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Isadore Kanfer *Editor*

Bioequivalence Requirements in Various Global Jurisdictions

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Preface

The introduction and application of bioequivalence (BE) testing as a surrogate measure of safety and efficacy was introduced in 1977 when the US FDA published its Bioavailability and Bioequivalence regulations which facilitated the entrance of generic products into international markets. Subsequently, in 1984, the Hatch-Waxman Amendments established the abbreviated new drug application (ANDA) process in the USA where a successful BE study would suffice as evidence of equivalent safety and efficacy of a generic product when compared with an acceptable innovator/brand product. Such evidence is required to establish Therapeutic Equivalence (TE) to declare that such a generic product is interchangeable with an innovator product. Hence a primary objective of a BE study is to circumvent the extensive lengthy time course and associated costs required to conduct clinical trials in patients to make medicines more affordable and more available to the wider public. It is important to note that a BE study is not specifically a tool only for the testing of the safety and efficacy of generic products. It is, in fact, a general surrogate approach for testing the equivalence of formulations, whether testing a new generic product against the innovator/brand product or when an innovator manufacturer intends to change the original formulation approved based on a clinical trial to a different formulation containing the same active pharmaceutical ingredient (API) in the same strength and dosage form. In other words, innovator companies often use BE studies for formulation changes and thereby circumvent the need to re-do clinical trials on formulation changes to the original product which underwent safety and efficacy studies in patients.

Since the introduction of BE, many countries around the world have developed rules, regulations, and guidance/guidelines for BE studies to obtain market approval in the respective country. However, while in most cases the BE requirements have usually been largely based on those early guidelines published by the US FDA, differences in various aspects exist in different countries. This conjures up an intriguing question which awaits a convincing answer, viz.: Why then do regulatory agencies in different global jurisdictions require different standards, rules, guidelines/guidance, and processes to provide the necessary evidence of safety and quality for the market approval of generic products? A further question that arises

concerns the clinical performance of generic medicines in different countries, i.e., do generic medicines made by the same manufacturer have different safety and efficacy profiles in different countries even though they contain the same active pharmaceutical ingredient (API) in the same amounts? Another intriguing issue is that when a generic medicine undergoes a BE study, a reference product which has been approved based on clinical studies in patients is usually required to be used as the comparator product. In most countries, there may be several approved generic products, and since each approved generic product was presumably shown to be bioequivalent to the reference product in that market, are such generic products interchangeable between each other as there are no requirements to show BE between generic products?

Despite the foregoing enigmas, the application of BE studies has served its purpose very well. However, although the BE requirements in many global jurisdictions have much in common, differences in certain approaches and requirements such as definitions and terms, choice of comparator (reference product), acceptance criteria, fasted and fed studies, single and multi-dose studies, biowaivers, and products not intended for absorption into the systemic circulation (locally acting medicines and dosage forms), among others, provide food for thought that standardization should be a high priority objective to result in a harmonized international process for the market approval of products using BE.

The attainment of a harmonized set of rules or guidelines to establish safety and efficacy of pharmaceutical products clearly has many desirable benefits. Standardization of bioequivalence testing including the collection, assessment, and statistical processing of the data including the acceptance criteria for the market approval of multi-source products has become an important goal by international drug manufacturers. This ideal has important cost-related benefits in the quest to make medicines more affordable and more accessible to the wider public around the world and, importantly, to ensure the necessary quality, safety, and efficacy. This second addition contains information based on recent guidance and guidelines from the respective regulatory agencies as well as important trends and descriptions relating to innovative approaches for bioequivalence assessment.

The Brazilian chapter provides some innovations in relation to the previous one (RE 1170/2006), which emphasizes the need to carry out bioequivalence studies for semi-solid topical products containing corticosteroids. The chapter traces the trajectory covered so far, bringing all the new Brazilian regulations adopted since the publication of the 2018 edition of this book, providing a history of the resolutions that deal with the criteria established for the implementation of generic medicines in the country, which is directly related to the development of bioequivalence studies in Brazil. Although Canada is a country that has a considerably lower population than the USA or the European region, Health Canada has been instrumental in establishing innovative guidelines and scientific recommendations for Bioequivalence for the last 40 years. Health Canada regulations are unique, and they are at times aligned with those of the European region and at other times with those of the USA. The Canadian chapter contains updated information since the publication of it's latest guidelines where a major change has been the removal for the need

for a clinical or pharmacodynamic endpoint study for orally inhaled drug products. The current guideline includes information relating to tyrosine kinase "inib" products such as *desatinib, imatinib*, etc. which, since sometimes a very low proportion of subjects do not show measurable concentrations with the reference products, makes provision to permit removal of a subject if the AUC for that period is less than 5% of the geometric mean AUC.

