

Chapter 2

Contextualising Drug Regulation

This chapter aims to provide a critical analysis of the literature on policy studies on generic drug regulation and contextualise the Brazilian case. Very few studies of the political process to implement generic drug regulation were identified. This type of study is particularly important in clarifying how the drug policy is discussed, approved and implemented. Because of the limited supporting literature, this section expands the scope of the review to explore broad studies on the regulatory process of the pharmaceutical sector. The last part of this chapter focuses on contextualising the case of Brazil. The country has one of the most stringent regulatory regimes for generic drugs in Latin America and has promoted significant reforms in its pharmaceutical regulation. This section provides background information about this reform by revising previous studies on this topic and identifying avenues for investigation.

Reforming Pharmaceutical Regulation

There are few studies on the political and historical perspective on generic drug regulation. The study of Ascione et al. [26] presents a historical analysis of the American case based on an extensive secondary data review through indexing services. The authors assess the events that preceded the Hatch-Waxman Act in 1984, suggesting that generic drug regulation resulted from the lobbying of the generic drug industry with the assistance of consumer groups that had pressured Congress to enact a legislation that would simplify and accelerate the generic drug approval process [26, p. 569]. These authors suggest that the history of generic drugs in the USA results from a conflict between economic actors; that is, innovator firms seeking to protect their market share versus a less unified coalition of consumer groups, health professionals and care organisations and generic manufacturers that seek to reduce health-care costs in general, or the rising costs of a particular therapy. Another source of conflict is between professionals, with the pharmacists trying

to expand their role in health care and dispensing or substituting pharmaceutical products, and those in the medical profession trying to limit pharmacist interference in their prescription practice. Finally, the authors point to the scientific debate within regulatory communities on the comparative efficacy of all pharmaceutical products. Note that these authors do not have a background in policy studies but in pharmacology. Although they provide a rich analysis of the evolution of generic drug policy in the States, they are less concerned with its underlying social and political process.

Carpenter and Tobbell [24], who have also analysed the American case, provide an in-depth analysis of the historical construction of the bioequivalence concept. The authors suggest that this is a joint scientific and regulatory concept developed within a network of pharmacologists, regulators, lawyers and American policymakers with a stake in generic drugs. They highlight the role of the state in shaping the scientific process, network of regulators and scientists, emphasising the regulatory concept formation. They point out that, during the 1970s, the Food and Drug Administration (FDA) progressively became responsible for developing a methodology to access bioequivalence and facilitate the entry of off-patent drugs into the market. This placed the Federal government as a guarantor of equivalence standards. A negotiation in Congress, through an agreement between both parties (democrats and republicans) and between innovators and generic manufacturers, led to the Hatch-Waxman Act. The nascent generic industry would benefit from a rationalised regulatory application process and a bonus of 1 year of exclusivity for the firm that first markets the product, while innovator firms would be granted a longer period of brand exclusivity. Progressively, these innovator firms dropped their claims against generic medicines. In another publication, Carpenter highlights the political relevance of the FDA's reputation, suggesting that its guidelines serve as a model to other countries [14]. This includes the diffusion of bioequivalence concept, which would be adopted by other countries taking the USA as a benchmark.

Both of these studies highlight two accounts of the pharmaceutical regulatory process. One refers to the diffusion of international regulatory guidelines and the other to positive theory of regulation.

Global Health and the Diffusion of International Guidelines

There is a group of scholars of pharmaceutical regulation who claim that international regulatory standards formulated by developed countries inspire developing countries to revise their local guidelines. This seems intuitively plausible as organisations, such as the European Medicines Agency, the American Food and Drug Administration, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), set the rules to enable pharmaceutical firms to access the market of developed countries. In addition, the scientific expertise of these agencies can encourage governments to emulate their guidelines.

The study of Brhlikova et al. [67] suggests that good manufacturing practices (GMP)¹ in Nepal and India could potentially harm local production of affordable pharmaceutical products. The authors suggest that GMPs, widely supported by developed countries and the World Health Organization (WHO), might represent a market barrier to entry, sustainability and perhaps market expansion of local pharmaceutical firms in India and Nepal. These norms imply costly adjustments, particularly for Nepali firms that focus mainly on the domestic market.

Dan Carpenter [14] studied the reputation of the FDA for its scientific expertise and responsibility for shaping concepts such as GMP and bioequivalence, which are widely used in other countries. The author argues that the organisational image of the FDA—understood as a set of symbolic beliefs about the FDA, embedded in multiple audiences—explains much about its reputation that inspires credibility. Through an extensive historical analysis of the activities of this organisation and how this image was built (e.g. scientific accuracy and stringency that avoided such a drug crisis as the Thalidomide scandal in Europe), he suggests that this has led to countries in Europe and India emulating much of their rules.

