

## GENERIC MEDICINES REGULATION IN BRAZIL

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### REVIEW ARTICLE

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#### ABSTRACT

The regulation of medicines in Brazil has proven to be one of the major concerns of government policies in recent decades. In order to improve access to quality medicines for the population, the National Drug Policy was instituted, culminating in the creation of the National Health Surveillance Agency (ANVISA) and the implementation of generic medicines policy.

The generic medicines was effectively introduced in Brazil with the publication of the Law n° 9.787 in 1999, resulting from an objective of the Ministry of Health to significantly reduce the costs of pharmacological therapy, stimulate commercial competition and facilitate the population's access to drug treatment. In the same year the resolution n° 391/1999 regarding the technical requirements for the registration of generics in Brazil was published. Since 1999, several legislation has been published in order to regulate the generic policy in Brazil.

The present article summarises the legal framework for the implementation of the generic medicines in Brazil. It also describes the current technical requirements and legislation for the registration and maintenance of the register of generics in Brazil, according to ANVISA.

**Keywords:** Generic drugs, Legislation, ANVISA, Registration, Technical requirements, Dossier.

#### INTRODUCTION

In 1999 the regulation of medicines in Brazil began to undergo significant transformations. The National Sanitary Surveillance System (SNVS) and the National Health Surveillance Agency (ANVISA) were created through the Law n°9.782/1999, which incorporated the competencies of the former Secretariat of Sanitary Surveillance of the Ministry of Health (1, 2).

The process of discussion about generic drugs began in the 70's, resulting in the publication of Decree n° 793 in 1993, revoked by the Decree n°3.181/1999, which regulated the Law n°9.787/1999 responsible for the introduction of the generic medicines in Brazil. The resolution of the collegiate board of directors of ANVISA (RDC) n° 391/1999, established the first technical regulation for the registration of generics in Brazil (3-6).

Both the enactment of the generic law and the creation of ANVISA represented a significant change in government policy for the segment

and caused a great impact on the structure of the Brazilian pharmaceutical market (7).

The policy of generics in Brazil was created, due to an objective of the Ministry of Health to significantly reduce the costs of pharmacological therapy, stimulate commercial competition and facilitate the population's access to affordable drug treatment. In addition, the creation of a generic medicines policy also intended to provide the Brazilian market with medicines of assured quality, due to their interchangeability with the reference drug which, in general, corresponds to the innovative drug registered after proving its efficacy and safety (2, 8).

The period between Decree n° 793/1993 and Law n°9.787/1999 was characterized by the existence in the Brazilian market of numerous medicines similar to the reference drug, commercialized by different Laboratories without evidence of therapeutic equivalence. In this period, it was allowed to register different pharmaceutical forms and dosages of the so called reference drug, and cases of different

formulations occurred, resulting in registration of many drugs that differed from the reference drug in relation to the base, salt or ester of the drug (3, 5, 9).

The technical regulation of the Law of Generics through RDC n°391/1999 introduced concepts never before used to register a drug in Brazil: pharmaceutical equivalence (proven by in vitro tests) and Bioequivalence (proven by in vivo assays). Thus, the Law of Generics established a new standard for the development and registration of medicines in the country (6, 8, 9).

In the year 2000, the first registrations of generic medicines occurred. In that year, 182 generic drug registries were granted and actions were taken to implement the production of these drugs in Brazil. From the year 2000 to March 2017, 4831 generic drugs were registered in Brazil. Of these, 1018 records were canceled, leaving 3813 generic medicines with valid records (10).

## GENERIC MEDICINE – GENERAL CONCEPTS

According to Law n° 9.787/99, the generic implies a pharmaceutical drug similar to a **reference or innovative medicine**, intended to be **interchangeable** and usually produced after the expiration of the patent protection or other exclusive rights of the innovative drug. It is equivalent to a reference product in dosage, strength, route of administration, quality, performance and intended use. The generic must have proven its **effectiveness, safety and quality** and it is designated by the Common Brazilian Denomination - **DCB** or, in its absence, by the International Common Denomination (**INN**), being marketed under its chemical name without advertising" (5, 11).

The innovative drug, is the first product registered and holder of the patent usually indicated as reference medicine, except in cases where there is no availability in the local trade. In this case, ANVISA indicates as reference another product with guaranteed effectiveness. The reference product is conceptualized as an innovative product registered in the federal agency and commercialized in the country, whose bioavailability was determined during

product development and the effectiveness, safety and quality were scientifically proven, on occasion of the registration of the medicine (5, 11).

The generic is usually produced after the expiration or waiver of a patent protection, but it is worth mentioning the possibility of generic production even during patent protection through compulsory licensing, which guarantees the supply of essential products to the market in extreme cases (12, 13).