The main focus of the EU chapter is on immediate release formulations. This chapter now contains information on the estimation of bioequivalence of highly variable drug or drug products, narrow therapeutic index drugs, and orodispersible tablets. A section on Product-Specific Guidances (PSG) has been included where mention is made that there are currently 77 such PSGs. New Drug and Clinical Trials (NDCT) Rules, introduced in 2019 amending the Drugs and Cosmetics Rules 1945 replacing Part XA and Schedule Y of the Drugs, is mentioned in the India chapter. The definition of New Drugs has been modified to incorporate Novel Drug Delivery Systems (NDDS), deoxyribonucleic acid (DNA)-derived product, living modified organism, monoclonal antibodies, stem cell-derived products, gene therapeutic products, or Xenografts. Other requirements are the inclusion of female members in BE studies. Requirements and guidelines for the conduct of a BA/BE study for a new drug or investigational new drug have now been prescribed.

Since publication of the previous Japan chapter, a revised current Japanese BE study guideline was issued in 2020. A fed BE study is now required for solubility-enhanced IR and enteric-coated formulations where, previously, a fasted study only was necessary. If there is a significant difference in dissolution rate between the reference and test products, or if ethnic differences in gastrointestinal physiology including the level of gastric acidity are thought to affect the evaluation of BE due to formulation characteristics, a BE study in Japanese subjects is required. A further new requirement involves setting separate dissolution test conditions for solubility-enhanced IR formulations. A further change involves the statistical analysis relating to the adaption of additional data acquisition where the probability of a type 1 error is controlled instead of the previous method using the sum of data obtained in the pivotal study and an add-on subject study conducted separately from the pivotal study or a pilot study.

The new USA chapter presents a comprehensive review of the scientific principles and recent advances in the field of bioequivalence as it relates to regulatory assessment and approval of generic drugs. Since the initial edition of this book, the US FDA has published a revised *Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application in August, 2021* (refers as 2021 FDA guidance thereafter). Important revisions in the 2021 FDA guidance include new information on reference listed drug (RLD) and reference standard (RS) in the Orange Book, expanded considerations for study populations regarding sex and age, modified recommendations for assessing formulation proportional similarity for modified-release (MR) drug products, the inclusion of sections addressing alternative routes of administration (e.g., products administered via a nasogastric tube or a gastric tube, orally disintegrating tablets, sublingual and transdermal products), appendices on reference

scaled average BE analyses and handling of outliers, and the removal of sections related to orally administered locally acting drugs. The new USA chapter emphasizes the growing role of modeling and simulation approaches in BE assessment and describes the utility in complementing conventional method for BE demonstration. In addition, the adoption of a totality of evidence approach for establishing BE, particularly regarding complex generic drug products is highlighted. The updates make a significant contribution to the advancement of regulatory standards and to the safety and efficacy of generic drugs marketed in the USA. The World Health Organisation (WHO) bioequivalence (BE) guidance has remained largely unchanged since the publication of the first edition of this book and the present update. Notwithstanding, the pending adoption of the ICH Harmonised Guideline M13A *Bioequivalence for Immediate Release Sold Oral Dosage Forms* is likely to trigger a review of the WHO guideline under the oversight of the WHO Expert Committee for Specifications for Pharmaceutical Preparations. Although the WHO does not adopt ICH guidelines directly because of differences in the development and consultation procedures for guideline development between the two entities, the authors state that it is expected that a new WHO guidance will be developed employing the ICH M13A guideline as a framework. Interestingly, the WHO biowaiver (BW) guidance has evolved since the previous edition of this chapter where the adoption of the ICH Harmonised Guideline M9 Biopharmaceutics Classification System-based Biowaivers has seemingly led to the introduction of a new WHO BW guideline in 2024 discussed in this updated chapter.

Whereas the main objective of this second edition is to provide an updated account of current bioequivalence requirements in various global jurisdictions, an additional important goal is to attempt to gather various BE requirements used in different global jurisdictions to provide a single source of relevant information. This information may be useful to drug manufacturers, regulatory agencies, pharmaceutical scientists, and related health organizations and governments around the world in the quest to harmonize regulatory requirements for the market approval of generic products.

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Chapter 1
Brazil

Leila Leal, Rodrigo Cristofoletti, and Kelen Soares

Abstract In Brazil, bioequivalence studies were initiated in 1999 with the law that established generic medicines and the creation of the Brazilian Health Surveillance Agency—ANVISA (Law 9782/1999).