Since the late 1980s, the WHO has disseminated the idea that the introduction of generic drugs could foster market competition and increase access to essential medicines [cf. 68]. The 2001 document “Guidelines for Developing National Drug Policies” dedicated a section to informing countries of the steps to be taken should they decide to introduce these products (e.g. market supply and demand mechanisms) [4, 68, 69]. The WHO also provides guidelines on the use of non-proprietary names, and further technical specifications of drug registration [e.g. 22, 25]. Following the rationale from this group of studies, generic drug policy could be understood as the emulation by other countries of international organisation guidelines, such as the WHO or other respectable agencies from the North.

Two elements in this discussion are important for this book. The first refers to pharmaceutical regulation as a cross border health-care business and global health concern. Harmonisation of pharmaceutical regulation is important as medicines (and particularly generic drugs, which are commodity products) are goods that can be manufactured but commercialised in a different country, thus have a direct impact on trading activities of firms and health care more broadly. This is particularly important in the context of economic integration and increased the number of bilateral and multilateral trade agreements [cf. 70]. A common regulatory environment for free circulation of pharmaceutical products might require a harmonisation of its members’ rules. International agencies, such as the Pan American Health Organization, have been discussing strategies and norms to conciliate different regulatory norms in Latin American countries [71]. The guidelines proposed by the WHO could facilitate this process of harmonisation, as these are legitimate and credible models. However, little is agreed between member countries on how to formulate these norms to secure public health interests [72].

¹ Regulatory aspects of the drug production process that assure that medicines are produced according to the quality standards necessary to their use and according to the marketing authorisation rules.

The second refers to how these guidelines are disseminated across countries. Although the authors discussed in this section are more concerned with the practical implications of diffusion and harmonisation of regulatory rules, the theoretical aspect underpinning their analysis resembles “policy diffusion” arguments. A path-breaking study from this perspective is Peter Haas’ epistemic communities [73]. In short, Haas argues that these communities are networks of experts whose shared ideas underpin their efforts to influence policy. Because policymakers face multiple problems with several choices and uncertain outcomes, they would turn to these epistemic communities for solutions and reduce uncertainty. In this sense, WHO’s guidelines on pharmaceutical policy and regulatory norms, such as bioequivalence and National Drug Policy, could represent a major blow to the worldwide expansion of generic drug policies.

The international context and best practices on generic drug policy are indeed relevant and of unquestionable influence when decision makers come across their recommendations. There is a certain level of organisational isomorphism between the international recommendation and a country’s regulation. Thus, pharmaceutical sector is a crucial case to assess evidences of policy diffusion. If the emulation of international guidelines affects government decisions, it does so in this sector. However, policy diffusion is not sufficient to initiate a regulatory change in pharmaceutical sector and, in reality, there are profound differences in generic drug regulation among countries [cf. 34]. The analytical model proposed in this book suggests that it is necessary to understand primarily how domestic pharmaceutical regulatory regimes shape the preferences of actors engaged in the policy process in order to understand the extent in which these best practices/international guidelines matter for policy development. In other words, the institutional arrangement in place mediates the adoption of policies proposed by these international organisations/agencies.

Access to political systems and the ability to make winning coalitions are determined by the domestic structure of the country adopting these ideas (cf. Risse-Kapfen 1994). Although these are well-established analytical arguments for studying regulation [cf. 74, 75], apparently those health policy scholars concerned with pharmaceutical regulation have not explored them in depth. Variations occur according to governments, institutional legacies and bureaucracies [76, 77]. These authors argue that normative aspects of regulatory design are deeply related to politics. Complicated pharmaceutical reforms, such as generic drug policy, require the acquiescence of a constellation of domestic agents and institutions. Although the WHO or the FDA can indeed inform policymakers, by looking at domestic structures we can better understand why and how policies developed the way that they did. International models of regulation are incorporated into the analysis of this book as stimuli to which Brazil responded rather than a determinant of the reform outcome.

