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Abstract

Generic drug substitution may constitute a core instrument of countries' National Pharmaceutical Policies, a way to reduce the price of drugs while expanding access to health care. Despite the potential importance of policy in this area and observed differences in national practices, scholars embarking on comparative analysis lack a roadmap of which dimensions of generic drug policy to assess and compare. We consider countries' rules and regulations across four dimensions: (1) the demonstration of therapeutic equivalence, (2) pharmaceutical packaging and labelling, (3) drug prescription, and (4) drug substitution. We maintain that to be able to understand and compare national approaches toward generic drug promotion, it is crucial to carefully distinguish among these four dimensions. Furthermore, we suggest that analysis must also consider how the diverse interests of actors in public and private sectors shape the design and implementation of generic drugs policies. To illustrate both the dimensions of policy and the conflicts around generics policies, we focus on the case of Brazil.

Introduction

To reduce the price of drugs, the World Health Organization (WHO) has long promoted generic drug substitution as a component of countries' National Pharmaceutical Policies (1). To that end, the WHO established the guidelines by which one product is interchangeable with another (2), that is, the technical criteria to define when one pharmaceutical product can be exchanged for another, as well as the policy mix that could lead to a higher rate of generic drug use.

We know a great deal about the policy instruments and mechanisms countries can use to promote both the supply of and the demand for generic drug products (1, 3, 4). Anecdotal evidence and casual observation suggests that there is significant variation in national pharmaceutical policies in this area (5, 6). One challenge for comparative analysis, however, is the lack of agreement on which dimensions of policy to analyze and compare. This paper innovates by proposing a taxonomy of generic drug substitution systems, which can be used in comparative analysis. To illustrate the utility of the taxonomy we apply it to the case of Brazil.

To understand the diversity in national practices, we need to consider key questions regarding the promotion and regulation of generic medicines. How, for example, do generic drug products demonstrate that they are therapeutically equivalent to originator products? Are generic drug products allowed to display brand names? Should doctors prescribe using the generic name or are they permitted to use a brand name? Are pharmacists authorized to substitute an innovator product with a generic version? These questions can serve as dimensions that can be used for comparative analysis. In the remainder of this paper we explain the significance of each of these issues (equivalence, packaging/labelling, prescription, substitution), and we then illustrate these dimensions with observations from the case of Brazil.

Dimensions of Analysis: Equivalence, Labelling, Prescription, Substitution

Regulatory authorities set standards for which drugs need to be therapeutically equal to reference products. This is demonstrated with tests of bioavailability (BA) and bioequivalence (BE). BA measures the extent to which a drug is absorbed into the body and available to act upon the drug's intended target (the site of action). BE is a regulatory concept that demonstrate that there is no significant differences on the rate

of two drugs over the course of a period of time, at the same dose and under the same conditions. That is, products that have the same BA are considered generic drug products, while products with different BA are considered similar drug products (or multisource drugs, according to the WHO terms).

Demonstrating BE is essential for generic drugs. Small differences in bioavailability may alter the effects of the drug, therefore, it cannot be considered equivalent. The concept of BE is crucial when considering medicines with highly toxic ingredients or in a Narrow Therapeutic Range (NTR)[1], i.e. small differences in the dose can have toxic effects in the body. National regulatory authorities have discretion to define how it will measure products' NTR but also which medicines will need to go through the BE tests.

The regulatory question is essentially about determining which drugs are required to demonstrate BE and this is a decision that lies with each country. BE has arguably been associated with quality control (7) and it has often been difficult to define which products need to undergo it (8).

The second dimension for comparison regards countries' rules on labelling and packaging of generic products. Use of the generic name or international non-proprietary name (INN), usually a simplified version of the chemical name, can remove the obscurities that brand names create in identifying pharmaceutical substances. Not only may the INN be displayed on the pharmaceutical packaging, but font size and presentation will differ according to local regulations. For instance, some countries require the INN to be no less than 30-50% smaller than the font size of the brand name, some require that both be of equal size, while others still have banned the use of brand names altogether (1). Regulation of pharmaceutical packages and brands is very important in this sector, as marketing strategies represent an important element of the product cycle (9). As we shall discuss in more detail below, this is true not just for "innovator" firms but also for follow-on "generic" producers.