Since then, several regulations have been published with the aim of establishing the necessary requirements for the registration of generic medicines, including resolutions on pharmaceutical equivalence and bioequivalence studies.

The current resolution that deals with the conduct of bioequivalence studies is RDC 742/2022 but will likely soon undergo further revision considering the recent recommendations of the ICH M13A guideline. This resolution provides some innovations in relation to the previous one (RE 1170/2006), establishing from this date the need to carry out bioequivalence studies for semi-solid topical products containing corticosteroids. In this way, it can be considered that Brazil is going through a second phase of development of bioequivalence studies.

This chapter traces the trajectory covered so far, bringing all the new Brazilian regulations adopted since the publication of the 2018 edition of this book and provides a history of the resolutions that deal with the criteria established for the implementation of generic medicines in the country, which is directly related to the development of bioequivalence studies in Brazil.

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1 Introduction

This chapter provides an updated account of the chapter in the 2018 edition of the book [1] and includes all new regulations approved after 2017. In addition, it summarizes the history, evolution, and perspectives for the regulation of generic drug products in Brazil, with emphasis on bioequivalence studies and biowaivers.

The 1990s can be considered as a landmark for the Latin American countries when extensive discussions began to incorporate the concepts of bioavailability, bioequivalence, pharmaceutical and therapeutic equivalence, and interchangeability for the regulation of pharmaceutical products [2].

The development of guidelines for *in vitro* and *in vivo* studies, as well as the need for harmonization of acceptance criteria for bioequivalence evaluations between a generic drug product and its respective reference drug product boosted the creation of the Working Group on Bioequivalence of the Pan American Network for Drug Regulatory Harmonization (PANDRH), coordinated by the Pan American Health Organization/World Health Organization, which culminated in the publication of the document entitled "*Framework for Implementation of Equivalence Requirements for Pharmaceutical Products. PANDRH Technical Report Series N° 8,* in 2011" [3].

The application of the Biopharmaceutical Classification System (BCS) for biowaivers included in the United States Food and Drug Administration (FDA) guidance resulted in a significant scientific advance, enabling the registration of generic drug products containing drugs with high solubility and high permeability without an *in vivo* bioequivalence study requirement [4, 5].

In 2016, the Brazilian Drug Regulatory Agency (ANVISA) was accepted as a new regulatory member of the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [6]. Since then, ANVISA has been working diligently to prioritize and update their resolution to adapt ICH guidelines.

2 Generic Drug Products in Brazil

2.1 Definitions and History

The major advances in the regulation of drug registration in Brazil occurred after the creation of the Brazilian Health Surveillance Agency (ANVISA, acronym in Portuguese) by the Law 9782 of January 26, 1999, which also established the Health Surveillance System [7].

One of the first legal acts after the creation of ANVISA was the publication of Law 9787 (February 11, 1999) [8], amending Law 6360 of September 1976 [9], and implementation of generic drug products legislation.

Law 9787 was regulated by resolutions issued by ANVISA (Tables 1.1,1.2,1.3 and 1.4 and Figs. 1.1, 1.2, 1.3 and 1.4). The first resolutions were based on the experience and regulations from countries such as Canada, the United States, and some European countries [10]. This law defines the following concepts:

Table 1.1 Resolutions from ANVISA related to the registration of generic and similar medicines in Brazil issued from 1999 until present

Resolution	Main characteristics
391/1999 [16]	Approves the technical regulation for generic medicines. It is the first step in the technical implementation of Law 9.787/1999, provides information on how registration and post-registration of generic medicines should be requested. It requires the submission of protocols for the pharmaceutical equivalence evaluation and in vivo bioequivalence studies for prior evaluation by ANVISA and describes the criteria for bioequivalence tests. Also, it presents a guide to biowaivers and a list of reference drug products
10/2001 [17]	Revokes resolution 391/1999, first revision of the law. The submission of protocols for pharmaceutical equivalence evaluation and in vivo bioequivalence studies for prior evaluation by ANVISA is no longer mandatory. It describes the criteria for imported generic drug products. It presents a guide for in vitro-in vivo (IVIVC) correlation studies and provides a list of reference drug products available on the ANVISA web site
84/2002 [18]	Revokes resolution 10/2001: bioequivalence, and biowaiver studies are now covered in specific guides
157/2002 [19]	Provides requirements for the registration of similar medicines and information to demonstrate similarity with the product registered in the country through equivalence studies
133/2003 [20]	Revokes resolution 157/2002 and requires the presentation of bioequivalence studies for similar medicines
134/2003 [14]	Provides for the suitability of similar medicines already registered establishing limits for equivalence and bioequivalence studies for similar medicines registered before resolutions 157 and 133
135/2003 [21]	Revokes resolution 84/2002 dealing with the criteria for registration and post-approval changes of generic medicines
16/2007 [22]	Revokes resolution 135/2003
17/2007 [23]	Revokes resolution 133/2003
60/2014 [24]	Revokes resolutions 16/2007 & 17/2007 providing criteria for registration and renewal of drug registration with synthetic and semi-synthetic active ingredients, classified as new, generic and similar products
200/2017 [25]	Revokes resolution 60/2014
675/2022 [15]	Revokes resolution 134/2003, without adding any new information
753/2022 [26]	Revokes resolution 200/2017

