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Chapter 9 : Regulating the copy drug market in Brazil : Testing Generics and Similar Medicines (1999 to 2015)

Marilena Correa, Maurice Cassier, Maria Andrea Loyola

Introduction

Biomedical innovation – as understood and discussed in the introduction and chapters of this book – involves developing and accumulating expertise and technologies, as well as regulatory policymaking to delimit the definition and status (quality, uses etc.) of these innovative goods and products.

This chapter considers how the new drug regulation process was constructed in Brazil, from its origins in the enactment of the Generics Law and the creation of the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA), both in the same year of 1999. The Generics Law – Law 9.787 of 10 February 1999 – was designed to bring quality to the Brazilian copies market, until then dominated by what were known as similar medicines, which proliferated alongside the brand-name drugs. At the time, the Ministry of Health secretariat responsible for authorising pharmaceutical products to enter the market did not require similar to undergo bioequivalence trials in order to grant registration. They were registered for similarity based on their active principle and dosage in relation to the reference medicine. That secretariat, set up in 1976 by Law 6360 and operating as part of the Ministry of Health bureaucracy, was known for the laxity of its rulings and its poor capacity to oversee registration processes. The requirement that, from 1999 onwards, certification of Brazilian copies would entail further tests and trials for them to be doomed as generics not only responded to health needs (access to safe, efficacious, quality medicines), but was to reinforce local capacity-building and capabilities in expertise and technologies, which would in turn benefit pharmaceutical innovation in Brazil.

In a concerted effort and a short space of time, a proliferation of legal texts (regulatory resolutions, decree-laws) laid down new rules, parameters and specifications for registering medicines and authorising their sale in Brazil. A regulatory process of this scope depended on setting up a robust, independent, new regulatory agency, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA¹), which was instituted by Law 9.782 of 1999.

ANVISA was to function as an independent agency, which meant its having administrative independence² and guaranteed tenure for its directors, but to perform functions closely connected with the powers of the Ministry of Health. It is the agency's responsibility to grant registration for therapeutic products and authorise their entry onto the market, to oversee the circulation and quality of these

¹ ANVISA is overseen by a collegiate directorate comprising five members with non-coincident three-year mandates. The members are reviewed by the Federal Senate before appointment and have tenure during their mandate. The chairman is appointed from among the five by decree by the President of the Republic. Decisions are taken in collegiate form, by simple majority.

² As an independent regulatory agency, it is also entitled to charge duties and levy fines, as well as other functions, such as customs activities at ports and airports, which render it revenue to supplement the budget funds allocated by the national treasury.

products (drugs, vaccines, diagnostic tests, cosmetics, foods, medical equipment and so on). The agency certifies bioequivalence-testing sites, industrial production lines for generics, and good manufacturing practices (GMPs), by granting, suspending or cancelling certification in periodical health audits of industrial facilities and testing sites. In addition, the agency oversees volunteers at each clinical stage of bioequivalence testing, maintains an anonymous, online register of potential participants in trials of Brazilian generic and similar medicines and enforces testing site compliance with good clinical practices (GCPs)³. The results of pharmaceutical and bio-equivalence testing of Brazilian generic and similar drugs must all be produced at ANVISA-certified sites.

A number of ANVISA managers and directors interviewed in our surveys⁴ repeated that they saw themselves, and governed their departments, as co-responsible, integral parts of Brazil's national public health system (SUS), which is inaccurate from an organisational standpoint, but reflects the spirit of the public policy pursued there. As we heard at interview from the general manager for generics: *'ANVISA is almost within the Unified Health System, under Law 8080 of the SUS [...]. It differs from the other regulatory agencies set up during reform of the State, such as Anatel [telecommunications] and Aneel [electricity]. They are all purely regulatory agencies, right? We have to have this concern, we contribute to an access policy; we have the public health outlook'*.

This comprehensive regulatory policy was introduced into the health sector by the efforts of the State in its political capacity for negotiation and intervention in the Brazilian drug market and the related industrial and laboratorial structures, an endeavour undertaken in the public interest. This chapter addresses that process and its public health impacts.

1) Copying medicines for public health

Since the mid-20th century, Brazilian pharmaceutical laboratories specialised in reverse engineering, copying and formulating medicinal products. For 51 years, medicinal products were not patentable⁵ in Brazil. In that period, strong growth in reverse engineering activities for local drug production permitted considerable local technological learning (as studied, in the case of antiretrovirals, by Cassier & Corrêa, 2003; 2007). Moreover, Brazilian laboratories were even encouraged to enter into copy programmes designed in a series of policies of pharmaceutical services, which have been renewed since the early 1970s. One example is the Medicines Centre (*Central de Medicamentos*, CEME), attached to the Presidency of the Republic, which supplied medicines to the public sector from 1971 onwards (Lucchesi, 1991).

³ <http://www.anvisa.gov.br/medicamentos/bioequivalencia/index.asp>

⁴ These were: "Local Knowledge, Market Construction and Globalization : two modes of Pharmaceutical Innovation in the Global South : Brazil and India" supported by the Agence Nationale de la Recherche (ANR), France, coordinated by Maurice Cassier and Laurent Pordié ; and "The new implications of the production of second-line ARVs in Brazil: Using the flexibilities of patent law to produce certified generic drugs » supported by the Agence Nationale de Recherches sur le Sida (ANRS), France, and coordinated by Maurice Cassier and Marilena C D V Corrêa.

⁵ In 1945, President Getúlio Vargas decreed pharmaceutical products excluded from patentability in Brazil. Once declared 'commons', it became legal to copy and produce drugs locally. That policy was designed to leverage two objectives at once: to encourage local production of essential drugs needed by Brazil's population and to foster the creation of a local industry, with a view to substituting imports of foreign products.

In the 1980s, the CEME's activities were still tied to those of the Technology Development Company (*Companhia de Desenvolvimento Tecnológico*, CODETEC⁶), which specialised in reproducing active pharmaceutical ingredients (APIs⁷) and raw materials. Sited in the area close to the University of Campinas where it was incubated, the CODETEC included researchers connected with the university and experts and technicians from multinational pharmaceutical corporations operating in Brazil. CODETEC provided custom-made industrial processes to Brazilian chemical and pharmaceuticals laboratories. Codetec reproduced the technology by reverse-engineering and then transferred the technology to its clients. Along with their other commercial targets, these laboratories filled orders from the public health sector and thus received government subsidies in those operations, from purchases of CODETEC technology through to local production of API and medicines.

Thus, even during the so-called 'lost decade' of the 1980s, a coordinated policy involving a four party association among University, API producer firms, Brazilian drug manufacturing laboratories and the State, pursuing a policy of subsidies for pharmaceuticals, led to growth in local drug production, mainly supplying medicinal products to the public sector.

Even with this favourable background, ANVISA's mission in pharmaceuticals – of ensuring that medicinal products were safe, efficacious and of good quality and of expanding access to them – was not fulfilled without tensions and conflicts. Until 1997, there were no restrictions on copying by reverse engineering of drug molecules and finished medicinal products. The non-proprietary status of pharmaceutical products (ingredients, raw materials, medicinal products and production processes) enabled Brazilian laboratories to develop whole copy-based programmes that fostered substantial technological learning, growth in local production of medicines and improved access as the domestic market was supplied with less costly products. However, reproduction by reverse engineering was to suffer the adverse effects of enactment of Brazil's new Industrial Property Law (IPL), Law 9.279 of 14 May 1996. This included pharmaceutical products and their production processes within the scope of patentable objects, thus bringing Brazil's IPL into harmony with TRIPS requirements and enabling the country to continue as a global player in international trade. From being a commons, which could not be appropriated exclusively by the various industries interested in producing them, as of 1997 medicinal products became the object of patents, generating proprietor-controlled monopolies and oligopolies (mostly multinational corporations) with strong impact on health product prices.

Moreover, assuring the quality of Brazilian generics, besides being of considerable importance for health reasons, became a sensitive issue in view also of conflicts connected with economic interests within the pharmaceutical industry itself. One argument that multinational corporations made widespread use of in their campaigns against Brazilian generics in the early 2000s was the supposed poor quality of those medicinal products. In order for copied (known as similar or 'generic') medicines

⁶ The CODETEC had its origins within the university as an incubated firm. This type of incentive to set up a new technology firm allows a 5-year grace period for it to become independent or incorporated into the university. Note that the CODETEC was first engaged in energy development and innovation processes, particularly in oil and fuel ethanol. Cf. CODETEC – *Companhia de Desenvolvimento Tecnológico* (re-edited by Rogério Cerqueira Leite) In: *Revista Brasileira de Inovação* Rio de Janeiro (RJ), 7(2), pp.483-489, July/December 2008. CODETEC.

⁷ Active pharmaceutical ingredient (API) or active ingredient or active principle (as it is known in Brazil) is a substance introduced into the formulation of a pharmaceutical form which, when administered to a patient, acts as an active ingredient. These substances can produce pharmacological activity or effects in diagnostic tests, cure, treatment or prevention of a disease, and can affect the structure and functioning of the organism. Meanwhile, the term 'raw material' describes intermediate products of synthesis and active or inactive substances employed in the manufacture of medicinal products.

to gain acceptance among the consumer population, prescribing doctors and distributor pharmacists, a veritable war was waged in public debate, particularly in the media, where stakeholders connected with the large multinational pharmaceutical industries were always afforded ample access to promote their interests⁸.