Prescription and substitution are the third and fourth dimensions of our typology. The use of the generic name facilitates the prescription and dispensing of pharmaceuticals to patients, as well as the communication among health professionals and scientists (2). It also allows for easy "comparison shopping", as there might be different suppliers of the same pharmaceutical product, that is, drug substitution.

[1] NRT drugs have less than a 2-fold difference between the minimum toxic concentration and minimum effective concentration in the blood.

Depending on national regulations, doctors might be required to prescribe by generic name; they may also include the brand name and recommend that the particular product be supplied or even forbidden the substitution for another drug. Other regulations might allow pharmacists to consult the patients to determine if they want the prescription filled with the brand name medicine or the generic medicine.

This discussion of prescription and regulation is, of course, closely related to the previous discussion of labelling and packaging. After all, pharmaceutical firms invest heavily in distinguishing their brands, and they actively promote their brands among doctors and pharmacists. These promotional efforts can create incentives to prescribe or substitute one product for another. Even if health professionals have no doubts about the quality standards of generic medicines, doctors may be disinclined to prescribe them and pharmacists may be similarly disinclined to substitute them for reference products (10).

In the remainder of this paper we examine Brazilian policies toward generic substitution, through the lens of our taxonomy. The findings are based on empirical data collected between 2007 and 2015, including government documents in Brazil (e.g., policy memos, official speeches, etc.); more than four hundred newspaper articles; and scientific papers. These data are supplemented by 60 interviews with key informants such as lobbyists, regulators, and representatives of local and multinational pharmaceutical companies that have participated in the policy process.

Generic substitution in Brazil

Brazil is a case study that is crucial to understanding the regulation of interchangeable pharmaceutical products. Among Latin American countries, Brazil has the largest generic drug sector, which represents almost 28% of the pharmaceutical sales in the country. While Brazil has witnessed high levels of generic market penetration, the process has been accompanied by a number of conflicts and challenges.

Equivalence

In 1999 the Ministry of Health took a decisive step to promote the substitution of a pharmaceutical product by its equivalent. With the enactment of the *Generic Drug Act* that established demonstration of bioequivalence (BE) as a condition for

market entry. The Generic Drug Act promoted a major reform in the pharmacological parameters for registering off-patent pharmaceutical products in Brazil. The introduction of rules for therapeutic equivalence represented one of the most contentious elements of regulation affecting the country's pharmaceutical sector, highlighting some of the political controversies surrounding drug substitution. Brazil introduced comparatively stringent requirements compared to other Latin American countries. A study conducted by PAHO concluded that of the eighty-six drugs analyzed in Latin American countries, fifty-one required demonstration of bioequivalence in Brazil. No other national regulatory authority examined by PAHO requested bioequivalence for so many drugs (11). Many local pharmaceutical firms claimed they would be unable to comply with these regulations given the high costs associated with them and the lack of expertise in Brazil necessary to conduct such complicated testing.

In Brazil, the regulatory authority took a decisive step in supporting and advocating for bioequivalence tests, but also promoted close collaboration with industrialists to help the national producers comply with the new requirements (12). For instance, the regulatory authority created a fast track approval process for firms prepared to register generic products and provided constant consultation and support to local firms to clarify and supervise changes to their regulatory departments. While in 2002, 27.3% of BE studies conducted in Brazil, by end of 2009, 87.6% were performed locally (13).

Local firms not only managed to adapt to the new requirements, but also became market leaders in the pharmaceutical sector (12). Local firms that adapted to the new regulations soon saw generic drugs as a valuable opportunity in terms of market share and improving industrial capability. Local pharmaceutical industries account for 88% of the domestic generic drugs market. Table 1, based on IMS Health data that includes both patent and off-patent products collected only from retail market (excludes government data, which are mostly essential medicines, drugs for AIDS treatment and other patent, high cost products), demonstrates the evolution in the growth of pharmaceutical sector and the current day status of local firms.

