

# Pharmacokinetic Tests: A Public Policy Tool of Science, Technology, and Innovation in Pharmaceutical Drugs for Brazil

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## Abstract

Bioavailability (BA) tests measure the variation over time in the availability, in the bloodstream, of the compound contained in a medicine. Bioequivalence (BE) tests compare the bioavailability of drugs with the same therapeutic indication, administered by the same route and at the same dose. Given the objectives of social regulation in the 1990s, the advantages of these tests explained their emergence in Brazil. The current article thus aimed to review the historical background for the regulatory framework of the Brazilian pharmaceutical industry and the organizational characteristics of BA/BE testing, and to highlight the latter's importance for the country's pharmaceutical policy within an open-economy growth model. The conclusion is that the number of certified centers in Brazil as of 2008 signaled the risk of an increase in the degree of concentration of BA/BE testing, while the perspective of cooperative research in the Brazilian government centers represented an incentive for innovation.

**Keywords:** welfare, innovation, pharmaceutical industry, social regulation, bioequivalence centers

## 1. Introduction

The pharmaceutical industry can be characterized in general by the requirements of process and product efficacy and safety, as well as continuous innovative activity. Given these characteristics, government regulation of the industry has grown, aimed at guaranteeing adequate manufacturing of pharmaceutical drugs, while conditioned by the attempt to avoid overly constraining the industry's economic performance.

The requirement of bioavailability/bioequivalence (BA/BE) tests prior to releasing drugs on the market is one of the more recent forms of regulation of this industry in Brazil. The purpose of BA tests is to determine how much of the administered drug is available in the body, when and where. For example, the drug reaches the bloodstream and its concentration increases, reaches a peak, and tapers off until it disappears. The test thus allows "tracing" the concentration/time curve. BE tests are used to compare the bioavailability of two drugs with the same therapeutic indication and administered by the same route and at the same dose.

This article aims to identify the potential effects of this regulatory mechanism on the development of the Brazilian pharmaceutical industry and specifically examine the characteristics of the industrial organization of pharmacokinetic tests, consistent with the objectives of the Brazilian national pharmaceutical policy in the 1990s.

The first concern was to assess the need for government participation in BA/BE testing, i.e., whether government should promote it or if the market itself should provide the incentives to private enterprise. Another question involves how existing government centers have evolved from the infant stage to meeting the so-called "high-throughput demand": whether through partnerships with international centers, with pharmaceutical companies, or exclusively with government support.

The article consists of nine sections, plus the conclusions and bibliography. The second section describes the industry organization of the Brazilian pharmaceutical industry until the 1990s and the next one discusses the underlying diagnosis and the results of public policies during Brazil's national-developmental period; the

fourth aims to characterize the first generation of State Reform in Brazil and its impact on pharmaceutical policy; the fifth discusses mechanisms in the National Health Surveillance Agency (ANVISA) for regulation of the pharmaceutical industry at the end of this period; the following two sections characterize, respectively, the genesis of BA/BE testing in the United States and Brazil and highlights its importance for the Brazilian pharmaceutical policy under the open-economy growth model; and the final two sections use industrial organization aspects and a case study to elucidate important issues in the microeconomics of this activity that influence policymaking to provide the incentives for its development in Brazil.

## **2. Brazilian Pharmaceutical Industry Organization until the 1990s**

The Brazilian pharmaceutical industry underwent three organizational phases until 1990: the first, during the early decades of the 20th century, characterized by family business for the production of medicines based on plant extracts and manufacturing products from mineral-based raw materials; the second, in the 1930s, marked by the predominance of biological products dating to the early 20th century; and the third characterized by the technological gap vis-à-vis the industry in advanced countries and denationalization beginning in the mid-20th century.

The following factors contributed to this third phase of the industry: post-World War II scientific and technical changes; the attractiveness of the Brazilian market for investment decisions; the economic policy of openness to participation by foreign capital; lack of economic support and sufficient government credit for companies to accompany the industry's evolution; and government directives 70 (1953/61) and 113 (1955/61) issued by the Currency and Credit Board (SUMOC) (Frenkel et al., 1998).

The technological gap appeared with the introduction of synthetic chemical drugs, when the leading international companies, unlike their Brazilian counterparts, incorporated systemic R&D of new compounds into their dynamics, and with the denationalization of the Brazilian pharmaceutical industry, which involved a fast-paced purchase of Brazilian domestic laboratories by foreign subsidiaries and a drop in the relative share of domestic Brazilian companies in the industry's sales.