Efforts by the Brazilian State to regulate copying and rationalise the domestic market in medicinal products date from the 1970s, as indicated by attempts to legislate on the use of trade names for medicines (Loyola 2008). In 1992, then Minister of Health, J. Haddad, continued these endeavours by framing them into a bill requiring that medical prescriptions specify the generic name of the pharmacologically active ingredient (Loyola, 2010). The bill provided for the immediate application of these denominations in the public sector and then in all prescriptions issued anywhere in Brazil. Efforts to bring this bill to a vote were ultimately frustrated (Loyola, op. cit.).

Despite these setbacks, the Generics Law enacted in 1999, while José Serra was Minister of Health, unquestionably heralded a major intervention in the local market in medicinal products by broadening access with quality and imposing extensive regulation. Similar drug copies already known to users and prescribers by trade names (as alternatives to brand-name drugs with patents valid or lapsed in other countries) now coexisted with new generic copies. Without a shadow of a doubt, one of the strategic aims of the Brazilian drug regulation policy piloted by Minister Serra was to propose and introduce a new, strong, public 'brand': the 'G for generic' brand, as it became known. Tested as bioequivalent and certified as generics by the ANVISA, these new-version copies, the G-copies, gained technical and social acceptance from their State-authenticated status. The G-seal was stamped, according to ANVISA rules, on the outside packaging of qualifying products. Brazilian generics were prescribed and recognised under their 'Brazilian Common Denomination' (*Denominação Comum Brasileira*, DCB)⁹, and barred from applying for a trade name (unlike similar drugs, which had to be identified by a name, known in everyday language as their 'trade name'). Generics, meanwhile, carry the manufacturing laboratory's name on the outside packaging.

Regulation of generics also addressed the issue of pricing: in order to make them more accessible, the text of the 1999 law (which on this point continues unaltered) stipulated a reduction of the order of at least 35% as compared with the price of the corresponding reference drug.

Even given quite a large low-income population and the relatively inelastic nature of demand for medicines (and the needs created by disease and discomfort), people can be led to consume 'at any price'. Accordingly, the public G-brand was launched to confront and compete with multinationals' brand-name drugs by introducing a new, State-guaranteed version of the product at more accessible prices. In addition, 'bioequivalence' became synonymous with quality of the copy, an idea that began to gradually penetrate into everyday language and to circulate along with the products, together with other adjectives associated with generics, such as less expensive and better and guaranteed quality. As shown in Figure 1, savings from the use of generics (not counting similar copies) was exponential.

⁸ With regard to this 'war', see Loyola, M-A.; Guimarães, E. R. de B.; Villela, P. Medicamentos e patentes na ordem do dia: mídia e 'a guerra de patentes'. In Corrêa & Cassier (eds.) *Aids e Saúde Pública: contribuições à reflexão sobre uma nova economia política do medicamento no Brasil*. Rio de Janeiro: EdUERJ, 2010. pp. 71-104.

⁹ From then on, the DCB denomination was to be used to designate the generic medicine. If no appropriate name existed in Brazil's official pharmacopeia, the Mercosur Common Nomenclature (*Nomenclatura Común del Mercosur*, NCM) could be used, or even the International Common Denomination (ICD).

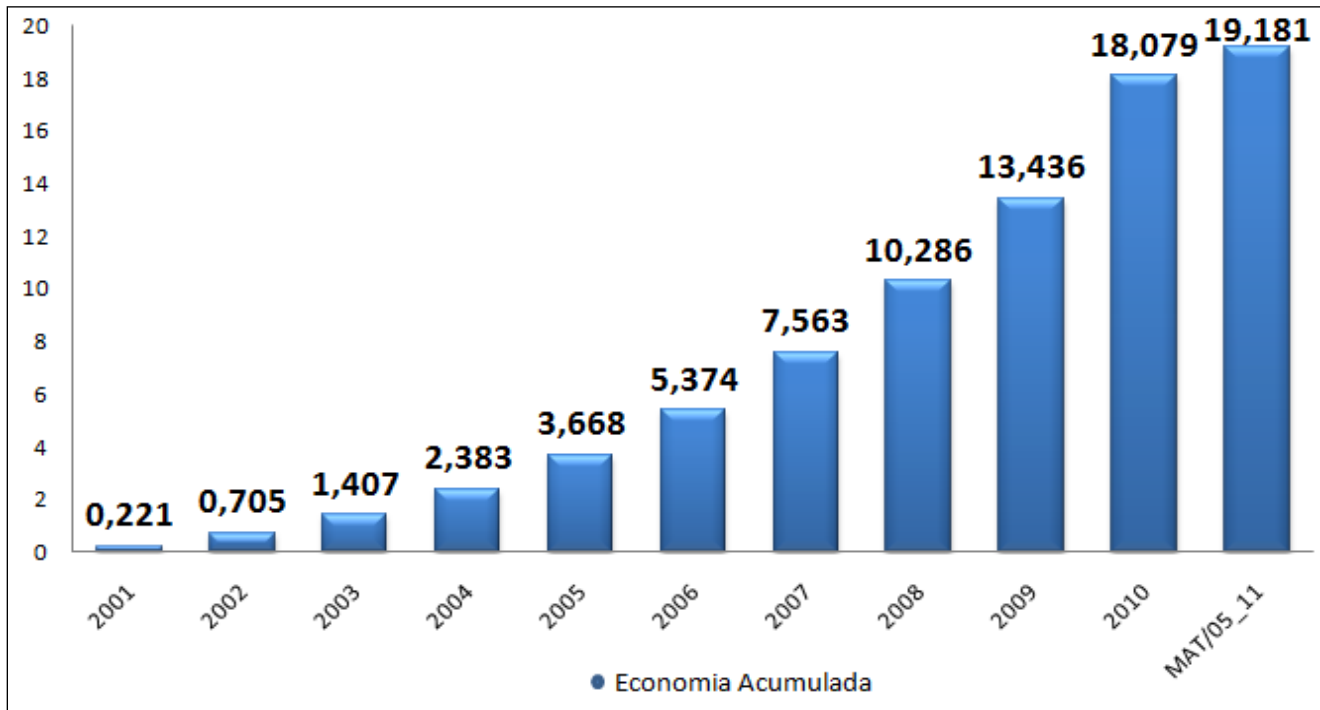


figure 9-1: Accumulated Consumer savings after the introduction of generics onto the market (R\$ billion)

Source: IMS-Health & Pró-Genéricos website: <http://www.progenericos.org.br/dados-do-setor>; accessed in February 2016

One of the main effects of generics' entry onto the market was to decrease drug prices (Casciano, 2011). The Medicines Market Regulatory Board (Câmara de Regulação do Mercado de Medicamentos, CMED) passed Resolution No. 2/2004, whose Article 12 stipulates that generics must be at least 35% cheaper than the reference drug, which contributed to stronger competition and lower drug prices. A study by the Economic Regulation Advisory Centre (Núcleo de Assessoramento Econômico em Regulação, NUREM) (ANVISA, 2010) profiles drug consumption and expenditure in Brazil and reports local average drug prices by type (Table 9.1: Consumption and average price by drug type in Brazil).

However, the table also shows that patented products' share in total drug spending is still 40% larger than generic drugs' share. Drugs under patent account for less than 1% of drug consumption, but more than 10% of drug spending in Brazil; by comparison, generics represent 13% of consumption and less than 8% of expenditures. Note also the huge difference between the average prices of generic drugs and those under patent. As a rule the prices of patented medicines bear no relation to their production cost,

but reflect their market value. The sad reality is that patent-holder laboratories evaluate the market and stipulate their prices on the basis of how much patients are able to pay for the drug (Grangeiro, 2006).

table 9-1: *Consumption and average price by drug type in Brazil*

Consumo de medicamentos no Brasil por tipo

Tipo de Medicamento	Participação em 2008		Evolução 2007/2008	
	Consumo ⁽¹⁾	Gastos da População ⁽²⁾	Consumo ⁽¹⁾	Gastos da População ⁽²⁾
Genérico	13,23%	7,62%	4,65%	5,55%
Patente	0,99%	10,74%	2,91%	24,86%
Referência	20,46%	36,90%	1,90%	8,23%
Similar	65,31%	44,74%	0,13%	4,65%
Total	100,00%	100,00%	1,12%	8,21%

⁽¹⁾ O Consumo de medicamentos refere-se às unidades vendidas no mercado brasileiro

⁽²⁾ Os gastos da população referem-se ao faturamento dos laboratórios no mercado brasileiro

Preço médio de medicamentos no Brasil por tipo de Medicamento

Tipo de Medicamento	Preço Médio		Evolução 2007/2008
	2007	2008	
Genérico	4,57	4,60	0,86%
Patente	86,03	104,38	21,33%
Referência	14,30	15,19	6,22%
Similar	5,43	5,68	4,52%
Total	7,93	8,49	7,02%

Source: Sistema de Acompanhamento e Monitoramento do Mercado de Medicamentos (SAMMED), 2009

2) Certification of Brazilian drug copies: concepts and controversies

Until 1999, the Brazilian market comprised: (i) reference medicines (original or brand-name *princeps*, imported or produced at facilities in Brazil); and (ii) similar copies bearing a trade name by which the copy was identified. With the new law, a third type of medicines – (iii) generics – would be introduced onto the market.

