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Second phase of generic drugs in Brazil: implementation of the vasoconstrictor assay for dermatological topical corticosteroids

Segunda fase dos medicamentos genéricos no Brasil: implementação do estudo Vasoconstritor para corticoides tópicos dermatológicos

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ABSTRACT

Introduction: In Brazil, the sale of generic medicines has been increasing, driven by the search for more affordable alternatives. However, this expansion necessitates the assurance of safety and efficacy, particularly in the case of topical medications containing corticosteroids. Until 2022, these products were exempt from bioequivalence testing, with only pharmaceutical equivalence being required. **Objective:** This study aimed to discuss the registration of topical medications containing corticosteroids in Brazil, highlighting recent regulatory changes and the impact of the mandatory implementation of the Vasoconstrictor Assay (VCA). **Method:** The methodology consisted of a systematic review of scientific literature and national and international regulatory guidelines, focusing on the registration criteria for topical corticosteroid medications. The study provided a detailed examination of the VCA, a pharmacodynamic test that evaluates the degree of skin blanching following drug application, divided into a pilot study (defining Emax and ED50) and a main study (comparison with the reference product). **Results:** It was demonstrated that the VCA is widely adopted in international regulatory contexts, such as by the U.S. Food and Drug Administration (FDA) since 1995. In Brazil, its introduction presents a technical challenge, as most bioequivalence centers require appropriate expertise and infrastructure. Nevertheless, studies indicate that the method has the potential to effectively demonstrate bioequivalence. **Conclusions:** The requirement of the VCA represents a regulatory milestone in Brazil, fostering greater technical rigor in the registration of topical corticosteroid medications. Its adoption is essential to ensure the quality, safety, and efficacy of these products for the population.

KEYWORDS: Therapeutic; Equivalency; Generic; Adrenal Cortex Hormones; Vasoconstriction

RESUMO

Introdução: No Brasil, a venda de medicamentos genéricos vem crescendo, impulsionada pela busca por alternativas mais econômicas. Contudo, essa expansão exige a garantia de segurança e eficácia, especialmente no caso de medicamentos tópicos contendo corticoides. Até 2022, esses produtos eram isentos de testes de bioequivalência, sendo exigida apenas a equivalência farmacêutica. **Objetivo:** Este trabalho teve como objetivo discutir o registro de medicamentos tópicos contendo corticoides no Brasil, destacando as mudanças regulatórias recentes e o impacto da obrigatoriedade do Ensaio de Vasoconstrição (EVC). **Método:** A metodologia consistiu em uma revisão sistemática da literatura científica e de normativas regulatórias nacionais e internacionais, com foco nos critérios de registro de medicamentos tópicos corticoides. O estudo detalhou o EVC, um teste farmacodinâmico que avalia o grau de branqueamento da pele após aplicação do fármaco, dividido em estudo piloto (definição de Emax e ED50) e principal (comparação com medicamento de referência). **Resultados:** Foi possível evidenciar que o EVC é amplamente adotado em contextos regulatórios internacionais, como pelo FDA (Food and

Drug administration) desde 1995. No Brasil, sua introdução representa um desafio técnico, uma vez que a maioria dos centros de bioequivalência necessitam de expertise e infraestrutura adequadas. Ainda assim, estudos mostram que o método tem potencial para comprovar a bioequivalência de forma eficaz. **Conclusões:** A exigência do EVC representa um marco regulatório no Brasil, promovendo maior rigor técnico no registro de medicamentos tópicos com corticoides. Sua adoção é essencial para garantir qualidade, segurança e eficácia desses produtos para a população.

PALAVRAS-CHAVE: Bioequivalência; Medicamentos Genéricos; Corticosteroides; Vasoconstrição