An interchangeable pharmaceutical product is understood to be the therapeutic equivalent of a reference medicine, having essentially the same efficacy effects and the same potential for adverse effects. Thus, interchangeability is the safe replacement of the reference drug by its generic, which is ensured by therapeutic equivalence, pharmaceutical equivalence and bioequivalence tests (4, 5).

The pharmaceutical equivalence doesn't necessarily result in therapeutic equivalence, since differences in excipients and/or in the manufacturing process may lead to differences in product performance. In addition, they will be bioequivalent if they are pharmaceutically equivalent and if their bioavailabilities are similar to such a degree that their effects are essentially the same when studied under the same experimental design (11, 14, 15).

## GENERIC MEDICINES IN BRAZIL

### Legal Framework

Legally, the implementation of generics in the Brazil has gone through fundamental milestones:

- Decree n° 793/1993: It disposed of the obligatory use of the generic name (DCB) of the active ingredient in the packaging of the medicines besides the commercial name or the registered trademark (3);

- Law n° 9.279/1996: Regulation of rights and obligations relative to the industrial property. The country has created a favorable environment for the development of a regulatory policy based on internationally recognized

scientific and technical criteria for generic medicines (12);

- Ordinance n° 3.916/1998: Institution of the National Medicines Policy (PNM), whose purpose was "to guarantee the need for safety, efficacy and quality of medicines, promotion of their rational use and access of the population to those considered essential." The generic drug was inserted in the National Medicines Policy, through Guidelines of the Rational Use of Medicines (16);

- Law n° 9787/1999: Established the legal basis for the implementation of generic medicines in Brazil, in order to guarantee the principles of safety, efficacy, quality and interchangeability. Numerous actions were taken by the Ministry of Health and ANVISA to meet this guideline of Rational Use of Medication and to increase the population's access to effective, safe and quality medicines at reduced prices (5, 8, 9).

With the Generics Act, the Law n°6.360/1976 was amended and the legal basis for the establishment of the generic drug in Brazil was created, determining a 90-day deadline for ANVISA to regulate the technical criteria for its registration. Forcing the Agency to create a technical group of Brazilian specialists in the areas of Pharmaceutical, Quality Control and Pharmacology, with the objective of elaborating the technical regulation for the registration of generic medicines. Subsequently, technical regulations were developed in the form of resolutions, which corresponded to an important process for the evolution of generic medicines in the country (5, 17).

### Technical regulations

The technical regulation of Law n° 9.787 occurred through RDC n° 391/99, which established the requirements for the registration of generic medicines in Brazil, based on the standards adopted by countries such as USA, Canada and the European Community (8).

RDC n° 391/99 presented conditions and criteria for registration and quality control of generic drugs, bioavailability tests of drugs in general, bioequivalence tests of generic drugs, prescription of generic drugs. There were also

several technical guides in attachment to the resolution. These guidelines included: criteria for carrying out a stability study, description of protocol and technical reports of relative bioavailability/bioequivalence studies, validation of analytical methods, and model of pharmaceutical equivalence studies and exemption of bioequivalence studies. The first list of reference medicines was also incorporated in this Resolution (6).

Approximately one year after this resolution was introduced, there appeared to be the need for a revision, and on January 2, 2001, the RDC n° 10 was published. It maintained the same pattern adopted by RDC 391, but with more detail. Also a new concept was introduced regarding the conditions and criteria for registration and quality control. This legislation was subdivided into: Part 1 - pre-submission, Part 2 - submission and Part 3 - post-registration (18).

RDCn°10/2001 was revoked by RDC n°84/2002, which adopted a different format in relation to the previous legislation, being subdivided into: measures prior to registration, registration, and post-registration. It included the list of drugs not accepted as generic and excluded the technical guides previously listed as an attachment to the technical resolution. The technical guides were published as individual documents (19).

RDC n° 84/2002 was revoked by the RDC n°135/2003, which followed the same format as the previous legislation, but containing further details regarding the technical requirements for registration of generic drugs. Information was included regarding the possibility of presenting results of stability studies of the highest concentration formulation for formulations with three or more different concentrations of the same drug; long-term stability studies for medicinal products with a shelf-life exceeding 24 months and the possibility of registration for coated tablets whose reference medicinal product was a single tablet or vice versa. (20).

RDC n° 16 of 2007 revoked RDC n° 135/2003. One of its inclusions was the permission for oral contraceptives and oral endogenous hormones to be registered as

generic drug. In addition, antiemetic, antithermic, antipyretic, topical antibacterial, antihemorrhoidal and topical nasal decongestant were added to the list of drugs that could not be accepted as generic. There have also been modifications and updates to the required documentation for the registration of the generic drugs (21).