As set out in the official texts – particularly ANVISA Collegiate Board Resolution (*Resolução da Diretoria Colegiada*, RDC) 391 of 1999 (which brought the concept of bioequivalence to certification of the new copies) and RDCs 16 and 17 of 2007 (which delimited, respectively, what was understood by ‘generic’ and similar medicinal products¹⁰ – the various drug types may be defined as:

¹⁰ Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada nº 391 de 9 de agosto de 1999. Regulamento Técnico para registro de Medicamento genérico. Diário Oficial da União de 10 agosto de 1999. http://www.anvisa.gov.br/hotsite/genericos/legis/resolucoes/391_99.htm (accessed in February 2016).

Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada nº16 de 02 de novembro de 2007. Diário Oficial da União de 5 de set 2007. Aprova o Regulamento Técnico para registro de medicamento genérico. 12 pp.

Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada nº17 de 03 de novembro de 2007. Aprova o Regulamento Técnico para registro de medicamento similar. 14 pp.

1) *medicine of reference* or *reference drug* – is the innovator product, whose composition comprises at least one active pharmaceutical ingredient (the object of the patent – even if extinct – granted to the firm responsible for its development and introduction onto the market in the country of origin) and whose efficacy, safety, quality and bioavailability have been proven by clinical trials. The specifications of the medicinal product of reference are the yardstick to which copies are compared;

2) *generic medicine*– equivalent to an innovator or reference product, with which it is intended to be **interchangeable**. Generally produced after expiration or waiver of patent protection or other exclusive rights, it contains the same active ingredient, in the same dose and pharmaceutical form, is administered by the same route and with the same dosage and therapeutic indication as the reference drug. It is granted registration when proven to be a pharmaceutical equivalent (by *in-vitro* testing) and bioequivalent (*in-vivo* trials) to the reference drug, thus ensuring its interchangeability with the medicinal product of reference. Brazilian generics are designated by their Brazilian Common Denomination (DCB) or, failing that, by their International Common Denomination (DCI). Granting of the status of interchangeability authorises a brand-name medication prescribed by a physician to be replaced by its generic equivalent, which can be done by the pharmacist at the retail outlet. The external packaging of the new Brazilian generic drugs features a yellow stripe with the expression ‘*Medicamento Genérico*’ [generic medicine], the G seal and reference to Law No. 9.787 of 1999. G-generics cannot have trade names, as mentioned above, but are identified solely by the medicinal product’s active ingredient, as expressed in the Brazilian Common Denomination. The packaging must identify the manufacturing laboratory by name (as can be seen in Figure 1, above). Regulation of generics in Brazil in 1999, also introduced a requirement regarding suppliers of raw materials and APIs. As Brazilian laboratories have major capacity for formulating and finalising medicines, but low capacity for producing APIs (pharmaceutical ingredients), the latter are nearly all imported. RDC 16 of 2007 stipulated that, in order for a generic to be interchangeable, manufacturers had to demonstrate that the APIs were sourced from at most three different suppliers. The rule also specified that, in order for the manufacturer to register the product as a generic, the medicines originating from only one of these three suppliers need to be subject to bioequivalence testing. The other two shall undergo *in-vitro* tests in order to study comparative dissolution profiles¹¹; and

3) *similar medicines* – defined as those that contain the same active ingredients (APIs), with the same concentration, pharmaceutical form, administration route, dosage and therapeutic, preventive or diagnostic indication as the product of reference, in addition to complying with the same physical and physical-chemical quality control specifications. They may differ only in the size and shape of the product, expiration date, packaging, labelling, excipients and vehicle. The study to demonstrate *of pharmaceutical equivalence* between the original drug and similar copies requires *in vitro* test, with no need for trials with human subjects. In Brazil, similar drugs must always **be identified by a trade name**, i.e., by a trademark.

According to ANVISA’s 1999 norms, the common criterion has been the requirement of *good manufacturing practices (GMPs) and production line quality control and assurance* for the certification of both similars and generics drugs. In this regard, manufacturers are required to comply with a series of requisites connected with manufacturing installations, such as operating license of the plant, pilot batch notification etc., known as ‘measures prior to filing’ the register formulary (*medidas pré registro*). This

¹¹ As will be shown in more detail later, the discussion of the certification and supply of raw materials for generics has gathered strength globally in recent years with an increasing number of publications showing that the vast majority of medicinal product manufacturers in the central countries (particularly the USA) source their supplies from India and China.

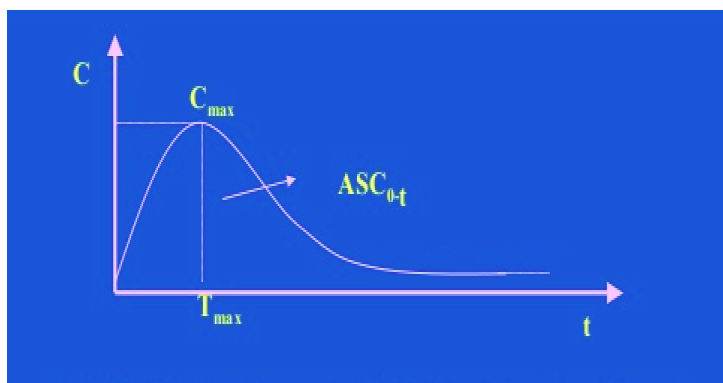
set of parameters described in rules considered very stringent to this day in Brazil. Similar and generic drugs have always been subject to the same requirements as regards assuring the quality of the industrial batches produced and the guaranteed quality of the whole manufacturing process.

At interview, ANVISA's manager for medicinal products explained: '*Our certification focuses strongly on the production line*' (authors' emphasis). *We are sometimes criticised for that. For example, we certify the solids line independently of what product is to be manufactured. If it changes and starts producing syrup, a new dossier will have to be submitted for the product. Our regulating of not just generics, but medicinal products in general, is very close to the large... to the developed countries... Canada, Australia... Those are the countries that serve as a basis on which we can ground our rulings – at a much further remove from, for example, Peru, Bolivia, Colombia... So to day Brazil has normative guidelines much closer to the developed countries than to Latin America*'.

Copy drug certification specifies not only control of the manufacturing process, but also pharmacokinetic parameters assayed by *in-vitro* and *in-vivo* testing. The measurements obtained from these trials with the copy drug are then compared with those of the reference drug. The main parameters observed by Storptitis, *et al.* (2012) in regulation of generic and similar drugs were:

(i) pharmaceutical equivalence - two medicinal products are considered equivalents when both have the same amount of the active ingredient (same salt, base or ester of the same API), the same administration route and may or may not contain identical excipients, providing these are firmly established for the stated function. They must meet the same current specifications of the *Farmacopéia Brasileira* and, failing that, of official codes authorised by current legislation. These are applicable quality standards for identity, dosage, purity, potency, uniformity of content, disintegration time and dissolution rate. The *study of pharmaceutical equivalence* thus comprises a series of physical-chemical and, when applicable, microbiological and biological, tests to prove *in vitro* that two medicinal products are equivalents. The tests of pharmaceutical equivalence provide indications of, but do not prove, bioequivalence;

ii) bioavailability – this concept describes pharmacokinetic parameters – the rate (time) and extent of absorption of an active ingredient originating from a pharmaceutical form (medicinal product). In the assays, these parameters are represented on a curve that reproduces the relationship between the concentration of a substance measured in the blood stream or in urine against absorption time. The main pharmacokinetic parameters are maximum concentration (C_{max}), time to peak (T_{max}) and absorption (ASC_{0-t} – the area under a curve representing the different measurements of levels of absorption of the substance over time; i.e., on the basis of samples collected from each volunteer at different times)¹².



¹² Bioequivalence testing in human subjects should, for ethical reasons, always be preceded by tests of pharmaceutical equivalence, because pharmaceutical equivalence testing assesses, *in vitro*, the dissolution profiles of the substances being compared (the reference drug and the candidate generic drug).

figure 9-2 : Example results of pharmacokinetic parameters measured in bioequivalence assays

Source: S. Storpitis (PPT presentation on line adapted by the authors)

*Bioequivalence testing*¹³ is the comparative study of the bioavailability of two or more medicines that have the same active ingredient and therapeutic indication, and which are administered by the same extravascular route in the same molar dose and under the same experimental conditions.

The result attesting to bioequivalence between the two is described statistically within a range that can vary from 80% to 125% in relation to the curve for the reference product. Studies are planned on an individual basis, setting the standards and acceptable absorption windows for the particular medicinal product being tested; i.e., which determines the concentrations within the limits of those ranges. In a trial to determine bioequivalence between two drugs, if 90% of volunteers (confidence interval) display measurements of the pharmacokinetic parameters C_{max} , ASC_{0-t} and T_{max} within the expected ranges, the copy will be termed bioequivalent to the product of reference. Once this set of *in-vitro* assays (pharmaceutical equivalence) and *in-vivo* trials (bioequivalence) are complete, and the industrial production line is shown to meet all requirements, the medicine of reference and the generic are considered to be interchangeable products.