Despite obsolescence and denationalization, there was no industrial policy for domestic pharmaceutical companies between the Post-War and the late 1960s or any government support for domestic companies or restrictions on divestitures to foreign groups. For example, the National Economic and Social Development Bank (BNDES) failed to assign any priority to financial support for the domestic pharmaceutical industry.

Another difficulty of domestic Brazilian companies was their competitive powerlessness in the face of foreign companies, which even resorted to dumping.

Finally, in order to guarantee the supply of medicines for the domestic market, Directive 70 on exchange reform, which established a multiple exchange rate system, and Directive 113 of 1955, ruling on authorization to CACEX for issuing import licenses without exchange coverage for equipment, failed to protect or stimulate national manufacturing of these products and were partly responsible for denationalization, particularly because the latter prevented payment for these imports in foreign exchange – such that foreign investors were not paid in currency but rather through shares in the company purchasing the equipment (Frenkel et al., 1998).

Post-World War II entry barriers (represented by the technological gap and the lack of compounds on the international market for manufacturing medicines) were overcome through the dissemination of new technologies for chemical synthesis to countries with non-restrictive patent legislation beginning in the early 1970s, which allowed expanding the supply of drugs at more affordable prices for countries like Brazil. Combined with the dissemination among Brazilian domestic companies of marketing techniques used by foreign subsidiaries, this process resulted in similar performance to that of subsidiaries.

In the late 1970s, early efforts by the Brazilian government to promote development of the pharmaceutical industry foretold the extension of the principles of the industrial policy from the national-developmental model to the production of medicines.

This policy shift resulted mainly from changes in patent legislation in Italy – the main supplier of compounds to Brazil during those years - and the balance of payments crisis, which stimulated the import substitution process by fostering domestic production of the compounds imported through the BNDES, the Federal research funding agency FINEP, and the Central Office for Medicines (CEME) (Frenkel & Ortega, 1985).

Thus, for half a century beginning in the 1930s, Brazil's national-developmental model consisted of: developing the domestic market as a source of dynamism for the economy; internalizing investment decisions; defining government priorities for investment; using direct government participation in the economy (Suzigan, 2000); expanding industrial capacity with public financing; protecting the nascent industry with tariff barriers;

assigning special treatment to domestic capital; and protecting local innovation with the industrial property regime (Jorge & Arruda, 1994). Direct price control played an outstanding role, becoming a tool for market organization and orientation of business strategies.

### **3. National-developmental Policies for the Brazilian Pharmaceutical Industry**

As for the pharmaceutical industry, in the face of denationalization, the technological gap, and the hypothesis of a drop in the pace of discovery of new compounds in the 1970s (Katz, 1976), policies focused on two main lines: (a) direct price control on products, which ended up discouraging investment and (b) stimulus for technological development in the domestic production of previously imported compounds, especially by structuring the National System for Scientific and Technological Development (SNDCT) in the early 1970s (Note 1).

A particularly important policy guideline for the consolidation of the SNDCT and the development of Brazil's national pharmaceutical industry was that of patents. Brazil joined the Paris Convention in 1884, which extended protection of industrial property to the pharmaceutical industry, but patents on chemical-pharmaceutical products were no longer protected after 1945, and the same occurred with production processes in 1969. Industrial Property Code of 1971, in force until 1996, failed to recognize patents on chemical-pharmaceutical substances, materials, mixtures, or products and medicines of any kind, as well as the respective processes for obtaining or modifying them. The aim of this economic policy decision was to obtain the necessary technology transfer for industrialization within a given time frame, along the lines of countries with late growth like Switzerland and Germany (Instituto Nacional de Propriedade Industrial [INPI], 1971).

The most important initiative during this period was the creation of CEME in 1971. As an agent for government procurement policy, the Central Office for Medicines combined the functions of regulating drug production and distribution by government laboratories, acquiring products from private companies, and promoting cooperation between the pharmaceutical care agencies. Subsequent expansion of its roles included R&D by government laboratories and funding.

In this context, the establishment of the Technological Company of Campinas (CODETEC) in 1976 and cooperation between CEME, the Secretariat of Industrial Technology (STI/MIC), and the National Council on Scientific and Technological Development (CNPq) resulted in a technological capacity-building program to generate production processes for compounds transferred to private Brazilian companies beginning in 1984 (Bermudez, Epsztein, Oliveira & Hasenclever, 2000).

As for trade policy measures applied to the pharmaceutical industry until 1990, the emphasis on protection of the nascent industry created a tariff regime with high tariffs and surtaxes and disparity in the level of protection in its various segments.

However, evoking the limits of the national-developmental model, the 1980s were marked by financial liberalization, opening of markets, pursuit of the minimum state, and drawback in government financing. In addition, the unsatisfactory performance of public expenditures led to new policy guidelines to reduce the state's presence in the economy.