Table 1 here

Thanks to the gains made in industrial capabilities brought about by the BE resolution and the increased relevance of local pharmaceutical producers, the local pharmaceutical sector became a national industrial policy priority. Pharmaceutical sector representatives assisted the Government in identifying bottlenecks to the sector's expansion in Brazil (14). As Brazil is highly dependent on the import of key inputs for medicine production, e.g. raw materials and active pharmaceutical ingredients, this was identified as one of the priority areas for investments in the industrial policies (14, 15). The consensus among representatives of the pharmaceutical sector is that the generic drug regulations, first seen as a threat to their survival, have ultimately been instrumental in improving manufacturing plants and processes.

Labelling

The regulation of pharmaceutical products labeling is not a recent issue in Brazil. Three attempts to regulate packaging and non proprietary names raised heated political debates. First, in the early 1990s, a Congress Bill proposed to ban the use of brand names from all pharmaceutical products (Bill 2022/1991). At that time, there were two types of products in the market: the reference product (usually the innovator product) and the similar medicine (a copy of the reference product, but without equivalence tests), both commercialized under their respective brand names. Bill 2022/1991, which was justified by the fact that 50 million people had limited access to medicines, proposed that all pharmaceutical products in Brazil should be commercialised using either the Brazilian or International Non-proprietary Name, BNN and INN, respectively (in the BNN is not available, doctors should use the BNN) . The rationale was that reducing the font size of the brand name would also reduce the cost of the product and facilitate interchangeability. The use of brand names, it was proposed, would be allowed only if they were presented in a smaller font size compared with the generic name; all public health service prescriptions should use the generic name.

In 1993, and parallel to Congressional negotiations, the Ministry of Health promoted a second attempt to regulate these dimensions of generic drugs. The Ministry of Health sponsored Presidential Decree 793/1993, which required, among others, that the font size of brand names could not exceed one-third of the generic name and all drugs prescribed and procured by the National Health System should use

the generic name. The pharmaceutical industries and drug retailers promptly reacted through judicial battle, arguing these requirements would harm their businesses (16), and neither the Executive Decree or the Congress Bill survived (17).

It was only with the Generic Drug Act in 1999 that the discussions on INN and labeling progressed. The Law also stipulates that all generic drugs would provide only the INN, and that the packaging would include a yellow stripe with the letter "G", indicating that this product was interchangeable. In contrast, for the labeling of innovator products, the trademark would be displayed in a larger font size, and the (BNN) or INN would come right below, in a font size no less than 50% of the brand name. The packaging of similar drugs would have the same regulatory standards as the innovator products, but would not be interchangeable because, unlike generic products, they did not provide equivalence tests.

Prescription and Substitution

During the debates in Congress that led to the Generic Drug Act, the prescription rules for doctors were also highly controversial with the government and pharmaceutical industries, both national and multinational firms, disagreeing starkly on this component of the bill. The pharmaceutical industry demanded that generic drug substitution only be allowed by a doctor's written request. However, the government did not agree to negotiate this aspect of the bill; thus, if doctors do not agree with generic substitution, they must indicate "substitution not allowed" on the prescription (18). While doctors at the National Health Service (SUS) are obligated to prescribe using the generic name, private physicians are not bound by this rule and thus can continue to prescribe by brand name.

Effects and emerging challenges in Brazil

The prescription of generic medicines, i.e., by INN, is still low but has increased over time, representing 20.9% of the total prescriptions in 2006, compared to 11.8% in 2002 (19). Despite the growth of the generic drug market in Brazil, there is still low consumer awareness regarding drug substitution and slow acceptance by physicians (20). Studies suggest that there is confusion on how to differentiate between pharmaceutical products (innovator, similar and generic) and a lack of confidence in the quality of generic drugs (21) (22)

In terms of generic drug prescription, academic studies, market assessments and a number of newspaper articles point out that health professionals are still

resisting prescribing generic drugs (23, 24). For example, a survey conducted in 2006 in eight Brazilian capitals assessed the opinion of 55 health professionals. Results showed that 44% of the health professionals surveyed believed that generic drugs were not as reliable as the original drugs, and that among those who trusted generic drugs, 17% did not prescribe them (25).