Table 1.2 Resolutions from ANVISA related to post-approval of generic and similar products in Brazil issued from 2002 until present

Resolution	Main characteristics
477/2002 [27]	Guide for making changes and additions to post-approval of medicines
893/2003 [28]	Revokes resolution 477/2002 and includes information on notifications for temporary suspension of manufacturing and cancellation of registration
48/2009 [29]	Revokes resolution 893/2003 and provides information about the request to resume manufacturing of an already registered product
73/2016 [30]	Revokes resolution 48/2009 having undergone some modifications. The last change was published in RDC 851/2024 without revoking RDC 73/2016

Table 1.3 Resolutions from ANVISA related to the study of pharmaceutical equivalence and dissolution profiles issued from 2002 until present

Resolution	Main characteristics
476/2002 [31]	First guide for carrying out the study and preparing the pharmaceutical equivalence report. Generic medicines need to fully comply with the pharmacopoeial requirements of the individual monograph
483/2002 [32]	First guide to dissolution testing for immediate-release solid oral dosage forms (FFSOLI)
900/2003 [33]	Revokes resolution 476/2002
901/2003 [34]	Revokes resolution 483/2002
310/2004 [35]	Revokes resolutions 900 & 901/2003. Unification of equivalence guides and dissolution profile
31/2010 [36]	Revokes resolution 310/2004 having undergone some modifications

Table 1.4 Resolutions from ANVISA related to the bioequivalence study issued from 2002 until present

Resolution	Main characteristics
479/2002 [37]	First guide for bioequivalence study protocols and technical report. Describes what must be presented in the bioequivalence study protocol and report but does not include details about the conduct of the study
484/2002 [38]	Guide for designs applicable to bioequivalence studies. First guide that describes the statistical design of bioequivalence studies
894/2003 [39]	Revokes resolution 479/2002, specifying only what must be included in the bioequivalence study protocol
895/2003 [40]	Specific guide for preparing a technical report for a bioavailability/bioequivalence study
896/2003 [41]	First guide to bioavailability/bioequivalence tests that describes the conduct of clinical and analytical parts of the bioequivalence study
898/2003 [42]	Revokes resolution 484/2002 detailing the statistical part of the bioequivalence study
397/2004 [43]	Revokes resolution 896/2003

(continued)

Table 1.4 (continued)

Resolution	Main characteristics
1170/2006 [44]	Revokes resolution 397/2004
742/2022 [11]	Revokes resolutions 898/2003 & 1170/2006 unifying information on the conduct of clinical, analytical, and statistical stages. It now requires the determination of partial AUC for extended-release formulations that are intended to be interchangeable and determines the need to carry out a pharmacodynamic blanching study for semi-solid formulations containing topical corticosteroids. For highly variable medicines, criteria are presented that make it possible to expand the acceptance range. For the first time, transdermal medicines are mentioned in regulations regarding bioequivalence, as well as medicines with a low therapeutic index
Resolutions on validation of bioanalytical methodology	
475/2002 [45]	Guide to Validating Analytical Methods which describes some bioanalytical validation requirements
899/2003 [46]	Revokes resolution 475/2002 and provides further details on bioanalytical validation
27/2012 [47]	Revokes resolution 899/2003 dealing only with bioanalytical validation
Resolutions related to biowaivers	
481/2002 [48]	First guide about biowaivers, waiving some dosage forms and lower dosages
897/2003 [49]	Revokes resolution 481/2002
37/2011 [50]	Revokes resolution 897/2003 and specifies that the study must be carried out with the highest or lowest dosage depending on the linearity of the drug's pharmacokinetics. Biowaiver based on the biopharmaceutical classification system (BCS) is now considered.
749/2022 [51]	Revokes resolution 37/2011—semi-solid dermatological formulations containing corticosteroids are no longer eligible for a biowaiver. There is now a need for formulations to be at least Q1 and Q2 similar in order to be eligible for a biowaiver. The biowaiver is based on the BCS and can now be applied to class III drugs

2.2 Bioavailability

Bioavailability is the rate and the extent of absorption of a drug product in a dosage form, based on its concentration/time curve in the systemic circulation or its excretion in urine, based on peak and extent (total or partial) of drug exposures. This definition was updated by Resolution RDC 742 from 08/17/2022 [11].