Meanwhile, price control by the Inter-Ministerial Price Board (CIP) aggravated the problem of shortage of medicines on the supply side in the 1980s, with serious effects on more traditional drugs.

Inefficiency of price control led to irregular supply, protecting inefficient companies and rewarding oligopolies, jeopardizing competition and thus consumers (the intended beneficiaries) (Lucchesi, 1991). To sidestep price control, companies adopted such strategies as introducing minor changes in the controlled products (which did not represent innovation) in order to justify higher prices, using raw materials and packages of inferior quality; and raising prices with forged government authorizations.

In the late 1980s, various foreign laboratories thus closed their activities in Brazil and some domestic laboratories filed for bankruptcy, while others were forced to merge with other brands.

Meanwhile, Brazil's trade policy review showed the clear need for modernizing the country's industrial capability and making it more competitive by reducing levels of protection.

Although CODETEC produced positive results in technological development, companies did not immediately incorporate such results, and CODETEC closed operations in 1995 (Bermudez et al., 2000).

In addition, lack of recognition of drug patents led to heavy pressure by companies and international agencies for a full-fledged patent system.

Another contributing factor to the precarious technological development of Brazil's pharmaceutical industry was the lack of real priority assigned to it by the National Economic and Social Development Bank (BNDES), whose

stated objective in associating with domestic companies or government laboratories was to make Brazil a major exporter of medicines and compounds (Frenkel et al., 1998).

The government laboratories, responsible for a major share of the production and acquisition of medicines by CEME, experienced difficulties in the 1980, since restrictions on the imports of raw materials jeopardized their production, generating delays in the supply of medicines, which were generally not produced by private laboratories due to price control. They were thus unsuccessful in becoming large government-owned laboratories as in India for example.

In short, the combination of the international scenario and criticism over the results of numerous government investments (even according to the government's official diagnosis in 1990) (Fritsch & Franco, 1992) led to a change in economic policy and the policy for pharmaceutical drugs.

#### **4. State Reform and the New Policy for Pharmaceutical Drugs in Brazil**

Globalization and the financial crisis in the public sector in the 1970s resulted in new expectations concerning the role of the state: according to influential analysts (Evans, 1997), its new role (Banco Interamericano de Desenvolvimento [BID], 2003) was to create a favorable environment for economic growth but without intervening directly in the economy (Pereira, 1996).

As a consequence, Brazil's industrial policy underwent a change in 1990, based on the search for macroeconomic stability and growth through competitive participation in international trade and investment flows.

The national-developmental model was replaced by one of growth in an open economy, whose main characteristics are: search for sustained growth through macroeconomic stability and elimination of the public deficit; use of the foreign market as a source of dynamism for the economy; increase in the exposure of domestic products to foreign competition; the state with "typical government roles", not as a producer but as a regulator; public financing concentrated on the sectors with dynamic comparative advantages; foreign capital with the same treatment allotted to domestic capital; and universal industrial property rights with the new Patent Law of 1996 (Fritsch & Franco, 1992).

With a view towards transition to the new model, efforts to introduce competition in Brazil during this period involved a set of reforms (La Forgia & Couttolenc, 2008), including currency exchange and trade reform, deregulation of the economy, and state reform. This led to a significant change in companies' strategies to withstand the resulting competition.

First, trade reform aimed mainly to increase companies' productive efficiency to make them more competitive. It aimed at a more transparent and less discriminatory tariff system. Most non-tariff barriers and special imports arrangements were abolished in the 1990s.

Second, combination of an overvalued exchange rate and high interest rates exposed companies to competition and increased privatization and denationalization of Brazil's domestic industry, without expanding its installed capacity.

In addition to these changes, price control was eliminated after having jeopardized the pace of investments due to its impact on companies' strategies.

For the production of medicines, this change translated as the replacement of command-and-control type regulation (Day, Reibstein, & Gunther, 1999) with regulation by incentives, oriented by companies' participation in the resulting productivity gains (Resende, 1997).

Finally, market liberalization, financial and trade integration, property rights policy, and privatization of state-owned assets in the 1990s required the pursuit of appropriate institutions through public sector reform (Brasil, 2003a).

Due to the substantial changes involved in the so-called First-Generation Reforms, one of the most extensively affected industries was the pharmaceutical industry.

Many considered Brazil's former patent law one of the main disincentives to investment in the pharmaceutical industry. Under pressure from the United States and foreign laboratories in the early 1990s, a new Patent Law (Act 9.279 of May 14, 1996) was enforced in 1997, covering pharmaceutical patents.