INTRODUCTION

A survey carried out by the Brazilian Association of Generic and Biosimilar Medicines Industries (PróGenéricos) reveals that sales of generic drugs in Brazil grew by 3.67% in the first six months of 2023, i.e. between January and June 2023, 979.4 million units of generic drugs were sold in Brazil[1]. And this, of course, is justified by patients' search for savings. However, the question is whether the lower price reflects the quality of the medicine purchased. In short, the generic drug program in Brazil was created in 1999 through the publication of the Generics Law[2], No. 9.787, of February 10, regulated by Decree No. 3.181, of September 23, 1999[3]. The Resolution of the Collegiate Board (RDC) of the Brazilian National Health Surveillance Agency (ANVISA) No. 391, of August 9, 1999[4], approves the Technical Regulation for Generic Medicines. This framework introduced new concepts into the country, pharmaceutical equivalence and bioequivalence of medicines among them. This culminated in a new organization of Brazilian laboratories/research centers in the search for certification in good bioequivalence/bioavailability (BE/BA) practices, awarded by the newly created national regulatory agency[5]. It took three years from the publication of the generics law for the first BE studies to be carried out. The obligation to carry out BE tests (usually on healthy volunteers) was initially imposed only for non-bioisent oral medicines. Almost 25 years after the publication of the generics law, it wasn't until 2022, by means of RDC No. 742, of August 10, that it became mandatory to carry out BE tests (vasoconstrictor assay - VCA) for the comparative evaluation of topical dermatological drugs in the corticosteroid class[6]. This is therefore a step forward in guaranteeing the safety and clinical efficacy of this class of drug, which is widely used by the Brazilian population to treat a wide variety of skin morbidities.

In the international context, liquid formulations are exempt from clinical studies to assess BE. However, in order to approve a semi-solid generic topical product, therapeutic equivalence studies are required by regulatory authorities in several countries, including the United States, Japan, South Africa, and European countries, among others. To this end, clinical studies are mandatory, except for dermatological corticosteroids, in which case pharmacodynamic testing or VCA can be used[7]. Despite the regulatory and scientific context, whose "gold standard" method for evaluating the BE of generic topical products consists of carrying out clinical studies, these have several disadvantages, since *in vivo* permeation is affected by factors such as the state of the disease and the type of skin[8,9,10]. That said, alternative substitute methods (dermatopharmacokinetics, skin microdialysis, *in vitro* release and permeation studies, near-infrared spectroscopy) continue to be discussed by the American and European scientific community[7,11,12,13,14,15]. To minimize the costs generated by clinical studies, as well as to define an expanded concept of pharmaceutical equivalence, investigations initiated by the United States - Food and Drug Administration (US-FDA) have led to advances in the BE approach based on the qualitative similarity (Q1) and quantitative similarity (Q2) of excipients, as well as the similarity of similarity (Q3). However, depending on the complexity of the formulation, *in vitro* permeation testing (IVPT) or another biorelevant performance test may be necessary[6]. In view of the above, the aim of this study was to highlight the importance, in the national context, of the vasoconstriction test as a test that ensures the quality of generic topical corticosteroids.

METHOD

This is a systematic review whose data was collected through a bibliographic survey of the following databases: Scientific Electronic Library Online (SciELO), PubMed, Latin American and Caribbean Health Sciences Literature (LILACS), and Elsevier. These searches used the following descriptors in Portuguese and English: "blanching test", "vasoconstriction test", "corticosteroids", "topical corticosteroids", "blanching test", "bioequivalence", "topical medicines", and "pharmaceutical equivalence".

As inclusion criteria, studies relevant to the research objective were selected: original and review articles published in national and international journals, books, normative instructions, and ordinances from official scientific bodies. The data search covered the period from 1999 to 2023. Duplicate studies and those referring to systemic corticosteroids were excluded.

History of the evaluation of generic topical drugs in Brazil

In Brazil, all topical and local medicines were considered bio-exempt from BE testing. This meant that, while most international regulatory agencies, in principle, required the evaluation of therapeutic equivalence (*in vitro* and *in vivo* tests) for topical generics, ANVISA only required the performance of pharmaceutical equivalence tests, according to RDC No. 31, of August 11, 2010[17]. In other words, it was only based on microbiological physicochemical tests[18]. According to Soares et al.[19], the relaxation of regulatory requirements at the national level has led to a greater number of registrations of generic and similar

topical dermatological drugs in Brazil than in other markets. In addition, RDC No. 73 of April 7, 2016[20] (post-registration changes, cancellation of registration of drugs with synthetic and semi-synthetic drugs) required comparative *in vitro* performance tests (IVRT and/or IVPT) only between the currently approved formulation and the proposed one, and calculated in accordance with the General Chapter of the American Pharmacopoeia[21]. However, these generic and similar product candidates had not been compared with the reference product using performance tests at the time of their registration.