3) Copying medicines in Brazil – the history of regulation

Certain peculiarities stand out in this history in Brazil: in the early stages (1999-2003) of the legal establishment of the generics market in Brazil, differentiated certification processes were maintained and both generic copies and existing similar drugs could be registered. Certification was differentiated, however: in order for a copy to be registered as a generic it had to meet two requirements: *control of the raw material used to formulate the medicinal product* and *bioequivalence testing*. By contrast, registration of similar drugs did not require evidence of analytical control of raw material nor *in-vivo* bioequivalence trials (even though, in fact, these were undertaken by Brazilian manufacturers). Registration of both similar and generic drugs called for certification of production line quality and industrial plant GMPs.

This regulatory framework was to evolve steadily, by 2014 the minor differentiation in requirements for certifying generic and similar drugs completely disappeared. By then, all similar drugs had also to be tested for bioequivalence. The requirements ceased to focus on raw material suppliers as such, leaving overall control of the analytical process, formulation and production to the manufacturer. The focus – as explained by the head of regulatory matters at the Farmanguinhos public laboratory – shifted to *'production line certification'*, which meant, for both similar and generic drugs, the ability to *'assure guaranteed quality, to GMP standards, across the whole production line'*.

All the same, the split in the Brazilian copy drug market remains to this day: generic drugs are identified by the Brazilian Common Denomination (*Denominação comum brasileira*, DCB), and similar drugs, by a trademark. Since 2014, if officially certified as bioequivalents, similar and generic drugs

¹³ The bioequivalence tests required for generic drugs are conducted on healthy volunteers and comprise three phases: clinical – volunteers are selected, generic and reference medicinal products administered at different times, then blood or urine samples collected at set times; analytical – the pharmaceutical ingredient in the samples is quantified by a specific method; and statistical – the values of the pharmacokinetic parameters found are calculated and subjected to statistical analysis comparing the reference and test medicinal products.

have become interchangeable between themselves, and with the medicinal product of reference. They are now two ‘different’ versions of the same copy, products certified as interchangeable by the regulatory agency. This split between copies has had – and will continue to have – impacts on the circulation and consumption (prices, sales volumes, use of one or another different form of the same copy) of medicinal products in Brazil.

Health policy managers’ unease at the lack of harmonisation in the copies market since 1999 was expressed technically and officially from early on: in 2003, it can be seen in the provisions of the new ANVISA Resolutions 133 and 134¹⁴. These documents make provision for adjusting existing similar drugs to the new requirements of bioequivalence, which in 1999 had been firmly established as synonymous with quality by Brazil’s Generics Law. In 2003, these two regulations required that similar drugs also undergo bioequivalence testing when their registration is renewed; i.e., manufacturers of similar drugs would have at most five years (the period for which registration is valid) to submit their product to new bioequivalence testing. RDC 134 also provided details of the required outcomes for certification of pharmaceutical equivalence (*in-vitro* assays): test tolerances, possible bio-waivers¹⁵ etc. Therefore, in 2003, it was hoped that unification between generic and similar drugs would come about by 2008.

In 2007, however, new resolutions admitted the possibility – for some therapeutic classes and for older similar drugs – of delaying bio-equivalence testing for a second renovation period. However, immediate bio-equivalence certification was demanded for certain classes, however, particularly antiretroviral, antineoplastics and antibiotics.

The ‘tolerance’ of Resolution 17 of 2007 with regard to bioequivalence and differential treatment for renovation of older similar drugs may reflect the facts, firstly, that by then many similar drugs had gone through a number of registration revalidation processes and had a history of pharmacovigilance reports that had never indicated any adverse events and, secondly, that no alterations had been made to the formulation, doses etc. of these products, which had gained quality assurance and good manufacturing practice certification.

In our research since 2000 on copying of medicinal products in Brazil, field work into the industry has found that similar drugs did in fact already undergo laboratory and bioequivalence tests, as can be seen in numerous scientific publications in the pharmaceuticals field and in documentation gathered from laboratories. In detailed interviews, manufacturers expressed their concern with the

¹⁴ Brasil. Agência Nacional de Vigilância Sanitária. Resolução RDC n° 133 de 29 de maio de 2003a. Dispõe sobre o registro do medicamento similar e dá outras providências. Diário Oficial da União 19 set 2003.

Brasil. Agência Nacional de Vigilância Sanitária. Resolução RDC n° 134 de 29 de maio de 2003b. Dispõe sobre a adequação do medicamento similar e dá outras providências. Diário Oficial da União 25 set 2003.

¹⁵ Bio-waiver is a concept of the bio-pharmaceutical classification system meaning exemption from bio-equivalence testing for the purpose of certifying a copy as a generic drug, in view of characteristics (properties such as solubility, permeability) proper to the active ingredient, pharmacokinetic parameters, such as dissolution profile, or final formulation (solid, liquid, injectable etc.). What this classification system contemplates is the product’s solubility in organic liquids and membrane permeability. For some generic drugs – a large number, actually – bioequivalence is inferred by simpler *in-vitro* tests.

quality, efficacy and safety of the medicinal products they produced, revealing the widespread practice of bioequivalence testing of Brazilian similar drugs, long before the 2007 standard was introduced¹⁶.

In addition, by definition, not all generic drugs need bioequivalence testing in order to be registered as such. That was accepted by ANVISA itself in its standards, which applied the *biopharmaceutical classification system*, exempting many copied products from the need for bioequivalence testing.

The recent history of the regulation of medicinal product copying in Brazil is indeed complex. In the scientific field of Pharmacy, controversies persist as to what material is considered necessary and sufficient for the various different mandatory tests, and how acceptable are the measurements and standards that have been established and validated, in a debate that continues today in the scientific community globally. On the Brazilian market, up to three versions of the same product can be found: i) the *princeps* (brand-name, patented) product; and two other copy types – ii) similar drugs; and iii) generic drugs – which enjoy identical status as regards their interchangeability. Also, generic drugs are known and circulate on the market with their Brazilian Common Denomination (*Denominação Comum Brasileira*, DCB) or Mercosur Common Nomenclature (*Nomenclatura Comum do Mercosul*). ‘Similar’-generic drugs, meanwhile, are known by a trade name. Different labels are used for separate versions that are maintained of identical entities. While, by 2014, according to ANVISA, all registered copies of medicines were officially bioequivalent and interchangeable, thus constituting a panorama of greater harmonisation among copies, the market continued to feature the older similar drugs, now re-baptised as ‘interchangeable similar’ drugs, as can be seen in the 2014 listing of certified medicines of that Agency¹⁷.

4) Local production, regulation and access: the public and private markets in Brazil¹⁸

The World Health Organisation lists nine required components of an access-oriented pharmaceutical care policy; one of them is a generic drugs policy contemplating countries’ and individuals’ purchasing power. Since 1998, Brazil has been formulating its National Medicines Policy¹⁹ (Miranda *et al.* 2009, p. 2147) providing, among other things, for the prioritisation of *registration* of generic drugs as a mechanism favouring access. This policy fosters expansion of local production, capacity and human resource capacity building. In its access strategies, Ministry of Health (MoH) pharmaceutical care policy clearly recommends integration among *public production, generic drugs policy and a list of essential medicines*.

The MoH is responsible for assuring availability of the medicines on the national list of essential medicines (*Relação Nacional de Medicamentos Essenciais*, RENAME), by way of institutional

¹⁶ Cassier M.; Corrêa M. 2003. Propriedade Intelectual e Saúde Pública: a cópia de medicamentos contra HIV/Aids realizadas por laboratórios farmacêuticos públicos e privados. RECIIS. Rio de Janeiro, Jan-Jul, 2007, 88-91.

¹⁷ Listing of similar medicinal products and their respective reference medicinal products, pursuant to RDC 58/2014. <http://portal.anvisa.gov.br/wps/content/anvisa+portal/anvisa/sala+de+imprensa/menu+-+noticias+anos/2014+noticias/publicada+lista+de+medicamentos+similares+intercambiaveis>

¹⁸ For the evolution of local production and growth in the generic drug market, see Loyola & Casciano, in this book.

¹⁹ Brazil. Portaria n. 3916. Dispõe sobre a aprovação da Política Nacional de Medicamentos. Diário Oficial da União 1988; 10 Nov.

procurement²⁰. In this way, it is hypothetically able to intensify competition among manufacturers, thus lowering prices, which would work in favour of increased access. In the private sector (pharmacies), meanwhile, users pay the full cost of medicinal products. In an extensive, robust study, which collected data on medicine supply and prices in 2007, using a methodology developed by the WHO jointly with Health Action International (WHO/AIS), and adapted and validated for Brazil, Miranda *et al.* (2009) compared public sector purchasing of reference, similar and generic medicines.

Their study results yielded a wealth of detail. They demonstrated that in every region of Brazil, that of the different versions of any given medicine, generic drugs accounted for a smaller proportion of supply, and reference drugs, a still smaller proportion; that is, the public sector is *buying more similar drugs than generic drugs* (*op. cit.* p. 2150), thus breaching²¹ Brazil's Generics Law 9.787 and ANVISA's resolutions establishing that the public sector is to purchase preferentially generic drugs for its hospitals and outpatient facilities and make generic versions of medicinal products available at SUS pharmacies²². As, in 2007, similar drugs had not been granted the status of interchangeability, the substitution of generics by similar products during tendering processes could be legally challenged. The aforementioned study thus demonstrated that similar drugs are leading on the public sector market. Likewise, in pharmacies (private sector), the narrow range of generic drug manufacturers prevents generics from fully performing their role in regulating (reducing) prices through competition²³. The strongest competition was found between generic and similar drugs, the latter's prices being the factor that had most influence in reducing generic drug prices.