In addition, direct government price control over pharmaceutical products (with the exception of herbal remedies, medicines produced by government laboratories, and homeopathic products) was eliminated between March 1990 and mid-1992 (Romano, 2005), which allowed the industry to recover its profit margins and

increase its turnover (Frenkel, 2002). Nevertheless, government established informal agreements with pharmaceutical industry every year following liberalization in order to protect population from harmful price hikes.

Across-the-board reduction in tariff rates in all stages of drug manufacturing beginning in 1989 and simultaneous elimination of price controls aimed mainly to increase imports of compounds, intensify competition, and thus reduce production costs.

However, the effects in Brazil in the 1990s were the opposite of expected: rather than decreasing the price of final products, there was an increase in prices and decrease in the amounts sold (Frenkel, 2002).

Given the adverse results, government then adopted a new mechanism for signaling specific social regulation in 1999, namely generic medicines, aimed at decreasing the persistent price increases in so-called brand name products and copy drugs since price liberalization and increasing the demand for medicines, given that a considerable share of the population remained excluded from the market.

Given the peculiarities of the pharmaceutical industry and its essential role for safeguarding human lives, the Brazilian government thus developed new ways of regulating the industry in keeping with the institutional transformations under way. The available literature allows identifying the motives underlying the policymaking efforts to introduce BA/BE testing as an instrument for regulating the Brazilian pharmaceutical industry in the 1990s.

### **5. Regulation of the Brazilian Pharmaceutical Industry**

Change in state's role in Brazil in the 1990s ushered in a new institutional design, namely the regulatory agencies. These agencies are of two types: executive agencies, which implement government guidelines (social regulation) and regulatory agencies per se, which (independently of transitory government options) promote supply of public services based on specific legislation (economic regulation) (Salgado & Motta, 2005).

The main reason for the existence of regulation is the presence of gaps or flaws that jeopardize market development: in other words, markets of goods or services with some flaw should be regulated. Regulation by these agencies aims to find an efficient price, whereby the industry's profitability and consumers' welfare are mutually compatible. In particular, social regulation, responsibility of executive agencies like ANVISA (the National Health Surveillance Agency) has the objective of ensuring industry's conduct in relation to health, safety, and environment (Brasil, 2003a).

In this sense, regulation of the pharmaceutical market is justified, as an extremely relevant market for society with highly peculiar characteristics: inelastic demand due to the essential nature of medicines for people's lives; concentration of drug supply by therapeutic class; high entry barriers for competitors, since the products are knowledge-intensive and require high R&D expenditures; and perception of the medicine's quality based on experience with its use (Ozcan, 2009).

Meanwhile, objectives of social regulation of the pharmaceutical industry are: guarantee access to products by new consumers through price cuts; prevent abuse of economic power against consumers that already use its products; and provide the incentives for innovation.

Thus, Law 9.782 (January 26, 1999) created the National Health Surveillance Agency (ANVISA) under the Ministry of Health (Brasil, 1999), with quite specific characteristics, since it conducts two types of regulation: regulation with a health objective, or social regulation, aimed at guaranteeing the safety and efficacy of medicines for consumers by setting standards; and regulation with an economic objective, to expand consumers' access to medicines by monitoring prices.

Further according to this guideline for institutional change, the Chamber for Medicines (CAMED) was created under Law 10.213 of March 27, 2001, with the following objectives: to rule on applications for exceptional price increases on medicines; to define and receive the documents for the companies' marketing reports on medicines; to rule on the enforcement of administrative sanctions; to set rules for average price adjustments, having adopted price ceilings based on the retrospective criterion; and to set criteria for prices on new formulations and new drugs (Brasil, 2001).

However, with government change in 2003, CAMED was succeeded by the Chamber for Regulation of the Medicines Market (CMED), absorbing its attributions with the main objective of taking over and coordinating activities involved in the economic regulation of the pharmaceuticals market, aimed at expanding pharmaceutical care for the population by encouraging supply and increasing competition (Brasil, 2003b).

In particular, CMED established a new tariff system for the industry starting in June 2003, with the characteristics of a “price cap” regime, a prefixed maximum price: a price ceiling calculated on the basis of the National Expanded Consumer Price Index (IPCA) published by the Brazilian Institute of Geography and Statistics (IBGE) and the application of a productivity factor, as well as a price adjustment factor within and between sectors; a productivity factor aimed at transferring the companies’ projected productivity gains to consumers; an intra-sector price adjustment factor, taking into account monopoly power, entry barriers, and asymmetry of information; an inter-sector price adjustment factor based on the variation in the prices of inputs; and annual price adjustments (Brasil, 2003c).