In recent years, ANVISA, together with Brazilian researchers, has held meetings and discussions on evaluation, as well as on conducting BE studies for topical products, as already described by Leal et al.[22], dealing with the Brazilian scenario and studies to demonstrate BE[22]. In this context, the VCA is the first *in vivo* BE test implemented in Brazil for the evaluation of topical semi-solid dermatological products, specifically for corticosteroids, according to RDC No. 742/2022[6]. This guide followed the vasoconstriction protocol, as described in the FDA's Topical dermatologic corticosteroids: *In vivo* bioequivalence Guide[23]. After this publication, all semi-solid formulations for topical application containing corticosteroids should prove BE through pharmacodynamic studies, and formulations already registered should be appropriate with proof of BE through these studies, according to the drug, considering a calendar with specific deadlines, according to the schedule first published in public consultation (CP) No. 760, of December 27, 2019 and then republished with a longer deadline in RDC No. 742/2022. Despite the considerable time between CP No. 760/201924, and the publication of the RDC[24], and the publication of RDC No. 742/2022[6], which makes this methodology mandatory for proving the BE of topical medicines registered in Brazil, its implementation is still a major challenge, considering that most Brazilian centers do not yet have the expertise to carry it out.

Topical corticosteroids

A topical corticosteroid is any synthetic steroid derivative that exhibits the same function as the natural corticosteroid hormone, formulated for topical action[25]. The first topical corticosteroid was hydrocortisone, isolated in 1948 by Kendall et al. whose efficacy was proven in 1952 by Sulzberger and Witten for the treatment of dermatoses[26]. Since then, topical corticosteroids have become the basis for the treatment of many inflammatory skin diseases, due to their ability to reduce inflammation. Among the dermal diseases that can be treated with topical corticosteroids are psoriasis, eczema, discoid lupus erythematosus, lichen sclerosus, lichen planus, vitiligo, chronic dermatitis, keloids, and acne[25,27,28]. The anti-inflammatory effect of topical corticosteroids is mainly attributed to their ability to induce the synthesis of lipocortin I, which regulates the activity of phospholipase A2, and this acts on the production of leukotrienes and prostaglandins, mediators of inflammation[25,29]. The importance of classifying the potency of corticosteroids lies in their therapeutic indication. As a rule, more potent corticosteroids are indicated for treatment in areas where absorption is reduced, such as the palms of the hands and soles of the feet, or in disorders that are less responsive to topical corticosteroids, such as psoriasis and lichen striatum. Less potent corticosteroids, on the other hand, are the best choice for treatments in children, for areas of the body such as the face and groin, or for mild, generalized diseases such as atopic and seborrheic dermatitis[26,28,30]. In Brazil, one of the classifications followed by health professionals is that described by the Ministry of Health (Chart).

In recent years, the classification of corticosteroid potency has been much discussed. This classification is mainly based on clinical data, but in some cases VCA has also been used[32,33]. However, according to Zvidzayi et al.[32], this evaluation should be guided by the analysis of Emax and not ED50 as is done in the BE study. Furthermore, although corticosteroids have potencies inherent to their physicochemical characteristics, this potency can be increased or decreased depending on the type of pharmaceutical form and the excipients/vehicles[32,33].

Pharmaceutical equivalence requirements for bioequivalence of semi-solid products

Medicines can be administered topically using new or conventional pharmaceutical forms, such as creams, gels, and ointments. However, their excipients and manufacturing process are critical quality attributes that can significantly influence, individually and collectively, the release of the drug and, consequently, the therapeutic effect of the medicine. This means that a generic drug must have the same therapeutic effect as the reference drug; in principle, they must be a copy of each other. To this end, reverse engineering has been used. This strategy guarantees Q1, Q2, and Q3 similarity[7], as already pointed out in the introduction. Finally, it is worth remembering what is described in Arts. 5 and 6 of RDC No. 742/2022[6], part of whose content has been transcribed below:

> Art. 5th Prior to the start of the BA/BE study, the test and comparator drugs must be analyzed in accordance with RDC No. 31, of August 11, 2010, or any successor thereto.
>
> § The difference in drug content between the test and comparator drugs, when they are of the same concentration, must not exceed 5.00% (five percent).
>
> § When the pharmaceutical equivalence study is not applicable, quality control reports must be submitted for each of the drugs used in the study.
>
> Art. 6th For drugs classified as generic or similar, the BA/BE study must be carried out with the same batch used in the pharmaceutical equivalence study.