2.3 Pharmaceutical Equivalency

Pharmaceutical equivalents are drug products that contain the same drug substance, in the same salt form or free base, in the same amount, in the same type of dosage form, with or without the same excipients. These products should comply with the

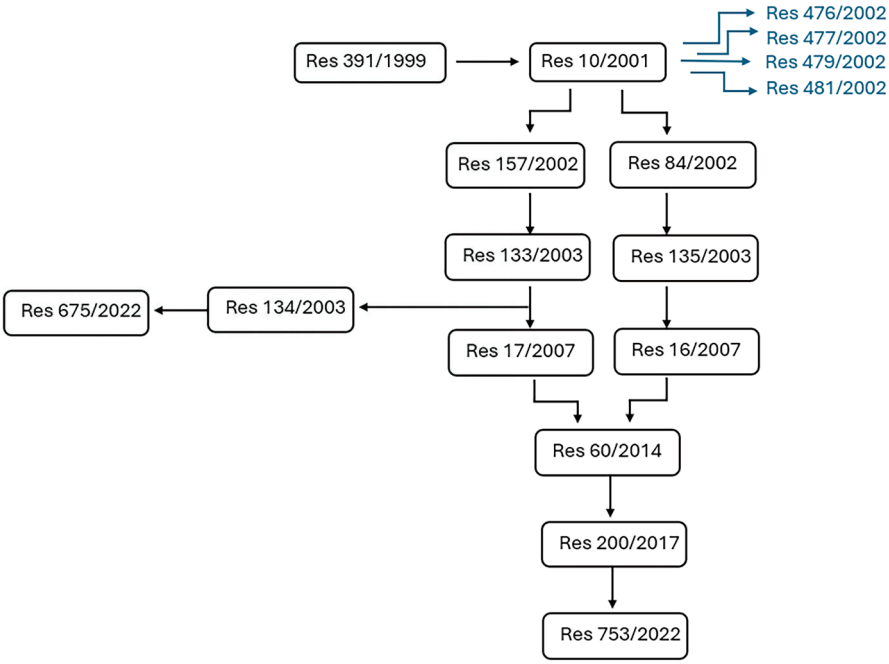

Fig. 1.1 Timeline of resolutions related to the registration of generic and similar products in Brazil

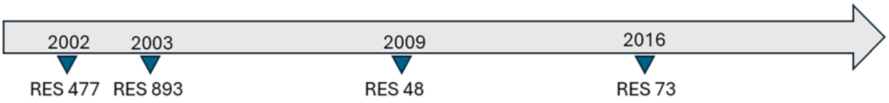

Fig. 1.2 Timeline of resolutions related to the post-approval of medicines in Brazil

corresponding monograph in the Brazilian Pharmacopeia [12]. In the absence of a specific monograph in the Brazilian Pharmacopeia, they should comply with the monograph in any other compendia accepted by the Brazilian health authorities, or with any other applicable quality standard. These quality standards include identity, strength, purity, potency, uniformity, disintegration, and dissolution, among others.

2.4 Similar Drug Product

A similar drug product contains the same active ingredient(s), with the same label claim, same dosage form, same route of administration, dosing, and therapeutic indication, and is equivalent to the drug product registered with the regulatory agency. It can differ in characteristics such as size and shape of the dosage form, shelf life, packaging, labeling, excipients. It needs to be identified by a brand name [13].