ANVISA is also responsible for developing the market for so-called generic drugs, medicines equivalent to the brand name products both in terms of their active ingredients and other characteristics, such as quality and expected results.

Generic drugs were not introduced in Brazil until 1999, although they were already highly important in developed countries and accounted for 50% of the North American market at the time. Brazil previously had only so-called copy drugs, unlike generics because even though they had the same active ingredient as the reference drug, their approval did not require BE tests, thus failing to guarantee that their effects in the body were identical to those of the brand name medicines.

Thus, generic drugs were introduced on the Brazilian market in order to increase industry competition and expand consumption of medicines through more affordable prices, since their production involves more modest R&D expenditures on synthesis pathways, because they are accurate copies of a brand name drug already existing on the market and whose patent has expired. Their seal of quality is provided by the BE test, without requiring marketing expenditures which for other kinds of drugs reaches 20 to 30% of a large company’s turnover (Romano, 2005).

## 6. BA/BE Tests for Drug Policy in the United States

In the United States, Congress passed the Food, Drug, and Cosmetic Act in 1938, requiring that new drugs be certified as safe by the Food and Drug Administration (FDA) before entering the market. In 1962, the Kefauver Harris Amendment to this law included two additional provisions: the requirement of proof-of-efficacy for approving a new drug and the establishment of regulatory control of clinical trials conducted with the candidate substance for a new drug.

Thus, the more in-depth control over the introduction of new drugs meant an increase in both R&D expenditures by laboratories and the period between the development of a new drug and its launch on the market. The average time for approving a new drug was twelve years at the time: three and half years for animal and laboratory studies; six for clinical trials in humans (safety and efficacy trials and extensive tests); and two and a half for FDA review – see Figure 1.

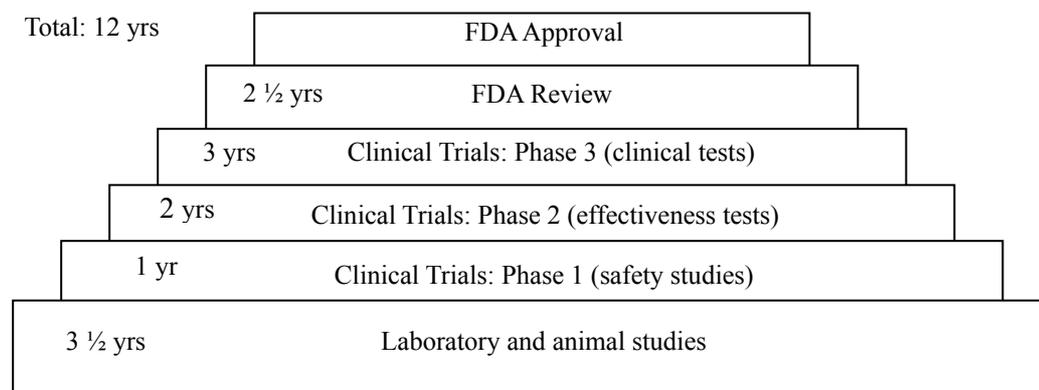


Figure 1. Antecedents for Pre-Manufacturing Drug Certification: Time Required for Approval of a New Drug in the United States in the 1960s

Source: Viscusi, Vernon, & Harrington, 2005.

To the extent that the pharmaceutical industry is innovative, patents are a crucially important issue. Research expenditures already accounted for some 20% of sales turnover in the mid-1990s and have continued to grow. Thus, when industry obtains new knowledge or information as a result of such expenditures, it expects new

drugs to be protected and not copied for a given period, to avoid a disincentive to investments. Without expectations of a sufficient return on investments, companies would not invest in the development of new drugs, which would mean a loss of welfare for society as a whole, given that new diseases emerge every year and many existing diseases still lack a cure (Garret, 1995).

Thus, market's mechanism for incentivizing investment is the patent, which prevents copying new knowledge during a predetermined period. However, society bears a cost while patent is in force, since the innovating firm exercises a monopoly on marketing the new drug and has an incentive to abuse its market power and reap extraordinary profits.

United States adopted one way of reconciling the incentive for invention with the population's level of welfare through Drug Price Competition and Patent Restoration Act of 1984. The law involved the extension of the patent's term from eight to 12 years and the requirement of the bioequivalence test for approving generic drugs, allowing the latter to enter the market faster than before 1984, when generics' producers had to duplicate many stages of preclinical and clinical tests already performed by manufacturers of brand name products in order to prove their drug's safety and efficacy, which ended up increasing the production cost of generics and delaying their market entry, indirectly extending patent life and jeopardizing consumers (Viscusi, Vernon, & Harrington, 1997).