Vasoconstriction assay (VCA)

The VCA is a test that makes it possible to compare the BA of topical dermatological products containing corticosteroids, serving as an indication of efficacy, and consists of observing

Chart. Classification of topical corticosteroids according to their potency by the Ministry of Health[31].

Class	Drug	Pharmaceutical Form
Group I - Superpotent	Clobetasol propionate 0.05%	Cream and ointment
Group II - Potent	Betamethasone dipropionate 0.05%	Ointment
	Betamethasone valerate 0.10%	Ointment
	Halcinonide 0.10%	Ointment
	Diflucortolone valerate 0.10%	Cream and ointment
Group III - Potent	Betamethasone diproprionate 0.05%	Cream
	Betamethasone valerate 0.10%	Cream
	Halcinonide 0.10%	Cream
	Triamcinolone Acetonide	Ointment
Group IV - Medium potency	Mometasone furoate 0.10%	Ointment
	Fluocinolone acetonide	Ointment
	Desonide 0.50%	Ointment
	Triamcinolone Acetonide	Cream
Group V - Medium potency	Mometasone furoate 0.10%	Cream
	Fluocinolone acetonide	Cream
	Desonide 0.50%	Cream
Group VI - Mild potency	Mometasone furoate 0.10%	Cream
	Fluorandrenolide	Cream or ointment
	Hydrocortisone	Ointment
Group VII - Mild potency	Hydrocortisone	Cream
	Dexamethasone	-
	Prednisolone	-

Source: Prepared by the authors, 2023.

the degree of whitening of the skin after topical application of these drugs. It was first proposed by McKenzie and Stoughton in 1962 and used visual assessment (by trained observers) of the whitening produced[34]. According to the scientific literature, until 1962, in the United States it was not mandatory to carry out BE tests (*in vivo* tests) to approve and market generic formulations of topical corticosteroids. When many of these generic formulations were submitted to VCA, it was observed that they were not bioequivalent to the reference formulation[35,36,37]. In view of this, in order to eliminate the subjectivity of this evaluation and in addition to the advances in technology, the FDA published a guideline in 1995[23], requiring that BE be proven by evaluating whitening using the Minolta® chromometer[23,38]. This equipment evaluates skin color by emitting white light from a xenon source incident on the surface to be evaluated, quantifying the reflected light in three color indices of different wavelengths. The signal is then converted into three coordinates, L* (luminosity), a* (amount of green or red) and b* (amount of yellow or blue). These three values define a single point on a three-dimensional color map, recording the color according to the recommendation of the *Commission Internationale de l'Eclairage* (CIE)[39]. The data is analyzed using the scale that shows the greatest sensitivity throughout the progression of the blanching response[23,32].

As previously mentioned, in Brazil, the requirement to carry out vasoconstriction tests to prove the BE of topical dermatological corticosteroids was introduced in 2022 with the publication of RDC No. 742/2022[6]. According to the proposed methodology, two studies must be carried out: a pilot study (using only the reference product), used to determine the duration of the dose (time the drug remains in contact with the skin), and a main study (comparative test x reference study)[6,23].

Pilot study

The pilot study should be a single-center, randomized, open, prospective, one-treatment, one-period study using only the reference drug and should be conducted with at least 24 healthy individuals, respecting the inclusion and exclusion criteria. To be included, participants must not have clinical conditions such as psoriasis, atopic dermatitis, or other skin conditions, a significant amount of hair or a difference in skin color between the two forearms, among other criteria[23]. Moreover, before starting the study, participants should be assessed for their ability to produce adequate vasoconstriction[6,23]. In the pilot study, different exposure times to the drug should be tested and randomly distributed on the participants' two forearms. To do this, six 1.5 cm diameter sites should be marked on

the skin of each forearm. In this way, four different exposure times will be applied to each forearm, and the other two sites should serve as a negative control, or blank (no formulation applied)[6,23]. According to Brazilian legislation, the application method must be staggered with synchronized removal, with the drug being applied at different times (at each of the sites) and removed at the same time (Figure 1)[6]. The sites should have a distance of 2.5 cm center to center between them, and at least 3 cm between the wrist and the elbow (Figure 2a)[6]. The drug exposure times suggested by the FDA[23] are: 0.25; 0.50; 0.75; 1.0; 1.5; 2.0; 4.0; and 6.0 h and should be determined according to the potency of the drug being tested.