Public pharmaceutical assistance programmes could represent an important opportunity for generic medicine substitution. The *Generic Drug Act* (Law 9787/1999) mandates that all public purchases and prescription of medicines should be done using the generic name. However, recent studies that assessed the availability of medicines in Brazil have demonstrated that, in the public sector, generic medicines are less available than similar drugs (26, 27). For the majority of pharmaceuticals assessed (71.4%), the availability of bioequivalent generic drugs was less than 10% (26). The authors suggest that public purchase of medicines has greatly privileged similar drugs. If correct, these numbers reveal an inconsistency between the pharmaceuticals that physicians prescribe in the Unified Health System (SUS) and the pharmaceuticals provided by public health facilities.

What might account for this inconsistency? The legislation that regulates the public procurement of medicines (and other goods and service contracts) determines that, if all technical requirements are met, the provider that offers the lowest price wins (Law 8666/1993). By contrast, generic drug legislation stipulates that in this case generic drugs should be given the priority (Law 9787/1999). Miranda *et al*. (2009) speculate that this inconsistency might be happening because: (a) generic drug producers are not interested in participating in public procurement, (b) better prices are offered by similar producers, or (c) there are difficulties following the legislation requirements.

Recent reforms and challenges

In 2014, as a response to the lack of confidence that many patients and health professionals have in generics and similar medicines, the government proposed a new regulation to clarify which pharmaceutical products are therapeutically equivalent. At the suggestion of the Ministry of Health, the National Regulatory Agency (ANVISA) proposed a new resolution to modify the packaging of pharmaceutical products[2]. The

[2] http://goo.gl/SwBa5r (accessed in August 26, 2014)

new resolution would allow pharmacists to substitute the reference product for a generic or a similar product.

To understand the challenges facing health policymakers in Brazil, keep in mind that most non-originator drugs have demonstrated bioequivalence. Most similar drugs are now BE; very few drugs that have yet to demonstrate this remain on the market. Yet most of these non-originator BE drugs continue to have brand names. These branded BE drugs, essentially like "branded generics" commercialized in retail markets in the US and UK, represent 47% of the pharmaceutical market (units), while formally "generic" drugs (i.e. BE and without a brand) represent 27% (Table 2). Yet substitution is only allowed for generics; similar drugs cannot be exchanged once prescribed by a doctor. The government's intention was to adjust the packaging of interchangeable pharmaceutical products to include the symbol "EQ" – a visual label that would show that one product can be switched for another one.

Table 2 here

The Government argued that the 2014 EQ regulation would increase consumer options among products that are proven to be therapeutically equivalent, thereby reducing their price. The government maintains that this regulation was a response to 2001 Resolutions 133 and 134, which established 2014 as the deadline for similar medicines to submit bioequivalent testing for agency approval, and a logical follow-up to the earlier initiatives. Different from the discussion in the early 2000s that centered on quality and manufacturing processes, the EQ debate is only concerned with the labeling of pharmaceutical products.

The announcement was made in January 2014 by the Minister of Health, Alexandre Padilha, one month before he resigned his position to campaign for elected office. This decision raised heated debates among pharmaceutical industry representatives. Technically, they argued, it was reasonable, as all products are the same, and have the same active ingredients and therapeutic responses (personal communication with the CEO of a Brazilian Pharmaceutical Industry in February 2014). However, opposition to the EQ regulation is based on the following argument. The EQ label, it is argued would commodify reference products and similar medicines; both products still hold a brand-name with strong marketing strategies focused on prescribers. Therefore, pharmaceutical firms (local and multinationals)

that commercialize their products under brand names feared that they would be adversely affected, that the presence of EQ on the label would essentially send a message to ignore their brand markings. After a heated discussion with the pharmaceutical industries and a public consultancy held by ANVISA (Public Consultancy No 01/2014), Resolution 58/2014 was issued in October 2014, responding to the demands of the pharmaceutical industries. The policy outcome was that no EQ symbol would be added to labels, but rather that the leaflets are inserted inside of pharmaceutical packages would indicate if that product can be interchangeable. In other words, this information will not be available at the first sight.