RDCn<sup>o</sup>60 was published on 13th of October, 2014. The new law harmonized and updated the requirements and documentation needed for the registration of new, generic and similar drug categories into a single Resolution, replacing the former RDCs 136/2003, 16/2007 and 17/2007 respectively. Resolution 60/2014, became valid on January 11 of 2015, and it is the currently legislation used to register and renew the registration of pharmaceutical drugs with synthetic and semi-synthetic active ingredients, classified as new, generic, and similar in Brazil (21).

This resolution also updated and restructured the technical reporting requirements according to the Common Technical Document (CTD) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The restructuring of the dossier was carried out in order to harmonize the information submitted to regulatory authorities for the evaluation of quality, safety and efficacy related to drug registration (22).

### Previous step to registration

Since 2001, the registration of generic drugs has included a phase prior to registration, which means that the drug must first be developed to then be registered. According to the RDC 60/14 the first step is to identify the reference drug, for that the registrant should consult the list of reference medicines available on the ANVISA portal to check if there is a reference drug in the concentration and pharmaceutical form for the product to be registered. In the absence of a reference drug, a request for the selection of a reference drug must be sent to ANVISA, in accordance with RDC 35/2012 (11, 23).

The second stage involves developing the product, producing pilot lots, validating the

production and its quality control. Subsequently, in vivo and in vitro tests should be performed in order to prove the pharmaceutical equivalence of the test drugs with the reference drug, using validated analytical and bioanalytical methods (11, 22).

Following the conclusion of the initial stages, a dossier for the drug should be prepared with all the technical and administrative information required by current legislation in order to request the registration of the drug by ANVISA.

### Registration

In order to register generic medicines in Brazil and, therefore, to obtain the right to commercialize those medicines in the country, it is necessary to present a complete dossier including administrative and technical documentation to ANVISA (11, 22).

The administrative documentation must include information such as the certificate of good manufacturing practices (CBPF) granted by ANVISA, while the technical dossier must include information related to production process, quality control and equivalence/bioequivalence tests (11, 24).

The Technical Dossier should include the following items:

#### - Active Pharmaceutical Ingredient:

The first item in the technical part of the Dossier disposes of the active pharmaceutical ingredient, in which the provisions of RDC n<sup>o</sup> 57/09, RDC n<sup>o</sup>45/2012 and RDC n<sup>o</sup>166/17 should be evaluated in addition to that required in RDC 60/14. RDC n<sup>o</sup>57/09 stipulates which active pharmaceutical ingredient must be registered separately in ANVISA, RDC n<sup>o</sup>45/2012 details the stability study and RDC n<sup>o</sup>166/17 on validation of analytical method. The main document submitted in this item corresponds to the complete and updated Drug Master File. (11, 25, 26-28).

#### - Quality Control Report of the active pharmaceutical ingredient (API), excipients and packaging material:

Subsequently, information should be sent regarding the quality control of the active



pharmaceutical ingredient (API), excipients and packaging material, carried out by the manufacturer of the medicine. The origin of the excipients should be verified and justified as described in RDC n° 305/02 regarding the transmissible spongiform encephalopathy. Specifications and methods of analysis according to Brazilian pharmacopoeia, or pharmacopoeia recognized by ANVISA (RDC n° 37/09), should be adopted. If there is no pharmacopoeial monograph, the method should be developed internally (11, 29, 30).

Regarding the API, the development method must be totally validated and when the pharmacopoeial method has been used, it must be partially validated, according to RDC n° 166/2017. The chosen analytical procedure must be justified in relation to the tests and specifications adopted, references used and divergences in relation to the analytical procedure used by the manufacturer of the API (11, 28).

- Technical report of the formulation:

For this item a technical report of the development of the formulation should be sent, informing the quantitative/qualitative composition of the medicine, justification about the inputs used, function of each component of the formula and compatibility between them. The report shall also include assessment of the compatibility between the primary packaging and the product, the development report of the dissolution method (RDC n°31/2010) and degradation profile study (RDC n°53/15) (11, 22, 31, 32).

- Dossier of Manufacture:

The main documents of the manufacturing dossier are batch production of the pilots (Normative instruction n° 2/2009) and the flowchart/production report containing the description of the production process. Bound to the manufacturing dossier, should be the process validation performed, including a summary of the critical stages of the process, challenge test and justification regarding the process control used. (11, 33).

- Quality Control Report of the Finished Product  
In this item, the quality control report of the finished product carried out by the manufacturer

of the medicine must be sent. The same assumptions used for the API regarding the RDC n° 37/09 and RDC n° 166/07 must be evaluated for the quality control report of the finished product. The finished product should be evaluated for the dissolution profile and degradation profile study made by the manufacturer of the medicine, the RDC n°31/2010 and RDC n° 53/15 respectively (11, 28, 30-32).