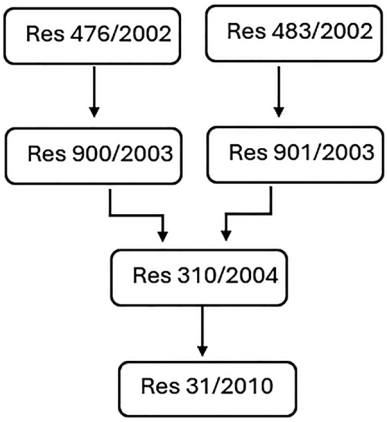

Fig. 1.3 Timeline of resolutions related to the study of pharmaceutical equivalence and dissolution profiles

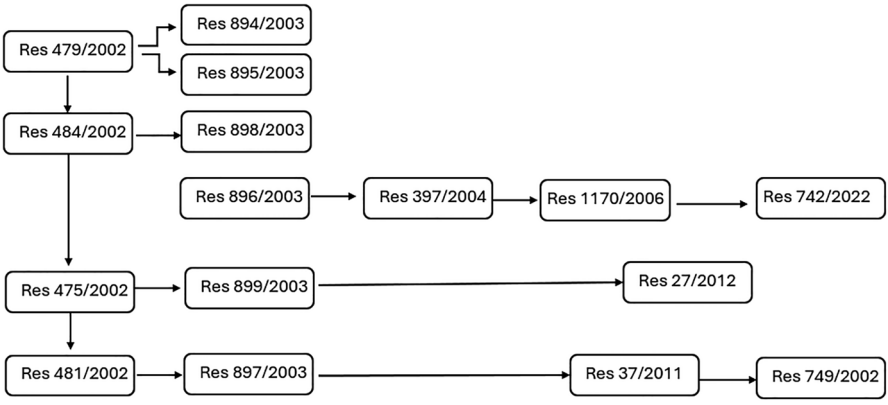

Fig. 1.4 Timeline of resolutions related to the bioequivalence study

2.5 Bioequivalence

According to the Law 9.787 (February 10, 1999) [8], bioequivalence is the demonstration of pharmaceutical equivalency between two products in the same pharmaceutical dosage form, with identical qualitative and quantitative amount of active substance(s), and that show comparable bioavailability when evaluated using the same study design. This definition was ratified by Resolution RDC 742 from 08/17/2022 [11].

Considering the successful experience of the implementation of technical regulations for generic drug products, ANVISA published RDC Resolution 134 (29 May 2003), current RDC 675/2022, to adjust the registration of similar drugs—not innovative drug products registered in Brazil according to different criteria from those required for the registration of generic drug products adopted in 1999 [14, 15].

According to RDC Resolution 675/2022 [15], pharmaceutical companies manufacturing similar drug products containing the active ingredients listed in Table 1.5 (drugs of high health risk), alone or in association, in any dosage form and containing any isomers, had until December 1, 2004, to present results of studies of relative bioavailability, employing the same acceptance criteria for bioequivalence previously established for the registration of generic drug products.

Other similar drugs already registered were also classified according to the criteria of health risk, namely:

- Medium health risk (antibiotics, antiretrovirals and antineoplastics)—Requirement to present results of *in vivo* relative bioavailability studies (adopting BE criteria) in the first registration renewal, after June 2, 2003 (at that time ANVISA required renewal of the registration every 5 years).
- Low health risk—Requirement to present results of *in vivo* relative bioavailability studies (adopting BE criteria) in the second registration renewal, after June 2, 2003.

According to the schedule established by ANVISA, all similar drug products registered in Brazil should meet the pharmaceutical and bioequivalence criteria required for generic drug products by 2014. Similar drug products have a brand name while generic drugs have a generic name of the active ingredient without the brand name [58]. RDC 58/2014 established interchangeability criteria for similar drug products. This guideline provided a list of interchangeable similar drug products indicating that the medicines were approved with the presentation of proof of therapeutic equivalence (bioequivalence studies). Also, all interchangeable similar drugs products required the following disclaimer in their package insert, "SIMILAR DRUG EQUIVALENT TO THE REFERENCE DRUG" [59]. At that time all similar products had already undergone adaptation although in Brazil, there are still similar non-interchangeable drug products that were unable to prove their therapeutic equivalence due to the absence of a reference product on the market [60].

3 Bioequivalence Studies in Brazil

According to the RDC 620/2022, all bioequivalence (BE) studies submitted to ANVISA to support the registration of generic or similar drug products must be conducted by a certified Contract Research Organization (CRO) (Tables 1.5 and 1.6 and Fig. 1.5) [56]. Such certification should be considered as an *a priori* step in the regulatory process, since the CRO must comply with Good Clinical and Laboratory Practices (GCP and GLP) before enrolling healthy volunteers in BE studies as well as analyzing biological samples. This resolution allowed the temporary and emergency use, by ANVISA, of remote online inspection, for the purpose of verifying compliance with the requirements for certification, secondary certification, and post-certification modifications of the CRO that intends to carry out bioequivalence studies. If the CRO complies with all mandatory requirements, a certificate is issued, and it is valid for 2 years. Besides publishing the certification in the Brazilian