Blanching should be assessed using a chromometer or spectrophotometer, and readings should be taken 0.5 h before application of the formulation (baseline) and at different times after removal of the formulation, in quadruplicate. Untreated sites (blanks) should also be evaluated in the same way, considering the time before application and all other analysis times[6].

After obtaining the blanching readings, the data must be corrected, taking into account the baseline (reading 0.5 h before the product was applied) and the untreated sites (white site). Figure 3, which contains corrected reading data, exemplifies the blanching behavior caused by a drug after different times of exposure (unpublished data). The area under the effect curve (ASCE0-t) should be calculated using the trapezoid rule, for each application site. From this, the dose response curve should be constructed considering all the points, from all the individuals, simultaneously. The statistical analysis should be carried out using all the observations from all the research participants at the same time. The ED50 and Emax values can be found using two different methods. One, the non-linear mixed effect model, considers inter- and intra-subject variability and requires suitable software. The other acceptable method for determining the parameters is to fit a non-linear model based on the least squares method, using the individual observations of all the subjects. The ED50 corresponds to the duration of the dose required to reach 50% of Emax, D1 and D2 correspond to half the ED50 and twice the ED50, respectively. These data will be used to conduct the main study[6,23].

Comparative study

The comparative study should be conducted using the same inclusion and exclusion criteria as the pilot study. It should be of the replicate type and should be conducted with 40-60 detector subjects, using the exposure time determined by the ED50 in the pilot study[6,23]. The drugs should be applied in a randomized manner, including the following sites, which should be arranged in a complementary manner (Figure 2c):

a. Test (T): test product at the exposure time corresponding to ED50 (two sites per arm);

b. Comparator (C): comparator product at the exposure time corresponding to ED50 (two sites per arm);

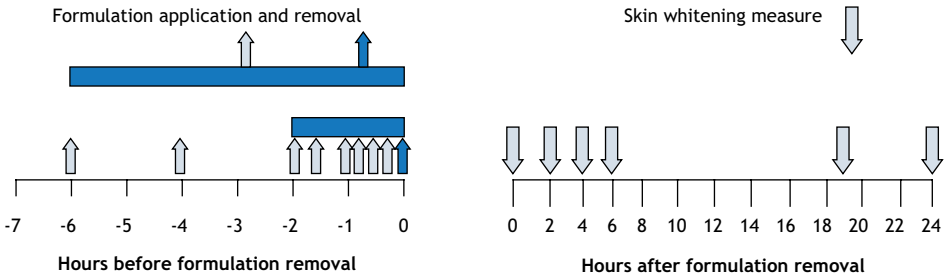
c. D1: comparator product at the exposure time corresponding to D1 (one site per arm);

d. D2: comparator product at exposure time corresponding to D2 (one site per arm);

e. White (two sites per arm)[6].