Extension of patent terms was important, because a major portion of the time in which the company was developing and obtaining FDA approval for a new drug (six years on average) was counted as time in which the drug was already protected by the patent. Thus, of the 14 years of a patent's term, the companies only really benefitted from eight years. Under the new law in 1984, the innovating company was thus offered an incentive equivalent to a four-year increase in the patent's effective term, corresponding to a reduction in the time the FDA took to process an authorization for a generic, around two and a half years, plus a year and a half of partial reduction in the time previously used for clinical trials, which took an average of six years.

As a result, the launch rate for new drugs decreased in the United States: for every four drugs that started clinical trials, only one was finally approved. There was also a major lag in their introduction on the market when compared to countries like the United Kingdom and Germany.

This delay has been attributed first to a fundamental difference between regulation in the U.S. and Europe: while the former was centralizing drug approval in the national regulatory agency (FDA), the European agency used expert committees to evaluate the safety and efficacy of new drugs, and these collegiate bodies issued more streamlined reviews, having the power to approve or reject a drug in most of the European countries. Although the U.S. also had expert committees, their importance was more limited and they were only used in selected cases. Second, the introduction of new drugs on the U.S. market was conditioned by pre-market control, unlike the European countries, where regulatory work focused more on post-marketing surveillance of new drugs (Grabowski & Vernon, 1983).

That is, the average time needed for launching a new drug on the U.S. market before enactment of the Drug Price Competition and Patent Restoration Act in 1984 was the only important factor in shaping expectations towards the introduction of BA/BE testing as a regulatory instrument (Note 2).

## **7. BA/BE Testing for Drug Policy in Brazil**

Development of the pharmaceutical industry generally required improving comprehensive regulation over time, especially for the introduction of new compounds. Due to the implications of BA/BE tests for the market's development, the economic literature focuses heavily on regulatory mechanisms for the pharmaceutical industry.

The focus of the current article is to characterize the functionality of BA/BE testing in the regulatory model associated with the reform in the U. S. patent system in 1984, and which served as a reference for designing the Brazilian regulatory framework in the 1990s.

Within the scope of the Generics Law, the role of ANVISA is to regulate the criteria and conditions for the registration and control of generic drugs, besides setting the criteria for conducting BA/BE tests.

However, the literature makes one distinction, since the Brazilian framework includes some peculiarities that the literature defines as having stemmed from the European regulatory model (Regnstrom et al., 2010), based on agencies like the European Medicines Agency (EMA) (Bottomley, Jones, & Claassens, 2009).

Regulation in Brazil is more similar to the U.S. standard than to the European. The Technical Chamber for Medicines (CATEME), created under ANVISA in 1998, was designed to issue technical reviews, which are frequently not subject to appeal, theoretically presenting the great advantage of reducing the time for approval

and marketing of new drugs. The agency was intended to consist of experts chosen by the scientific community, with a two-year term and working on a pro bono basis. However, as in the United States, the role of CATEME was not highly relevant in Brazil and the government ended up limiting its functions (Oliveira, 2003).

In addition, the drug approval process in Brazil also focuses on the pre-market phase, with a series of requirements for approving both generic drugs and copies and brand names, where BA/BE testing plays a fundamental role in both approval of these drugs and renewal of their registration.

BA/BE tests are performed by Bioequivalence Centers, authorized by ANVISA. While private companies conduct such tests in other countries, in Brazil a significant proportion of the centers (25% in 2003 and 20% in 2007) are still government-owned (ANVISA, 2009b).

Thus, the requirement of BA/BE tests is an instrument for incentivizing the supply side, because it reduces the cost of generic drugs for manufacturers and speeds up their entry onto the market, increasing the potential period for obtaining sales revenues.

The requirement of these tests is also an incentive for the demand side, since the result is a sign of quality that guarantees the possibility of replacing the brand name product with the generic, facilitating acceptance of the generic by consumers and physicians and fostering access to medicines.

Since there is little literature on this subject, the open question on organization of BA/BE testing in Brazil is whether government should participate directly in this activity, or subsidize it, or on the contrary, let the market meet the demand for tests, given the promotion aspects mentioned above.

### 8. Industrial Organization of BA/BE Testing in Brazil

Due to the importance of these tests, some problems in the area of microeconomic analysis for developing the market of the Bioequivalence Centers in Brazil deserve discussion, since the resulting challenges still need to be overcome by regulation.