Table 1.5 Marketed drugs of high health risk required to present bioequivalence studies by December 1, 2004 [15]

Drug substance	Dosage form	Reference product/manufacturer
Aminophylline	Tablets	Aminofilina®—Novartis
Carbamazepine	Tablets and oral suspension	Tegretol®—Novartis
Clonidine	Tablets	Atensina®—Boehringer Ingelheim
Clozapine	Tablets	Leponex®—Novartis
Clindamycin	Capsules	Dalacin C®—Pharmacia Brasil
Cyclosporine	Capsules	Sandimun®—Novartis
Digoxin	Tablets	Digoxina®—Glaxo Wellcome
Disopyramide	Tablets	Dicorantil®—Aventis
Isotretinoin	Capsules	Roacutan®—Roche
Lithium	Tablets	Carbolítium®—Eurofarma
Minoxidil	Tablets	Loniten®—Pharmacia Brasil
Oxcarbazepine	Tablets and oral suspension	Trileptal®—Novartis
Phenytoin	Tablets, capsules, and oral suspension	Hidantal®—Aventis
Prazosin	Capsules	Minipress®—Pfizer
Primidone	Tablets and oral suspension	Epidona®—Wyeth Whitehall
Valproic acid	Capsules and oral solution	Depakene®—Abbott

Table 1.6 Resolutions from ANVISA related to authorization of pharmaceutical equivalence and bioequivalence CROs issued from 2000 until present

Resolution	Main characteristics
41/2000 [52]	Defines criteria for companies intending to register with ANVISA to be qualified to carry out pharmaceutical equivalence, bioavailability and/or bioequivalence tests
103/2003 [53]	Defines bioavailability/ bioequivalence CROs as institutions that carry out at least one of the bioequivalence study stages: clinical, analytical, or statistical
56/2014 [54]	Revokes resolution 103/2003 regarding certification of bioequivalence CROs and defines which Bioavailability/Bioequivalence studies must be carried out
67/2016 [55]	Partially revokes resolution 41/2000 relating to article 4 and its §§ 1 and 2 and article 7. Makes provision for petitions requesting qualification, renewal of qualification, post-qualification modifications, testing outsourcing, suspensions and cancellations of CROs carrying out pharmaceutical equivalence studies
620/2022 [56]	Revokes resolution 56/2014 regarding certification of bioequivalence CROs
621/2022 [57]	Revokes resolutions 67/2016 and 518/2021. Makes provision for petitions requesting qualification, renewal of qualification, post-qualification modifications, testing outsourcing, suspensions, and cancellations of CROs carrying out pharmaceutical equivalence studies

Official Journal (DOU, acronym in Portuguese), all certified CROs are listed on the ANVISA website (www.gov.br/anvisa). The CRO inspection checklist is established by Normative Instruction—IN No. 123, of March 24, 2022 [61].

Currently there are 12 certified CROs within the Brazilian jurisdiction and 43 certified CROs overseas (27 from India).

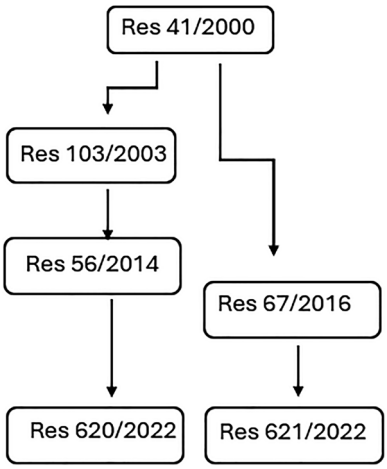

Fig. 1.5 Timeline of resolutions related to authorization of pharmaceutical equivalence and bioequivalence CROs

In 2016, ANVISA, together with Brazilian researchers, initiated a series of discussions regarding the need to conduct bioequivalence studies of topical drugs products [62]. At that time bioequivalence studies were not required for topical generic products intended for local action according to RDC 37/2011 [50]. Whereas many regulatory agencies required the evaluation of therapeutic equivalence for such products, ANVISA strongly relied on *in vitro* data for the approval of topical generic products intended for local action.

Accordingly, the pharmacodynamic study using the vasoconstrictor assay for topical corticosteroid products was the first bioequivalence test implemented in Brazil for the evaluation of topical products, according to RDC 742/2022 [11]. This followed the vasoconstriction guidance as outlined in the FDA Guidance for Industry published in 1995 [63].

The main regulatory requirements for conducting BE studies are stated in Resolution RDC 742/22, which was the latest update of the Brazilian BE guideline. The main points of this guideline are described below [11].