In addition to studying prices, the above mentioned research results also addressed supply and availability²⁴ (if at least one unit of the product is in stock, it was considered available), revealing a lack of availability of generic drugs in the public healthcare sector, while similar drugs were the versions most encountered in all regions of the country. In their conclusions, they '*estimate that generic drugs are competing among themselves and with similar drugs, but not with reference drugs*' (Miranda *et al.*, 2009: 2157).

In another study (Santos Pinto *et al.*, 2009) arising out of the WHO/AIS research mentioned above, the same group of researchers examined the federal government's role in Brazil's Popular Pharmacy Programme (*Programa Farmácia Popular do Brasil*) in promoting access to medicines. That study singled out four medicinal products for conditions highly prevalent in Brazil's population (two

²⁰ Medicinal products from public procurement are stored in municipal health department stockrooms, hospital pharmacies, or in the network of public health posts and clinics, where outpatient care is given, and in emergency departments.

²¹ They also note that different copy versions (similar and generic, for instance, or generic and reference) should not compete to deliver the same active ingredient; or, put differently, there is discussion over whether or not it is acceptable for public procurement to entertain tenders for different versions of the same active ingredient.

²² In the private sector too, where individual users pay the full purchase cost, pharmacists are to be encouraged to substitute brand G.

²³ As already mentioned at several points in our work, Miranda *et al.* 2009 and other authors cited in the course of this chapter revisit the issue of the copy drug market's present-day slavish valorisation of bioequivalence taken in isolation, and emphasise GMP, quality and bioavailability, which can be inferred by simpler tests.

²⁴ Santos Pinto *et al.* (2010) write: 'the measure of availability proposed by the WHO/AIS is flimsy in that it considers a medicinal product to be 'available' when there is one dosage unit in stock, regardless of treatment needs, seasonality, demand and so on. It would be useful to have information on stocks of units sufficient to provide for a therapeutic regime', so as not to compromise rational access and use (by improper substitutions).

anti-hypertensive and two anti-diabetics). Prices and availability were compared for the reference versions and generic and similar drug copies in three sectors: the public sector (comprising central municipal government stockrooms or dispensing pharmacies within public health facilities of the SUS); the *Programa Farmácia Popular do Brasil* (FPB, which comprises the programme's own public pharmacies managed by the MoH and Fiocruz – at the time of the study there were 407 such pharmacies with a schedule of 107 medicinal products, representing 96 active ingredients); and a third sector, the Extended Popular Pharmacy Programme (*Programa Farmácia Popular Estendido*, FPB-E), comprising commercial pharmacies accredited and subsidised by the government to sell medicinal products from the FPB schedule. They indicated that, by virtue of its reach, the *FPB-E represents the capillary penetration of the FPB programme. In 2007, there were 4,300 accredited pharmacies nationwide and an expectation that accreditation would extend to 50% of the commercial pharmacies (estimated that year at 50,000) (op. cit.)*. In the FPB-P, availability was high overall (over 96%). Considering the volumes of the different versions of medicinal products supplied, it can be seen that in the public sector and among the programme's own pharmacies (FPB-P, which are also public), supply of reference and generic versions is almost non-existent, with similar drugs always predominating – given that procurement in this field is always by lowest-bid tender (least price). Similar medicinal products account for 100% of the public-sector market for three out of four of the medicinal products examined (the exception being the anti-diabetic, a generic version of which was available in 80% of cases). By comparison, all four of the drugs examined were more available in the public sector. It is thus to be supposed that the medicinal products prescribed at SUS facilities are sometimes 'dispensed' to patients at the FPB's own pharmacies; or where unavailable, free provision is supplanted by subsidised sale at pharmacies under contract in the FPB-E. In the FPB-E programme, meanwhile, all versions (reference, generic and similar) were 100% available, because these are private pharmacies, which operate partly under contract to the government to make subsidised or co-payment sales and partly selling directly in retail outlets to private consumers. Ultimately, the FPB-E has become an alternative access route for SUS users.

Certainly, the similar copies segment is the one that is growing most in Brazil; it accounts for the total volume of pharmacy sales, in terms of both units and sales revenues, as shown in Figure 3.

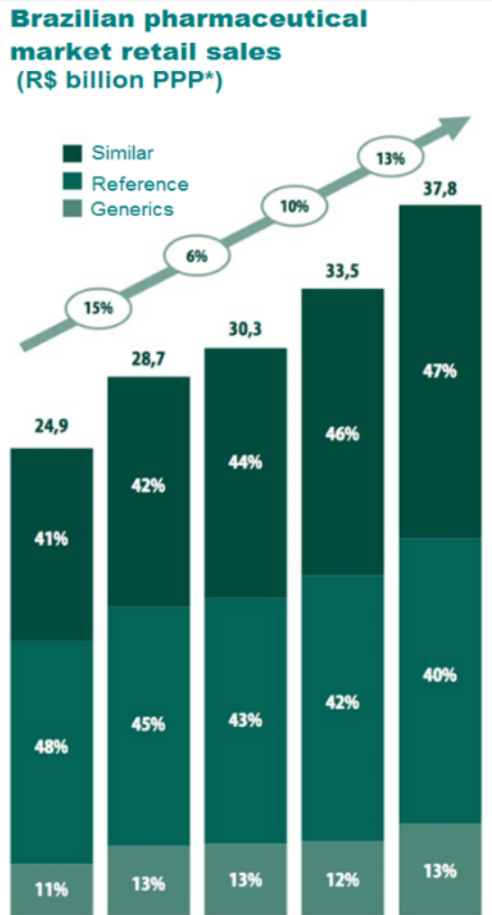


figure 9- 3 : Brazilian Pharmaceutical Market Retail Sales (*RPP retail purchase price)

Source: IMS/ Health

Totalling the above figures, which were drawn from robust scientific studies of public procurement (Miranda *et al.* 2009; Santos Pinto, 2010; Silva, 2016), reveals that in both public and private spheres, growth in the market is synonymous with considerable increase in consumption of similar drugs, followed by a minor increase in generics and a slight loss of market share by proprietary medicinal products. That dynamic is of great importance to the discussion of the market in copy certification testing centres, a relatively new market that saw growth after the Generics Law was enacted and is growing again now, with the new testing requirement for similar drugs.

Corroborating the tendency illustrated above, the former Brazilian laboratory, Ache, which was very strong in the similar drug segment, ranked first in sales, according to Interfarma report (op. cit. 2014), followed by the (also Brazilian) laboratory, EMS, which invested heavily in producing generics locally (table 9-2).

Rk	Laboratories	Sales	Part. %
1	ACHE	2,215	5,85

2	EMS PHARMA	2.169	5,73
3	SANOFI	2,069	5,47
4	EUROPHARMA	1,698	4,49
5	MEDLEY	1,130	2,99
6	NOVARTIS	1,094	2,89
7	NEO QUIMICA	1,031	2,72
8	PFIZER	1,027	2,71
9	BAYER PHARMA	983	2,60
10	BIOLAB-SANUS-FARMA	892	2,36
11	TAKEDA PHARMA	877	2,32
12	MSD	857	2,27
13	BOEHRINGER ING	830	2,19
14	MERCK SERONO	811	2,14
15	LIBBS	760	2,01
16	ASTRAZENECA BRASIL	694	1,83
17	MANTCORP Q FARM	651	1,72
18	DM IND. FTCA	627	1,66
19	GLAXOSMITHKLINE	617	1,63
20	ABBOTT	571	1,51

table 9-2 : Largest pharmaceutical laboratories in Brazil – (in R\$ million, Pharmacy purchase price PPP)

Source: IMS Health, MAT december 2013,

IMS Health, published in *Guia Interfarma*²⁵ (Interfarma, 2014), measures the size of the retail pharmaceutical market (sales in private pharmacies), counting reference, generic and ‘similar’ drugs. In the study cited (2014), the association talks in terms of overall sales of the order of US\$ 1.1 trillion in 2015, with Brazil accounting for a growing share of that figure (Figure 5, below).

Rk	2003	Rk	2011	Rk	2016 (estimates)
1	United Sates	1	United Sates	1	United Sates
2	Japan	2	Japan	2	China
3	Germany	3	China	3	Japan
4	France	4	Germany	4	BRASIL
5	Italy	5	France	5	Germany
6	United Kingdom	6	BRASIL	6	France
7	Spain	7	Italy	7	Italy
8	Canada	8	Spain	8	India
9	China	9	Canada	9	Russian

²⁵ Guia 2014 – Interfarma Brasil p. 2/1.

10	BRASIL	10	Great Britain	10	Canada
11	Mexico	11	Russian	11	Great Britain
12	Australia	12	Australia	12	Spain
13	India	13	India	13	Australia
14	Polland	14	Korea	14	Argentina
15	Holland	15	Mexico	15	Korea
16	Belgium	16	Turquia	16	México
17	Korea	17	Polland	17	Venezuela
18	Turkey	18	Venezuela	18	Turkey
19	Portugal	19	Holland	19	Indonesia
20	Greece	20	Holland	20	Polland

table 9-3 : World pharmaceutical market ranking

Source: IMS Health (adapted Interfarma 2014, p.)