ANVISA participated in the establishment of the first centers in Brazil, furnishing essential (and high-cost) equipment for their activities. ANVISA's interest in developing these centers resulted from the increased demand for the tests after the generic drug policy entered into force. The result was the multiplication of such centers in Brazil under stimulus from ANVISA, which financed purchase of the equipment through funds-in-grant to universities, research institutes, and hospitals.

The subsequent passage of Directives 133 (ANVISA, 2003c), 135 (ANVISA, 2003b), and 136 (ANVISA, 2003a) further highlighted the prospects of increasing demand for the tests. These directives led to the tests' use for the approval of generic drugs, copies, and some new compounds, as well as for renewing their registrations (every five years in most cases) – see Table 1.

Table 1. Market for BA/BE Testing in Brazil

TYPE OF DRUG	REGISTRATION	RENEWAL
Copy	BA test	BA test only for second renewal
Generic	BE test	BE test
New drug	BA test in specific cases	–

Source: (ANVISA, 2003b, 2003c).

The testing centers must meet a series of requirements for ANVISA to authorize their operation, without which they are subject to de-accreditation.

As of October 2003, 201 tests had been conducted in Brazil, but ANVISA predicted a large increase in the following years, and 776 tests had indeed been performed by late 2007, or an increase of 286% from 2003 to 2007 (ANVISA, 2008). Meanwhile the number of certified centers in Brazil increased from 20 to 25 and the number certified abroad – “international centers” – increased from 3 to 25, or 117% (ANVISA, 2009a, 2009b).

There were thus two possibilities: a prevailing upward trend in the average scale of operations in the centers (up 77% from 2003 to 2007) or incentives to certify more centers in order for the test requirements not to jeopardize the effectiveness of the new pharmaceutical policy launched in Brazil in the 1990s (ANVISA, 2009a, 2009b).

Added to this, testing actually consists of three stages, namely the clinical, the analytical and the statistical, but the centers perform all these stages, conditioned by their available financial and human resources. As, despite their importance, the Brazilian centers have experienced various difficulties, of the first 50 centers certified by ANVISA, only 25 perform all three stages (ANVISA, 2009a, 2009b).

Semi-structured interviews on the microeconomics of the testing centers conducted in 2008 by the authors with administrators and experts at the Evandro Chagas Institute of Clinical Research (IPEC) revealed some difficulties for the regular functioning and expansion of these organizations that provided the basis for policy measures needed for their development in Brazil. Although the answers are not sufficient to generalize the results, they do provide a relevant reference for a set of policy guidelines to regulate the testing market that have not been explored in the literature, and which can serve to help accumulate structured evidence through other similar case studies.

### **9. Microeconomics of the Development of BA/BE Tests in Brazil**

The first difficulty involved the development of test methods. Each active ingredient requires a different analytical method, the development of which entails varying degrees of difficulty. Elsewhere in the world there are already firms specialized in developing the methods and selling them to interested parties, but there are no such companies operating in Brazil. However, since 5 certified centers are government organizations (ANVISA, 2009b) and evidence points to economies of scale and scope in researching new methods, there are gains of efficiency to be obtained through cooperative research among these centers, with a view towards not having the method developed by other centers (thereby wasting scarce public funds).

Another difficulty identified by the study is that each test method only serves for a given type of equipment, generally imported (a phenomenon known as technological lock-in), which limits the centers' possibilities for acquiring methods to diversify their production portfolio (a potential source of competitive advantage reported in the interviews). In fact many costs (including infrastructure) can be shared in developing the different methods.

Thus, greater integration among the centers becomes important, particularly among the government-based ones, in order to reduce the inherent costs of research on methods, with a view towards a lower final test price and also for the domestic pharmaceutical industry, where the firms are smaller than their foreign competitors, and which have their budgets bound by the requirement to perform the tests, an additional expense of some 50 thousand US dollars per drug (Câmara dos Deputados, 2000).

Meanwhile, there are also economies of scope for conducting the tests, sometimes by therapeutic class (BA), other times by groups of similar molecules (BE). However, not all the studies can be performed concurrently, since they can display major differences leading to what is known as high set-up and change-over costs (Note 3) (Alcorta, 1992). Even so, similar studies can share campaigns with common use of the equipment, thereby cutting costs. Again, this points to the importance of cooperation among the centers, but it mainly highlights the importance of management capacity-building as a source of competitive advantage for each center's expansion.

In fact, in order for a center to respond to the "high demand" – or operate in "high throughput" conditions according to the expert jargon – and ensure its strategic positioning, it becomes necessary to develop the managers' marketing and operational skills to optimize the choice of the mix of products and operational plans targeting the search for technical efficiency (Ozcan, 2009).

