-administration thereof.[7)]

The number of volunteers required to conduct the study is also outlined in protocol, once this determination is presumed by the test power, drug variability and level of significance, whose recommendation by the regulatory body is that the power of the test is at least 80% and that the pharmacokinetic variables AUC and $C_{máx}$ are transformed into natural logarithm in order to obtain a distribution similar to a normal distribution in relation to their original values.[7,19)]

In this context, regarding the analytical stage and corroborating with the aforementioned information, the items contemplated in the guideline are described in Table 2.

Table 2 - Data evaluated in the analytical stage

Substages	**Evaluated Items**	**Degree of impact for the study (1 to 3)**
Protocol of the analytical method validation	Validation of the analytical method through the selectivity, precision, accuracy, residual effect, matrix effect, analytical stability and calibration curve parameters.	3
Validation Report	Validation report with data of each parameter (selectivity, precision, accuracy, residual effect, matrix effect, analytical stability and calibration curve) as recommended by legislation.	2
Bioanalytical methodology	Performance of analytical methodology in accordance with validation protocol for each parameter (selectivity, precision, accuracy, residual effect, matrix effect, analytical stability and calibration curve).	3
	Processing of samples according to the validation protocol.	3

	Used solvents and additives were provided in a validation protocol.	2
	Accomplishment of the analytical and internal standard extraction in accordance with validation protocol.	2
	Range of linearity within specification limits.	2
Analytical run	Records and justification of missing samples and / or problems in chromatograms.	3
	Obtaining clear chromatograms that allow the identification of the retention time of the analytical and the internal standard.	3
	Analytical runs performed in accordance with the validation protocol.	3
Plasma Concentration Sheet	Suitable reporting of analytical concentrations in each sample.	3
	Traceability of plasma concentrations transfer of the samples to the statistical stages.	3
Analytical report	Calibration curve within the specification criteria.	3
	Quality control within specification criteria.	3

Legend: 1- low criticality; 2- moderate criticality; 3- high criticality.
* Both items categorized as 1 or 2 may become 3 if there is recurrence, or there are a large number of items that are recurrent.

The absence of collection points during the study might generate a trend in the estimation of pharmacokinetic parameters, especially AUC and $C_{máx}$, and therefore influence the statistical decision regarding PB of the formulations under study. For this reason, the confirmation of the accomplishment of collections and deviations related to these ones is very relevant.

In this sense, as shown in Table 2, it is crucially important to use the blood concentration curve without the interpolation of missing points, which does not influence obtaining the pharmacokinetic variables. On the other hand, the lack of a sample close to the peak of maximum concentration may interfere in the estimation of this parameter. Thus, it is important to consider the values that were indeed quantified, ruling out any type of procedure for the estimation of missing data, since they may compromise the quality of the study.[7)]

Thus, considering the importance of the statistical evaluation of pharmacokinetic parameters for the demonstration of bioequivalence between test and reference formulations, the items recommended in the guideline for this study stage are shown in Table 3.

Table 3 - Data evaluated in the statistical step

Substages	**Evalauted Items**	**Degree of impact for the study (1 to 3)**
Study outline	Randomized method for allocation of volunteers to medication intake.	3
Data treatment	Statistical evaluation of pharmacokinetic parameters ($C_{máx}$, AUC_{0-t} and AUC_{0-inf}).	2
Statistical analysis	Transformed data for ANOVA modeling according to experimental design.	2
	Sequence effects (groups), volunteers within the sequence, period and treatment are contemplated in the variance analysis.	2
	The proposed confidence interval (90%) in protocol is suitable for the study.	3

	Obtained data are within the confidence interval (80-125% or as adopted in protocol).	1
	Records of volunteers excluded in bioequivalence assessments.	2

Legend: 1- low criticality; 2- moderate criticality; 3- high criticality.
* Both items categorized as 1 or 2 may become 3 if there is recurrence, or there are a large number of items that are recurrent.

According to the data analysis in Table 3 and in line with national regulatory guidelines, we shall not exclude more than 5% of the volunteers during the whole study or the lack of more than 10% of the concentration values administration of each drug per volunteer.[7)]

The pharmacokinetic parameters at the analytical stage shall be evaluated according to the drug concentration versus time curves and statistically analyzed for PB determination. For the analysis, it is necessary to perform the calculation by using the trapezoid method. AUC_{0-t} must be equal to or greater than 80% of AUC_{0-inf}, except in cases where truncated AUC is used, another consideration is that we shall obtain the drug $C_{máx}$ and $T_{máx}$ directly without interpolation of the data. The clearance (C), the apparent volume of distribution (Vd) and the elimination half-life ($t_{1/2}$) of the drug and / or metabolite shall also be determined, even if there is no statistical treatment.[7)]

As the pharmaceutical industry, that is, the sponsor of the study spends a long period developing a drug, requiring the use of personnel, resources, tests, as well as other tools for quality assurance, safety, traceability and satisfactory evidence to prove interchangeability regarding the reference product, it is essential that all stages are conducted within a high level of excellence, since the occurrence of deviations, non-compliances or lack of traceability in the execution of activities may lead to a rejection of the registration process. This rejection may be related to failures of execution by the contracted center, which may imply financial losses and affect the schedule for product launch in the market, directly affecting the benefit that the population has in having more reduced cost treatment options, besides loss of portfolio and market by the manufacturer.

FDA encourages study sponsors to monitor studies performed at contracted centers. In addition, it recommends that each sponsor assesses the risks of the studies and thereby implement study monitoring plans and corrective actions, such as process, training and qualification of monitors and auditors, suspensions and premature termination of the study, when applicable.[11)]

Normally, monitoring at the research center is performed before, during, and after the study, based primarily on the objectives, purpose, design, complexity, presence of the blind or non-blind character, sample size, and study endpoints. For this purpose, the sponsor of the study shall appoint a person responsible for conducting the monitoring, in which, in order to ensure the efficiency of the monitoring process in the PB center, he/she shall meet a series of pre-defined requirements.[20)]

4. CONCLUSION

The monitoring performance in contracted center provided a systemic view of the evidence process related to PB, where the monitoring guideline is the summary of the items of greater relevance that need to be evaluated so that any properly trained employee can apply it. Thus, it is possible to ensure the maintenance of organizational memory in the evaluations carried out by the sponsor. In addition, we emphasize that monitoring is a fundamental process for the improvement of contracted centers and a way to support compliance with norms, requirements, procedures and study protocol by the contracted center.

In conclusion, considering that the sponsor of the study is co-responsible for the performed research and also the most interested one in evaluating the quality and safety of its formulation, which is the main affected in case the contracted center performs some activity in non-compliance with the legislations such as GCP or GLP, the monitoring of a study is essential to control the activities performed and to minimize regulatory inquiries or even high costs due to failure of a study for quality or safety reasons, since it allows the sponsor to monitor the study in real time.

The design of the critical points in the RB / PB studies determined in this study is much more than evaluating the quality of the clinical trials carried out, but rather supporting the safety of the volunteers involved. We emphasize that the function of the monitor is to act in the prevention of mistakes and deviations so that the study is conducted as established in protocol. Therefore, it is the responsibility of the monitor to evaluate regulatory and ethical compliance, enabling the protection of participants in the PB study, as well as preserving the safety, quality and efficacy of the generic or similar candidate drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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