5) Growth in the testing market in Brazil: local learning, capacity building and technological capability

Soon after the Generics Law was enacted in 1999, the first registrations were granted to a total of 182 products. In 2015, there were 3,629 presentations of generic medicines, involving 519 different APIs, produced by 110 generics firms²⁶. These figures, taken together with the vast body of regulations cited in the course of this chapter, point to considerable growth in the local market for generic certification testing. This raising of the regulatory requirements, a barrier to acquiring the status of interchangeability – which, from 2003, also affected the former similar drugs – has amplified the phenomenon of growth in the testing market.

The head of ANVISA’s bioequivalence department reports that, in the year the agency was set up, 80% of testing were carried out at international centres and mediated by Contract Research Organizations CROs²⁷, which almost always used international reference drugs. Products that entered the generics market with this kind of authorisation – termed ‘special registration’ (*registro especial*) – had to submit bioequivalence study results within five years (the deadline for revalidation of

²⁶ <http://www.anvisa.gov.br>; accessed on 10 January 2016.

²⁷ Contract Research Organisations (CROs) have become established at the global level as a specialised industry directed to recruiting subjects for clinical research. Their goals include ‘rationalising’ clinical trials by lowering the cost of forming pools of volunteers, while meeting all ethical and scientific requirements. Petryna (2005) describes how attractive Eastern Europe and Latin America are to this process. Brazil has highly-qualified doctors, a well-developed system of university hospitals, treatment-naïve patients, miscegenation and policies to expand access. The country would thus seem to be coveted as a field for such trials, but comparison using the international platform at www.clinicaltrials.org shows that the density of such clinical trialling is still low.

The global trend is towards pharmaceutical bioequivalence and bioavailability testing also to be conducted through CROs, which are now a widespread presence in operationalizing clinical trials. In the case of generic drug testing, CROs are in the process of internalisation and ANVISA certification.

registration), using a Brazilian reference drug from the list of reference medicines published by ANVISA.

The first pharmaceutical bioavailability and bioequivalence research results came out in Brazil in 1989, most notably in studies undertaken by the Campinas State University (UNICAMP), in São Paulo State. As demand grew for bioequivalence testing to certify generic drugs, so it became necessary to invest in training and capacity-building to make Brazil self-sufficient in this field. Accordingly, part of the drug regulation policy introduced in 1999 included strategically fostering the establishment of testing laboratories across Brazil, initially with funding for nine new university-based testing centres in 2000 and 2001. That policy was designed to accelerate internalisation of this stage in drug copying, which involves bioequivalence certification tests, in turn entailing recruitment of healthy volunteers. The centres supported by this policy could be public or private.

This involved was not only expansion, but also complexification, as in the case of the compulsory licensing in Brazil of the antiretroviral Efavirenz, which would come to be produced locally. According to the team tasked with the reverse engineering of Efavirenz, a great deal of laboratory work was required to establish internal analytical benchmarks, because the information provided by Merck proved insufficient to reproduce the molecule. Control of raw material, whether legally required or not, had already been routine in Brazil's ARV-copying programme piloted by Farmanguinhos since the mid-1990s. All that analytical work and constant reformulation of the ARV reengineering projects placed a heavy economic burden on Farmanguinhos. The information was so dated that, as reported at interview by the doctor responsible for the human-subject phase of the generic certification trials of the Brazilian Efavirenz, the bioequivalence study had to be designed and conducted twice, because the first run was unsatisfactory (Cassier & Corrêa, 2013).

Regulation of medicinal products in Brazil thus brought about the opportunity to incorporate more knowledge and technology in laboratory methods for assessing pharmaceutical equivalence, capacity-building in bioequivalence clinical trial design and so on. Continuing with the interview of the doctor who was responsible for the clinical trials platform at the Oswaldo Cruz Foundation (FIOCRUZ) and who conducted the medicinal product bioequivalence studies of Efavirenz, we heard: *'when a bioequivalence test is required, it is a Brazilian professional who is going to plan and monitor these studies: the contracting party [e.g., the FIOCRUZ pharmaceutical laboratory, Farmanguinhos] makes a pre-study visit to the CRO, designs, discusses and then monitors all the stages. The decision making is also kept in Brazil, as regards the number of volunteers, the important points to be documented, the speed of the study and so on'* (A. Daher). The doctor planned, monitored and coordinated the study, but the testing took place under contract at a CRO operating in Brazil, because at that time the FIOCRUZ did not yet have a bioequivalence centre (today the CEFAR tests Farmanguinhos' generic and similar drugs within the FIOCRUZ itself).

This has constituted an important body of expertise for Brazilian clinical research personnel, who now plan studies locally, sometimes in association with experts from CROs operating in Brazil, thus ceasing to be mere executors of studies designed abroad, as was (and still is) the case in the multicentre clinical studies conducted by transnational pharmaceutical corporations (Thiers *et al.*, 2008) and was also reproduced in Brazil during the early period of the very first generics tests, which had to use international centres to test Brazilian generics.

ANVISA issued standards for certification of CROs authorised to test Brazilian generics, stipulating also that only bioequivalence studies performed at centres certified by ANVISA itself would be accepted for the purposes of registering generics (RDC 103/2003). This attests to a regulatory endeavour pursued as a broad process that involves not only issuing and enforcing standards, but funding and setting up testing centres specialising in pharmacokinetics, building a laboratory network

sufficiently robust to meet the growing demand for testing in Brazil, enrolling volunteers and so on. Later, the Brazilian network of health analytical laboratories (*Rede Brasileira de Laboratórios Analíticos em Saúde*, REBLAS²⁸) was set up, linking up certified laboratories in all regions of Brazil.

The ratio of Brazilian to international bioequivalence and pharmaceutical equivalence testing centres has varied widely over time. In 2008, there were 51 ANVISA-certified CROs, 23 of which were international (16 Indian) and 28 Brazilian (9 public and 19 private)²⁹. On its website, ANVISA posts the listing of certified centres by geographical location, during the certification validity period, and then tabulates the centres by regional location. As a result, it is not clear what the ratio might be between test units produced in Brazil and abroad. Total numbers of tests processed per centre are not available for on-line consultation.

When the listing of centres on the ANVISA website was consulted at various different points in the course of our studies (between 2000 and 2013) and during finalisation of this book (2015-2016), the locations of testing centres in Brazil also varied. In any case, from 2000 onwards, the policy of public subsidies³⁰ for setting up testing centres encouraged a growing number of ANVISA-certified centres in all regions of Brazil, always with a higher concentration in the southeast region, reflecting Brazil's sociodemographic and economic profile.

Although not all test results are published, since 2003 the methods required and the forms for reporting bioequivalence study results have been specified and displayed online. It must be emphasised here that, in 2003, it was already established that: (i) a *Brazilian medicine* on the ANVISA schedule must be used as the reference drug; and that (ii) the testing centre *must be ANVISA-certified*; these two points signal the direction set as regards to the internalisation of local technology and capability.

Set up in 2006, the Brazilian Society of Clinical Research Professionals (*Sociedade Brasileira de Profissionais em Pesquisa Clínica*, SBPPC) reported participation of around 7,000 healthy volunteers in these tests, a number that rose to around 9,000 in 2007 and 10,000 in 2010. The SBPPC set up and gave training courses, at times in association with universities, as was the case with the first courses in bioequivalence, which had the use of skilled personnel and material infrastructure of the University of São Paulo (the state with the largest number of Brazilian centres). That same year, an association of CROs was set up, the *Associação Brasileira de Organizações Representativas de Pesquisa Clínica* (ABRACRO), which also contributed to increasing the number of CROs installed in Brazil, regrouping centres that perform pharmaceutical equivalence and bioequivalence studies. As told by one of its leaders: '*today there are more people able to carry out tests than there are institutions in a position to plan and fund them*'.

²⁸ The Rede Brasileira de Laboratórios Analíticos em Saúde (REBLAS) comprises public or private, ANVISA-authorized, analytical laboratories able to offer quality, reliable, safe and traceable healthcare-related services. Accreditation relates the REBLAS Code to the laboratory's address and analytical scope and its criteria are set out in RDC No. 12, of 16 February 2012. Authorized laboratories may display the REBLAS logo on printed or electronic trial or test reports, providing these are within its authorized scope. Use of the ANVISA logo is prohibited on pain of legal sanction, in addition to cancellation of accreditation.

²⁹ Source: presentation by Rodrigo CRISTOFOLETI, head of the ANVISA bioequivalence department, at the 13th International Conference of Drug Regulatory Authorities (ICDRA).

³⁰ See Pan-American Health Organization (PAHO): www.paho.org TC 37 - Reorganização do Sistema Nacional de Vigilância Sanitária 2006 (Reorganizing the National System of Health Surveillance, 2006), that includes among other initiatives financing public and university centers for bioequivalence trials and pharmaceutical equivalence tests. See also ANVISA: "Workshop discute atividades dos Centros Públicos de Bioequivalência (2006)", at www.anvisa.gov.br/divulga/noticias/2006/220306_3.htm

Regarding global location of certified Centres testing Brazilian generics, the most recent consultation of the ANVISA website³¹ displayed the following distribution: Brazil counted for 16 local centres; and 32 were in foreign countries - 17 in India; 4 Canada; 3 in Germany; 2 in the USA; 1 Argentina; 1 Italy ; 1 Mexico; 1 Portugal; 1 Romania. There is a clear tendency towards South-South cooperation and circulation of people, knowledge and technologies, while more than 50% of the tests performed outside Brazil were at Indian centres.