Finally, in this activity's "infant" stage in Brazil (Lisboa, 2002), the lack of a well-defined government policy for the centers, i.e., a research coordination plan that serves to effectively back the efforts already made at the initiative of ANVISA, constitutes another problem, for this activity to be able to serve as the basis for the development of new drugs, as suggested by the experts interviewed here.

Thus, considering that the market does not provide the incentives for technical cooperation among the centers, and that from the point of view of overall efficiency some type of government incentive is needed to promote cooperative research for the production of knowledge for crosscutting use in the development of test methods, the coordination of R&D efforts with incentives would bring a positive net benefit for society as a whole.

In other words, the available evidence shows that BA/BE testing is a path-dependent activity (Romer, 1994) that benefits from scale economies and thus allows access by innovative entrepreneurs to subsidized direct public financing (with or without partnership with public laboratories), since by combining minimum critical capability an experienced center ensures self-sustainability (threshold effect), thus not producing the risk of permanent dependence on subsidies (Prasad, Rogoff, Wei & Kose, 2003).

Beyond enforcement, complete compliance with the legislation's test requirements prior to drug approval is fundamentally important for the centers' future and will create a permanent demand for the tests, allowing more structured planning of these centers.

The interviewees also identified some existing cooperation among the centers. Such cooperation is acknowledged as one of their main objectives, based on all the advantages cited above; however the initial

attempts were made exclusively at the centers' initiative and not as the result of a government policy to promote cooperative research.

Another need identified by the experts was to identify new management models in keeping with the expectations from the early 1990s to operate the government centers under management conditions consistent with the demand for tests resulting from the new legislation and the industry's requirements (see Table 2). At the time, only one high-throughput center was operating in Brazil, created in one of the laboratories at the University of São Paulo (USP).

Table 2. Challenges and Prospects for Government BA/BE Testing Centers in Brazil

<ul style="list-style-type: none"><li>• Consolidation of Human Resources Training</li><li>• Expansion of Installed Capacity</li><li>• Meeting the Institutional Demand</li><li>• Meeting the "High Demand"</li></ul>
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Source: Prepared by the author.

Therefore, public policies involving temporary assistance aimed at efficient industrial organization of BA/BE testing in Brazil can contribute to greater autonomy for Brazilian pharmaceutical companies. This can involve direct financing of new centers, expansion of existing centers, or channeling the institutional demand through procurement (Laffont & Tirole, 1993) in order to promote investment by domestic companies and provide the incentives for an increase in the average scale of operations in the domestic centers (both public and private).

## 10. Conclusion

This study sought evidence on the characteristics of the technical change, industrial organization, institutions, and dynamics of the Brazilian pharmaceutical industry in the 1990s and especially on the organization and functioning of BA/BE testing in the country with a view towards investigating the need for government participation in this activity and identifying a self-sustainability strategy for the existing government centers given the prevailing technical and economic environment in the initial decade of this century.

The collection and analysis of relevant evidence on this theme has received little attention in the literature, and the specific examination of the implications of the new world trade order for the organization of BA/BE testing helps explain the genesis and functioning of mechanisms for social regulation to provide the incentives for this activity.

Introduction of BA/BE tests appeared as a consistent mechanism for the promotion of social welfare policy to the extent that it combines the extension of drug patents' effective term (an incentive offered to innovative companies), reduction in the manufacturing cost of generic drugs, acceleration of their entry into the market (a supply side incentive), and substitution for generic drugs of brand name (a demand side incentive), while contributing to the development of the pharmaceutical market.

In this sense, the pace in the certification of centers by ANVISA became decisive. Contrary to policymakers' wishes, the number of test centers certified in Brazil in the 1990s, and especially the number of international centers, in the absence of a proactive stance by the agency and without government participation in production, proved insufficient to meet all the demand created by the new legislation, signaling the risk of increased concentration of the activity and adverse implications for competition and innovation.

Finally, given the legislation of the 1990s, support from ANVISA for systematic market studies on the potential number of tests predicted for the following years was considered important for the centers to deal with market uncertainty.

This study showed the need for new case studies to fill gaps in knowledge on the microeconomics of BA/BE testing centers in order for the industrial organization of the activity (size and ownership of the assets) not to limit the efficacy of the Brazilian national policy for medicines.

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### Notes

Note 1. This System aimed to provide support for R&D efforts in chemistry by government universities and research centers (Frenkel & Ortega, 1985).

Note 2. Nevertheless, it is a known fact that the time needed for the development of a new compound decreased subsequently, but that this trend did not affect the need for tests during the period analyzed here.

Note 3. Refers to the costs of alignment with a type of test and of changing to another type.