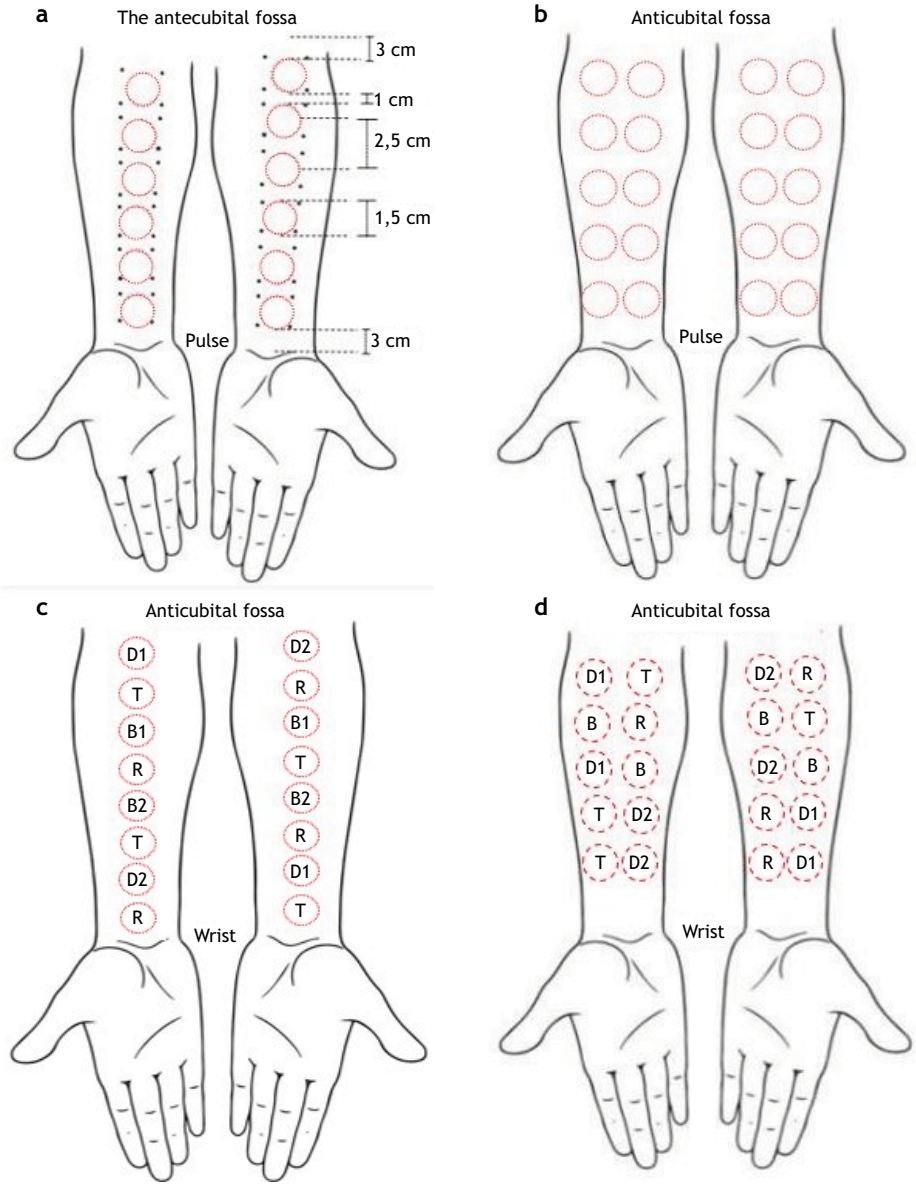
As in the pilot study, the vasoconstriction reaction should be assessed at the same times and the data adjusted in the same way.

In this study, the *in vivo* response of the test product is compared with the reference, using appropriate statistical tools to assess whether or not BE has been achieved. The Area Under the Curve (ASC) for D1 (ASC1) and D2 (ASC2) are calculated for each participant, and those with an ASC D2/ASC D1 ratio greater than 1.25 are considered "detectors". The data from these detector research participants is used for the BE assessment. Based on this model, the proposed generic and reference drug must meet the BE acceptance criteria, presenting a 90% confidence interval (CI) with limits between 80.00% and 125.00% for the observed pharmacodynamic response. Statistical analysis should be carried out using the Locke method, which provides an accurate CI from untransformed data[6,23]. Although VCA has been an FDA-approved test since 1995[23], some scientific publications have reported problems with the method, including baseline and blank correction (a source of error propagation); the use



Source: Wiedersberg et al.[40].

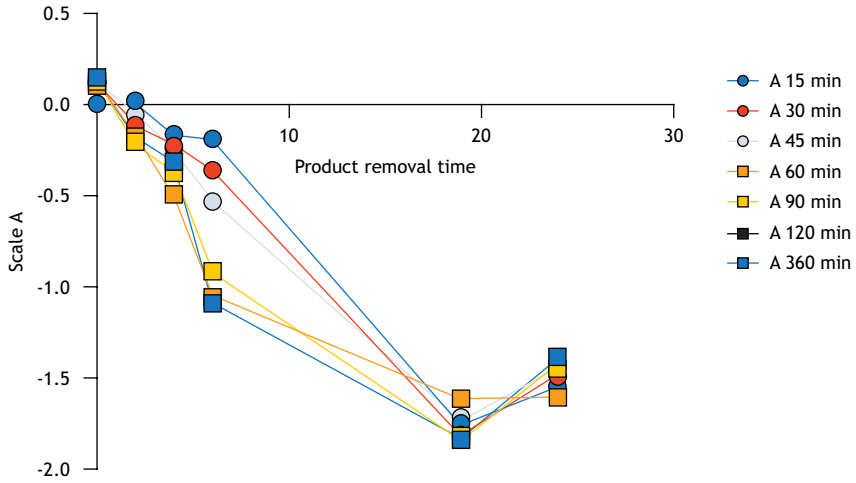
Figure 1. Schematic representation of sequenced application with synchronized removal.