- Stability and Photostability Study

In order to create the stability and photostability study, it is necessary to evaluate the requirements stipulated by the Resolution n° 01/2005 and the guide of photostability published by ANVISA in 2005. For multi-dose packaging it is also necessary to send the in use stability study and for reconstituted pharmaceutical forms, it's necessary to send stability after reconstitution. (11, 34).

- Therapeutic equivalence (11, 25, 31, 35, 36).

Therapeutic equivalence is composed by Pharmaceutical Equivalence (in vitro test) and Bioequivalence (in vivo test) (11, 25).

The equivalence study must be carried out according to RDC n°31/2010 which describes the realization of Pharmaceutical Equivalence test and Comparative Dissolution Profile Studies (11, 31).

In order to evaluate the possibility of exemption from the bioequivalence test, RDC n° 37/2011 must be evaluated, which contains the guide for exemption and replacement of relative bioavailability/bioequivalence studies. If the generic product is not bio-exempted, the bioequivalence test should be carried out according to Resolution n° 1170/2006, which contains the guide for relative bioavailability/bioequivalence test of medicines (11, 35, 36).

All Equivalence tests and Bioequivalence studies should be performed in laboratories of the Brazilian Network of Analytical Laboratories in Health (REBLAS) authorized by ANVISA. (11, 25).

- Packaging material

Labeling shall follow the provisions of RDC n° 71/09 and the package leaflet shall follow the provisions of RDC n° 47/09 (11, 37, 38).

During the analysis of the dossier, the vast majority of generic registration processes are subject to technical requirements from ANVISA, in order to minimize the possible health risks in the manufacturing process of the drug. After the issuance of the technical requirements, the company has 120 days to present the necessary adjustments in the registration dossier. Once the fulfillment of the requirement is presented, the process follows its normal course of analysis, and it may be deferred or rejected after a technical analysis of the sector responsible for the registration. (8, 9, 39).

Upon completion of the technical review, the generic drug registration dossier is forwarded for publication in the Official Diary of The Union (DOU) with deferred or denied status. The companies whose cases were rejected can appeal against the decision in accordance with RDC n° 25/2008 (Brazil, 2008a). Registration is valid for five years, throughout the national territory of Brazil. The term is counted from the date of publication of the registration in DOU (11, 40, 41).

### **Post Registration and Renewal of Registration**

After the publication in DOU of the registration concession, the product is authorized to be marketed throughout the national territory. The registration of the generic medicine is valid for 5 years and must be renewed in the first half of the last year of the five-year period of validity of the registration. It is necessary that the marketed product correspond to the registered process, and any post-registration changes must be made according to the provisions of RDC n° 73/2016 (11, 42).

After registration of the drug, it is necessary to inform the market price of the drug to the Technical Chamber of Medicines in ANVISA (CMED). The CMED was created by Law n°10.742/2003, which aims to give an opinion on taxation and ensure the protection of the interests of consumers, establishing criteria for

fixing and adjusting prices of the pharmaceutical drugs (43).

In addition to RDC n°60/14, specific technical documentation that must be followed to maintain the registration of a generic drug in Brazil. Among the most important, to mention are: RDC n°25/2007 that describes the outsourcing of the stages of production and quality control; RDC n°4/2009 covering pharmacovigilance; RDC n°55/2005, which deals with the collection of medicines and RDC n°96/2008, which regulates drug advertising (44-47).

### **CONCLUSION**

The creation of ANVISA by Law 9,782/1999 and the establishment of generic medicines in Brazil through Law 9.787/1999 represented a new milestone for the country's health policy.

The institution of the generic policy was mainly aimed at reducing the costs of pharmacological therapy and facilitating the population's access to drug treatment by making available in the Brazilian market medicines of assured quality, in view of their interchangeability with the reference drug.

The Law of Generics introduced concepts never before used to register a drug in Brazil as: pharmaceutical equivalent and interchangeable drug. Requirements such as pharmaceutical equivalence and bioequivalence tests are now required to prove the safety and efficacy of certain drugs, setting a new standard for the development and registration of medicines.

Since the implantation of generics, continuous norms have been published and edited, either to establish new technical regulations or to equalize the demands that arise within society, aiming to establish adequate criteria and parameters to regulate generic medicines in Brazil.

Currently, the Brazilian legislation on generic drugs is very detailed and robust, having as guidelines regulations adopted by countries such as the United States, Canada and the European Community. It is possible to infer that the rules for registration and maintenance of the current

registry of generic medicines in Brazil include necessary studies for the guarantee of safe, effective and quality of these medicines.

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## CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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