Centres localized in Brazil followed the same geographic concentration of wealth and health services found among the official regional division of the country: 13 were installed in the Southeast region, 2 in the Northeast region, and 1 in the Mid-west (zero in the north, Amazonian area),

6) Copy regulation: setting standards and parameters in a scenario in movement

The reasons why the market was kept partitioned between generic and similar drugs are not clear. Similar drugs were allowed to retain their trade names and, unlike generic drugs, were not required to be identified by the generic BCD nomenclature. On a pharmaceutical drug market like Brazil's, where an enormous range of therapeutic classes are offered directly to patients and customers in retail pharmacy sales, having a (trade) **name** assures a competitive advantage over presentations that people are traditionally familiar with and request directly at the pharmacy counter.

On that basis, it is to be supposed, on the one hand, that this point has weighed considerably in the recent history of drug regulation in Brazil, which always involves margin for negotiation to accommodate the interests of manufacturers, public policy makers and the regulatory agency³². On the other hand, before 2014, there was no authorised interchangeability, i.e., the substitution by the pharmacist of similar copies for prescribed brand-name medicinal products; only generics gained that status immediately, from the moment they came into production in 1999.

In an extensive article on this subject published on the scientific journalism portal *Prontuário de Notícias*³³ on 6 January 2010, manufacturers of similar drugs complained that the government, for 'political reasons' would not authorise the substitution of similar copies for brand name medicines. One ANVISA technician, recalling the 2003 ruling, said that by 2010 similar and generic drugs has been undergoing the same tests for a long time ago. In the article, according to ANVISA, '*similar drugs have quality and are efficacious, but are not equivalent to generics*', an ambiguous statement.

Even though, for experts like Professor of Pharmacy, T. M. Gonçalves, responsible for an ANVISA-certified testing centre, instated in 2010, that similar and generic drugs underwent the same testing. The difference lay in the terminology used: "*for generics, they are tests of bioequivalence and for similar drugs, of relative bioavailability... Technically and scientifically, they are synonymous and are regulated by the same ANVISA Resolution [1170/2006, which was in force at the time], which provides for relative bioavailability/bioequivalence tests*". In the same article, another pharmacist contacted by the web portal, Professor G. de Nucci of Unicamp, declared: "*the two tests guarantee the same product efficacy and safety, and 99% of similar drugs would also have undergone bioequivalence tests*".

³¹<http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Medicamentos/Assunto+de+Interesse/Bioequivalencia+e+Biodisponibilidade/Centros> - accessed in February 2016.

³² On this issue, see the differing discussions in Greene, 2010; Hayden, 2008; and Sanabria, 2014.

³³ <http://www.prontuariodenoticias.com.br/noticias.asp?secao=ME&id=8394>. (This publication has been discontinued).

ANVISA, on the contrary, insists that bioequivalence testing is more complete than bioavailability testing (even though both work with the same pharmacokinetic parameters to measure concentration and absorption, as described above). *'The agency claims that bioequivalence guarantees that the (reference and trade name) drugs are exactly the same, while relative bioavailability assures that the products have the same absorption and the same reaction speed in the organism'*. Another professor of Pharmacy, who is from the São Paulo University, and also responsible for a centre in São Paulo certified for pharmaceutical equivalence testing, notes that other aspects, such as the product's formulation, have to be studied in order to assure bioequivalence; i.e., the excipients and overall production process have to be taken into account. This means that, to achieve the level of bioequivalence, **work must be done on developing the copy throughout the whole manufacturing process** (quality guarantee). Tests of bioavailability (of the active ingredients in the bloodstream) do not, on their own, attest to precision in the overall production process so as, on their own, to grant the status of bioequivalence.

Indeed, ANVISA Resolution RDC 60 of 2014, which was to provide for the homogenisation of the copies market in terms of bioequivalence, would devote much more attention to factory production line and quality assurance issues (manufacturing practices, quality standards etc.). At interview in 2015, Farmanguinhos' head of regulatory matters reported that, in the new Resolution, excipients and colorants may vary if the final medicinal product is equally bioavailable and prove to be bioequivalent. Also, generic and similar drugs may have unlimited numbers of suppliers. Under the new regulation, the focus of the certification process is directed to the production line. If a generic or similar drug prove bioequivalence, the manufacturers will not be required to repeat those tests at the next revalidation of registration. They will have to repeat the bioavailability and bioequivalence testing **only if the production line is modified**. As the Farmanguinhos expert warned, however, although this is an open question worldwide, the issue remains in the international discussion as to how to treat the case of the industrial plants that produces both the reference medicine and the generic drug?

Today, as is well known, many industries produce the *princeps* product and the generic drug at the same industrial plant. Accordingly, once the reference medicinal product (*princeps*) is certified by clinical trials, one would infer that the generic drug from the same manufacturer should be bio-exempt and would not need to undergo bioequivalence testing. However, it is also known that generic drugs are manufactured today using APIs supplied by third parties – nearly always Indian and Chinese companies. For that reason, this discussion has once again become central to the bioequivalence agenda³⁴ in the United States and in countries of Europe, neither of which required compulsory tests to imported

³⁴ Cf., Araújo LU, Albuquerque KT, Kato KC, Silveira GS, Maciel NR, Spósito PA, et al. Medicamentos genéricos no Brasil: panorama histórico e legislação. Rev Panam Salud Publica. 2010; 28(6):480-92; Bate R., Aparna M., Lever H., Thakur D. et al. Generics substitution, bioequivalence standards, and international oversight: complex issues facing the FDA. Trends in Pharmacological Sciences; in press Elsevier Ltda. 8pp. (<http://dx.doi.org/10.1016/j.tips2015.11.005>); Borg, John; Joseph et al. 'Licensing of Generic Medicines: Are There Any Challenges Left? A Pharmaceutical Regulatory Perspective'. Scientia Pharmaceutica 82.4 (2014): 847-856. PMC. Web. 30 Jan. 2016; Brazil. Agência Nacional de Vigilância Sanitária. Resolução – RDC n. 60 de 10 de outubro de 2014. 'Dispõe sobre a concessão do registro de medicamentos com princípios ativos sintéticos e semissintéticos, classificados como novos, genéricos e similares e dá outras providências' http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2014/rdc0060_10_10_2014.pdf; Carpenter D.; Tobbell D. A. Bioequivalence: the regulatory career of a pharmaceutical concept. Bulletin of the history of Medicine, v. 85, n. 1, Spring 2011, pp. 93-131; Storpirtis S. et al. 'Aspectos técnicos relativos ao registro de medicamentos genéricos no Brasil'. <http://www.anvisa.gov.br/medicamentos>; accessed in February 2012.

ingredients. In the USA, 80 per cent of APIs used in producing generic drugs originated in a foreign country. As in Brazil, GMP compliance is still obligatory. Accordingly, in 2014 the FDA sent out 18 letters to GMP-noncompliant manufacturers, six of them in China and six in India (Bate *et al.*, 2015).

As shown by Borg *et al.* (2014) a great deal of experience has been built up regarding the value of the bioavailability requirement and bioequivalence testing, although the details of pharmacokinetic standards do remain controversial. Acceptable ranges of pharmacokinetic parameter values for two products to be considered bioequivalent are still a subject for discussion in scientific circles. Thus, for the reference medicine A, there may be one generic drug B that behaves at one point of the acceptable range and another generic drug C that displays different behaviour.

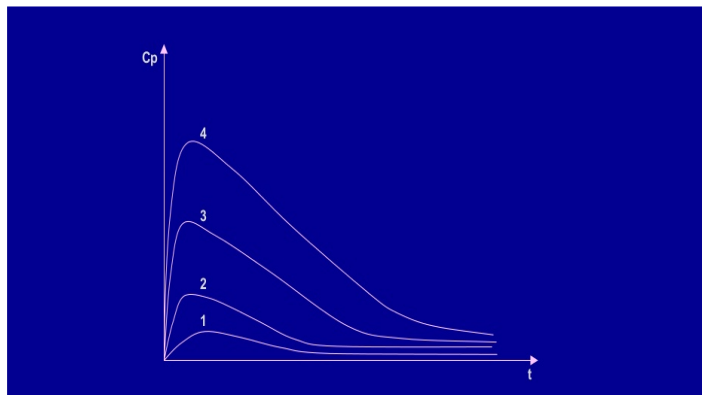


figure 9- 1 : Mean plasma levels in healthy volunteers in a bioequivalence study of 500-mg coated tablets of chloramphenicol from four different manufacturers in the USA (1960s)

Source: Storpitis (PPT presentation), adapted by the authors

For that reason, the putative need to narrow the acceptable range (absorption window) for certification of generic drugs has been resurfacing and gaining increasing attention in present-day discussions of pharmaceutical research. Also, interchangeability – which, in Brazil, is a status which generic drugs must achieve (as now must the renamed *interchangeable-similar drugs*, because it is inherent to their status as generics) – is conceived differently in the USA, where, regulations for substituting generics vary among the states of the US federation (Borg *et al.* 2014), and are accepted in some and not in others states.

Bate *et al.* (2015) discuss the need to update the criterion for bioequivalence as an indicator of the quality of generic drugs. They consider the failure to review existing standards to be harmful for a number of reasons. The United States law on generic drugs, known as the Hatch-Waxman Act, dates from 1984 and a large number of therapies have become '*substantially more complex*' since; the interchangeability between an innovator medicinal product and a generic drug '*is not an innocent process*'. In addition, unlike the 1980s, today pharmaceutical active ingredients for finished products are sourced from multiple different suppliers.