Source: Prepared by the authors, 2023.

Figure 2. Schematic diagram showing the application sites of the formulations demarcated in the ventral region of each forearm according to (a) FDA, 1995[23]and (b) FDA draft, 2022[43], and (c) FDA, 1995[23] randomized application and complementary (d) FDA, 2022[43] D1 and D2 in duplicate.

of different computational methods to calculate ASC (can lead to appreciable variance in the calculated ASC); inaccurate reading (pressure/angle of the equipment on the skin); the presence of hair on participants' arms; circadian variation in intrinsic skin coloration/wrist and antecubital fossa variation and operator fatigue[41,42]. Over the years, the FDA adopted important changes to the methodology of pharmacodynamic studies with the publication of the "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence Guidance for Industry - Draft Guidance" in October 2022[43]. The guide, like the 1995 guide, provides guidelines for conducting pilot and main studies, but with revised recommendations since its last publication. Among the new recommendations was the requirement to qualify the equipment and operators, a test aimed at demonstrating the robustness of the measurements of the different operators and instruments to be used in the study[43]. In the pilot study, the suggested exposure times to the drug have been maintained, however, they must now be carried out in duplicate. This means that the eight times should be randomly distributed together with the negative control on each forearm (Figure 2b). In the new guide, the suggested blanching reading times are 0, 2, 4, 6, 8, 10, 12, 20, and 24 h after product removal, but these may vary depending on the test drug[43]. In the comparative study, the number of sites per forearm was also increased, from eight demarcated sites on each forearm to 10, and doses D1 and D2, previously applied to just one site, now have to be applied in duplicate per forearm (Figure 2d)[43]. In addition, in the current guide,



Source: Prepared by the authors, 2023.

Figure 3. Dose-response profile of the reference formulation (clobetasol propionate).

the statistical analysis model is predetermined. The data must be adjusted using all the observations from all the individuals simultaneously, using a non-linear mixed-effect model[43].

Drug Bioavailability/Bioequivalence Centers

BE tests are carried out by centers certified by ANVISA. By official definition, Drug Bioavailability/Bioequivalence Centers are:

> research institutions, both public and private, which carry out at least one of the stages: Clinical, Analytical, or Statistical of a study of the BA/BE of medicines, taking technical and legal responsibility for the veracity of the data and information contained in the entire process, under the terms of the Resolution in force.

The checklist for inspecting centers is established by Normative Instruction (IN) No. 123 of March 24, 2022[44]. After the inspection, if the center meets all the mandatory requirements, it is issued with a certificate valid for two years. In addition to publication of the certification in the Official Gazette of Brazil (DOU), all certified centers are listed on the ANVISA website (www.anvisa.gov.br). There are currently 52 certified centers in the country, of which 42 are international (27 of them in India), and 12 Brazilian centers, only one of which is public - the Pharmaceutical and Cosmetics Development Center at the Federal University of Pernambuco (NUDFAC/UFPE)[45].

CONCLUSIONS

Since in Brazil it was not mandatory to carry out a clinical study for the approval of a generic/similar drug for topical use, and considering the fragility of the tests that make up pharmaceutical equivalence, the implementation of VCA for the evaluation of semi-solid formulations containing topical dermatological corticosteroids should be considered a significant guarantee of the safety and quality of this class of drugs for the population. Therefore, as this is a new methodology in the country, it is necessary to gain skills in conducting the technique, which will require studies and practice on the part of the Bioequivalence Centers. This article brings together the most important legislation on VCA and its changes over time by the FDA. Furthermore, it addresses the unpublished Anvisa guidelines, bringing with it the state of the art in implementing the test, which will be of great importance in determining the BE of topical corticosteroids.

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Authors' Contribution

Leal LB, Santana DP - Conception, planning (study design), and writing of the paper. Barbosa ICF - Acquisition, data analysis, and writing of the paper. Ferraz C - Data analysis and interpretation. All the authors approved the final version of the paper.

Conflict of Interest

The authors declare that there is no potential conflict of interest with peers and institutions, political or financial, in this study.

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