The debate over the EQ resolution is important for two reasons. The resolution intended to diminish the role of branding by emphasizing the equivalence of equivalent products. In doing so it would increase the scope of substitution and, it was expected, reduce the price of drugs. Although the idea behind the EQ proposal has a strong public health rationale, the structure of the pharmaceutical market in Brazil creates economic interests that were able to dilute the measure – and may yet subvert this policy instrument. The debate also illustrates how Brazil innovates in generic regulation, not just using traditional instruments of interchangeability (i.e., the INN) but with additional information in the package leaflet.

Conclusion

We began this analysis by calling attention to the diversity of national generic drug regulation and its core policy instruments. We contribute to the literature by building new conceptual and empirical evidence on developing countries' compliance with generic drug guidelines. To understand regional differences and regulatory choices, one must clarify what the incentives and public health interests of these instruments are and also what the country's institutional opportunities are to promote them. To demonstrate these relationships, we focused on the regulation of INN and prescription rules; bioequivalence and of pharmaceutical packaging in Brazil.

The case of Brazil demonstrates that regulation of INN and bioequivalence are not just technical concepts but highly contested political decisions. The Generic Drug Act in 1999, which introduced a new pharmaceutical product into the market, was an opportunity to foster the use of the INN in Brazil as a prescription rule and improve

the pharmacology requirements to register non-patent drugs. Though in the 1990s and early 2000s, the debate revolved around the font size of the INN in relation to the brand name and the prescription rules and the therapeutically equivalence. This paper highlighted the strong conflicts of interest in applying these generic drug instruments.

Core lessons and implications from this case study are that: (a) The diverse interests of actors in the public and private sectors shape the design and implementation of the four core dimensions of national generic drug regulation. To design regulations that are effective and long lasting, it is crucial to understand the politics of drug substitution, i.e., their effects on public health, business preferences and strategies. (b) The task ahead is to think more clearly about the set of dimensions that influences national generic drug systems. This paper provides an initial step, which hopefully will attract the interest of scholars to evaluate our claims, refine, and apply them to other contexts.

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Table 1. Ranking of pharmaceutical industries in Brazil (US$), 1999 and 2001-2011

Industry	YEAR												2011 Market Participation (%)
	99	01	02	03	04	05	06	07	08	09	10	11	
EMS	29	12	6	5	5	5	3	2	1	1	1	1	7,77
Medley	32	19	12	7	6	7	6	4	4	4	2	2	7,11
Ache	3	2	2	2	2	2	2	3	3	3	4	3	5,24
Sanofi	1	1	1	1	1	1	1	2	2	2	3	4	4,63
Eurofarma	28	25	21	19	16	9	8	6	6	6	5	5	4,14
Neoquimica	*	48	48	39	36	39	38	36	31	20	8	6	3,71
Novartis	2	4	4	4	4	4	4	5	5	5	6	7	3,54
MSD	*	9	7	8	10	16	17	7	8	8	9	8	2,56
Pfizer	7	3	3	3	3	3	5	6	7	7	7	9	2,43
Bayer	23	16	12	17	11	6	7	7	8	8	11	10	2,16
AstraZeneca	19	21	22	23	23	22	20	15	12	9	10	11	2,03
Teuto	*	37	39	48	50	54	50	43	38	29	16	13	1,89

Source: (28 - with IMS Health data) and updated information from Sindusfarma (email).
Obs. Bold cells refer to local pharmaceutical industries.
(*) I was not able to get information for these years

Table 2. Distribution of pharmaceutical products by value (R$) and units in Brazil, Aug 2013–Jul 2014.

Pharmaceutical product	Value (R$)	Units
Similar drugs	44.48%	47.75%
Similar drugs (without BE)	0.39%	0.57%
Reference product	30.83%	23.81%
Generic drug	24.29%	27.86%
Total	62,132,559,369	3,010,750,992

Source: IMS Health, 2014 (information provided by email).