3.1 Dose Difference Between Test (T) and Reference (R) Drug Products

Only differences of up to 5% are acceptable to avoid having a dose difference biasing the results of BE studies. For instance, in cases of T/R ratio of the pharmacokinetic parameters (C_{max} or AUC_{0-t}) higher than 1.0, using an R whose drug content is higher than 5% of the T could bias the calculated 90% confidence interval (IC 90%) to fall within the current BE criteria, even though both products are not bioequivalent on a molar basis.

3.2 Ethics

As a BE study is a particular type of clinical study, it must be approved by an independent ethics committee (IEC). In Brazil there is a federal body named Brazilian National Ethics Commission (CONEP, acronym in Portuguese) responsible for authorizing the operation of local IEC. Brazilian CROs must get approval of study protocols as well as informed consent form from the IEC prior to beginning a BE study.

3.3 Subjects

The main goal of a BE study is to detect differences, if there are any, between *in vivo* dissolution and absorption of T and R drug products. Variability not related to pharmaceutical issues, such as natural history of disease, should be mitigated since it could bias the conclusion of the BE study. Under this assumption, the most suitable model is using healthy volunteers, unless there are ethical concerns involved (*e.g.* cytotoxic drugs).

If the drug substance of interest is indicated to a specific group (gender or age-related), only volunteers representing such populations should be enrolled. One example is BE studies for a drug product containing letrozole, for which only post-menopausal women should be recruited.

The latest version of the Brazilian BE guideline discusses the feasibility of phenotyping and/or genotyping of subjects. Such practices may be acceptable, in the case of parallel study designs, to mitigate the risks of having group-formulation interaction biasing the BE conclusion. Furthermore, genotyping and phenotyping subjects may be required to mitigate safety concerns related to the drug.

The number of subjects enrolled in a BE study should be calculated based on the within-variability of the drug, the expected difference between T and R formulations and the *a priori* statistical power (normally 80%). A more detailed explanation about the sample size estimation can be found in Section II of Chapter VI of RDC 742/2022 [11]. To determine the number of participants in a BD/BE study, one must consider:

I. the estimated intra-individual coefficient of variation based on a pilot study, previous studies, or scientific literature.
II. the desired level of significance (5%).
III. the desired statistical power of at least 80%.
IV. the average deviation of the comparator product compatible with bioequivalence and with safety and efficacy.
V. the need for the 90% confidence interval of the geometric mean ratio to be within the bioequivalence limits, normally 80.00–125.00%, for log transformed data.

No less than 12 volunteers should be used. In the case of highly variable drugs, section III of Chapter VI of RDC 742/2022, deals with the possibility of expanding the acceptance range. The extent of the expansion should be defined based on the intra-individual variability of the comparator drug where the maximum accepted range is 69.84–143.19%.

3.4 Fed Versus Fasting Study

In general, BE studies for immediate release formulations should be conducted under fasting conditions, unless the drug pharmacokinetics are significantly affected by food and the product label restrains its intake under fed conditions. Normally, if a drug can be taken with or without food, a potential food effect is highly unlikely to be found clinically relevant and the study should be conducted on an empty stomach. If the product label establishes that the drug can be administered with or without food and the drug pharmacokinetics are significantly affected by food, two BE studies should be performed under fasting and fed conditions. Before starting a BE study, sponsors as well as principal investigators of the CRO are encouraged to visit List 1 (fasting vs. fed conditions), available on the ANVISA website [64] containing information whether the tested drug product should be administered under fed or fasting conditions.

Prolonged-release dosage forms must be evaluated under both fed and fasted states in order to identify potential formulation-specific food effects.

For delayed-release oral pharmaceutical forms with gastro-resistant coating, a study must be conducted while fasting or with food, as described in the label of the comparator medication.

3.5 Partial AUC Assessment

Regarding the evaluation of prolonged release formulations, the recommendations of the European and American agencies (EMA and FDA) are different. Whereas the EMA requires multiple-dose bioequivalence studies, the FDA has no specific requirement [65].

To publish RDC 742/2022, ANVISA carried out a survey of the studies submitted to the agency to investigate whether the evaluation of the partial AUC could detect differences between two prolonged-release formulations that have demonstrated bioequivalence by the usual metrics (AUC_{0-t} and C_{max}).

Twenty-four studies in a total of 117, which were already approved by ANVISA considering the usual metrics in the last 14 years, failed to demonstrate bioequivalence for partial AUC, which is related to 33.9% of evaluated prolonged release products. The results demonstrate that the usual metrics for assessing the bioequivalence of some prolonged-release formulations were insufficient and that the