This brings us back to the central importance of quality assurance and GMP in certification of copied drugs, which pharmaceutical regulation in Brazil has addressed since 2014 by focussing on control of the overall production process and plant (as indicated above by the responsible of Farmanguinho's regulatory issues).

It also brings us to reconsider the importance of the concern – written into the Brazilian 1999 Generics Law and reiterated in ANVISA ruling RDC 16 of 2007 – over raw material sourcing: there was

talk of setting a maximum of three suppliers and of analytical monitoring of samples from only one of the three. But in 2014, this point ceased, as such, to be a compulsory item in certifying bioequivalence for generics. In fact, in Brazil, the emphasis on quality assurance makes it implicit that this requirement is addressed. The present tendency for the international discussion to address product quality in suppliers of APIs for generics can be expected to revive – this time globally – the discussion of minimum regulatory standards for APIs.

As the information in the dossier known as the Drug Master File (DMF) is inaccessible or inappropriate (exception for the proprietary patented medicine), characterisation of generics has always demanded an enormous amount of work in analysis and formulation to finalise copied products (with raw materials testing, repeated reformulations and so on).

Since 2014, all copies of pharmaceutical drugs present on the Brazilian market have been tested for bioequivalence (in addition to quality control of the commercial production batches and biobatches), and their accompanying information leaflet states: *similar pharmaceuticals equivalent to product of reference*. That information is found in the section ‘Identification of the Medicinal Product’, along with the trade name of the similar drug and the generic name of the API as given in the Brazilian Common Denomination or the Mercosur Common Nomenclature. ANVISA RDC 58 of 2014 defined *interchangeability* between similar and reference drugs (as officially listed by ANVISA). That list is available for consultation by the general public, health personnel or any other interested party and is updated monthly as new similar drugs are registered or renewed³⁵.

About the dynamics of the market after 2015, it is still too early to forecast the most likely growth pattern trends for similar and generic drugs. In the case of Brazil, one must always bear in mind, on the one hand, the size of the public procurement market and, on the other, the vast range of medicinal products sold directly to the consumer public in retail pharmacies. This chapter has been less concerned with examining the Brazilian copies market and its growth in quantitative detail. Here, the interest has been more in posing and examining hypotheses on the basis of those data and others, of a different nature, collected in our field studies and in the literature. That corpus can help explain this continuing three-way split in the market, where there are products – similar and generic drugs – that have retained their former names, even though all the copies can be said to be equivalents, given that the regulatory authority has certified them to be *interchangeable*. What strategies may lie behind maintaining this situation – a market with equivalent products identified as *G-brand* ; *generics* ; and *trade-name ‘similar’-generic drugs* that are mutually interchangeable, together with the respective medicinal product of reference – is still a difficult question to answer. Both types of copied drug bear the manufacturer’s name on their packaging. Might positioning for a market share lie behind this feature (the manufacturer’s name)? There is also the question of consumer loyalty to the trade name of the similar drug: is it greater or lesser than loyalty to the manufacturer’s name? The phenomenon is still so novel that there are nearly no scientific publications, from our standpoint, that examine the Brazilian phenomenon of *interchangeable similar drugs* that emerged after 2014-2015.

Once the lack of regulation that reigned until 1999 was surmounted, the Generics Law and the succession of resolutions issued by ANVISA, as one agency director noted at interview, entailed [a task that] ‘*is very often more than inspection; it involves a labour of proactive education, visiting factories, dialoguing... Regulation is much more all-encompassing than the legal instruments of regulation*’. He told of ANVISA’s role ‘*concretely on the factory floor*’, of supporting and fostering GMPs, GLPs and the means to achieve quality assurance on the production line. Also, as can be seen from what the policy

³⁵<http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Medicamentos/Assunto+de+Interesse/Medicamentos+similares> (withdrawn on 6 February 2016).

managers said at interview, ANVISA directs its actions in a manner integrated with the needs of the SUS, implementing provisions, including priority testing (a procedure invented to expedite registration of drugs that combat urgent health problems in the public interest), and also setting itself up as a player in testing for the granting of patents on pharmaceutical products, which is a juridical innovation ushered in by amendment to the 1996 Intellectual Property Law and the introduction in 2001 of Article 229c, which instituted the agency's Intellectual Property Coordinating Office (*Coordenadoria de Propriedade Intelectual*, COOPI ³⁶). This new division of ANVISA, which forms part of its medicinal products management, came to assent to INPI findings, granting or denying patents on the basis of its examination, which was considered more stringent and informed by a 'public health viewpoint'.

Lastly, it must be said that the scope of such actions – which ranged across the laboratory testing dimension, industrial plants, the patent system, the sales market – is strongly associated with public policy making on health, industrial property and public-private partnerships designed to meet SUS (national health service) priorities. To that end, ANVISA will seek to support Brazilian industries and the establishment and equipping of medicinal product testing centres (including funding). It can be seen that all this regulatory activity will reverberate in the dimension of innovation, as affirmed in the introduction to this chapter.

Conclusions

Concerning the dynamics of the pharmaceutical market after 2015, it is still too early to forecast the most likely growth pattern trends for similar and generic drugs. The regulation of generics in Brazil, which has been closely associated with the development of local drug production and health policies, has been going on for more than 15 years, since the 1999 Generics Law, and numerous additions and corrections in 2003, 2007, 2009 and 2014, that have structured the pharmaceutical market by organizing the growth of generics: the creation of the G brand; later the convergence of standards for generic and similar drugs, the latter being called to fusion themselves with the firsts; and finally managing the duality between generic and similar drugs, which are now required to satisfy the same technical requirements (bioequivalence), while covering different markets (similar drugs are marketed with private brands, while generic drugs boast the "public" G brand and common national or international denomination).

In the case of Brazil, one must also bear in mind, on the one hand, the size of the public procurement market, and, on the other, the vast range of pharmaceutical products sold directly to the consumer public in retail pharmacies. This chapter has been less concerned with examining the Brazilian copies market and its growth in quantitative detail of this book. Here, the interest has been more in posing and examining hypotheses on the basis of those data and others, of a different nature, collected in our field studies and in the literature. That corpus can help explain this continuing split in the market, where there are products –generic and similar drugs – that have retained their former names, even though all the copies can be said to be the same, given that the regulatory authority has certified them to be *interchangeable*. What strategies may lie behind maintaining this situation – a market with the same pharmaceutical products identified as *G-brand generics*, or *trade-names 'similar'-generic drugs*, mutually interchangeable – is still a difficult question to answer. Both types of copied drug (similar and generics) bear the manufacturer's name on their packaging. Might positioning for a market share lie

³⁶ Already in 1999 – before the IPL was amended as such in 2001 – the government issued a decree (Provisional Order No. 2.014-1 of 1999), instituting the juridical provision of *anuência prévia* (pre-grant opposition) for pharmaceutical patents. On this point, see Guimarães, in this book.

behind this feature (the manufacturer's name)? There is also the question of consumer loyalty to the trade name of the similar drug: is it greater or lesser than loyalty to the manufacturer's name? The phenomenon is still so novel that there are nearly no scientific publications that examine the Brazilian phenomenon.

While laboratories that produce similar drugs are interested in the lastingness of their brands and their markets, it is the similar drugs market that has been growing, while the G brand market is stagnating, and the reference drugs market has been relatively declining. Therefore, organizing the duality between similar and generic drugs is essential, as noted by a market study: "*the larger domestic manufacturers have successfully protected their similar brands by investing in the necessary drug compliance (often taking market share from smaller players who do not have the resources to adhere to compliance requirements).*" (Eyeforpharma, nov 2014, Marc Yates).

There are no equivalence hierarchies in chemical or therapeutic terms between generic and similar drugs, but different positions and dynamics in the market dimension. Pharmaceutical regulation in Brazil was built in the context of public health policies (access to medicines since the late 1990s and the Constitutional individual right to health principle). Therefore, while regulation of generic drugs and the norm of bioequivalence are the subject of a general discussion in many countries, these issues also feature local aspects, concerning the local pharmaceutical industry, local institutions, national laws as the duality generics and similars. Bioequivalence standards have gradually become a strategic tool used to certify the quality of local production and to counter the accusation of Brazilian copies being "bad similars". Bioequivalence measures have been used in disputes over medicine copying. In the early 2000s, the director of the federal laboratory performed bioequivalence tests on all ARVs produced for the Health Ministry. The idea was both to rally patients and their organizations to support national generics, and to ward off the attacks of multinationals.

Regulation, thus, is played not only by evaluating and sanctioning the certification of pharmaceutical products. ANVISA's follow up of pharmaceutical industries broadens the concept of regulation, so as to encompass changing production norms and applying them in the industrial practice. ANVISA's rulings and the actions of its agents shape and foster industrial change, and may thus be considered references for industrial learning.

The process of standardizing Brazilian copies has until now been oriented primarily towards the needs of the domestic and regional markets. Obtaining the WHO prequalification standard could represent a new frontier of this standardization, aimed at international donor markets such as those of the Global Fund. To date, no Brazilian firm has acquired WHO prequalification unlike Indian firms which use them massively to conquer global generics markets.

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