Positive Theories of Regulation

The seminal contribution to this literature was the study of Stigler on regulatory capture that assumes that regulation tends to favour economic actors [78]. It states

that, because regulation necessarily implies a redistribution of income, some groups would benefit while others would bear its costs. Thus, groups with low organisational costs and higher per capita benefits would tend to be more successful in influencing the regulatory process. By contrast, diffused groups, as consumers, would be less likely to influence the process than small and homogeneous ones. For instance, business groups would lobby for regulations to keep potential new entrants out of the market and enable them to raise the price of their own products.²

Overall, the literature on the positive theory of regulation is vast and has been the mainstream in studies of politics of regulation.³ For the purpose of this book, it is important to understand that for these scholars all agents behave strategically in order to maximise their utility (e.g. profit, election). It assumes that the economic world is constantly in equilibrium, that the economic agents are able to identify opportunities to achieve their preferences and would always act in a purposive manner. Although this understanding of interactive activity is rather simplified, it has advanced the discipline substantially in the past decades. Yet studies on the policy process of the pharmaceutical sector and other social regulation has received less attention in this field, perhaps due to the considerable uncertainty about the social phenomenon itself and the consequences of its policy alternatives [75]. Nevertheless, the existing studies on pharmaceutical regulation agree, to some extent, with this notion of actors' identity.

Abraham has published several studies on the politics of pharmaceutical regulation in Britain, Europe and the USA [84–86, cf. 87]. He developed the concept of “corporate bias” to explain the social process of regulatory development. In this sense, corporate bias has the meaning: “pharmaceutical industry was, and is, permitted to have privileged strategic access to, and involvement with, government regulatory policy over and above any other interest group; and more often than other factors, the industry was, and is, decisive in determining regulatory policy outcomes (or lack thereof)” [84, p. 873]. His studies emphasise heavily the idea that actors engage in the regulatory process to maximise their utilities [84]. Assuming that pharmaceutical industries are interested in profit maximisation and patients have objective interests in “drugs having the maximum benefit-risk ratio possible”, the author suggests that the regulatory process in this sector tends to be biased towards commercial interests [84, p. 869, 85]. For example, in the 1970s, while the FDA rejected or delayed the approval of many drugs, including beta blockers (to treat coronary illness), the British authority constantly approved them [88]. The authors note that, during this period, British pharmaceutical firms contributed heavily to the national balance of trade, thus the government had prioritised the industry's commercial goals and productivity over patient safety.

² Other scholars have expanded this theory by taking into account the fact that politicians/regulators combine the interests of firms and consumers, while others combine normative elements of efficiency to positive emphasis on distribution of rents [79, 80, 81, pp. 16–18].

³ Comprehensive reviews of this theoretical approach can be seen in Noll [82], Pitelis [83] and Baron [75].

Similarly, Dan Carpenter has also studied the politics of pharmaceutical regulation from a rational perspective, but with less emphasis on the role of the pharmaceutical industry as the main driver of the regulatory process. For instance, he posits that the FDA is interested in maximising its reputation for protecting consumers' safety and public health (considering not just a selfish motivation but also a possible element of altruism). Looking at the pre-approval process of pharmaceutical regulation, he argues that health advocacy groups, more than pharmaceutical firms, influence drug-reviewing time. He suggests that pharmaceutical firms create/foster patient advocacy lobbying, or collude with these groups in pushing for priority status etc.: "politically strategic pharmaceutical firms know that industry lobbying is less successful than patient advocacy, and their regulatory behaviour adapts to this fact" [89, p. 56]. He provides empirical evidence of patient groups that used the media to demand faster approval for a particular product.

Thus, reforms in pharmaceutical regulation represent a crucial case to study theories of interest groups influence. Pharmaceutical firms are reported as one of the most powerful groups in the world for their wealth and capacity to provide rents for political campaigns [90]. They operate under a highly politicised environment and as previously mentioned, regulation affects their business more than any other policy (labour policy, for instance). If firms would be prominent to dominate a sector, it would be reasonable to expect that to happen in pharmaceuticals. Nevertheless, a key problem with the positive theories of regulation is the assumption that regulation emerged in order to serve the interests of particular groups. Attributing the outcome of regulatory policy to rational, purposive actors might be incomplete for several reasons. Analysing the process of institutional design based on numerous empirical examples, Paul Pierson presents several limitations for understanding the origins of institutions (in this case, the regulatory norm) as a rational, functional activity [91, Chap. 4]. Regulation might have multiple or unexpected effects, thus its existence cannot be explained by observing their creator's preference (usually these innovative changes require a coalition or a group of supporters that propose them for different reasons). Its designers might not act instrumentally, for instance they might reflect cultural specificity. Additionally, actors might change their preferences over time, as institutions remain stable or politicians may change, or a new generation may inherit norms that reflect a predecessor's preferences rather than their own. In this sense, the author suggests that a more promising avenue of investigation is to take a qualitative, historical approach [91, pp. 130–131]. By observing the historical circumstances that make the presence of these favourable (or unfavourable) conditions more or less likely, it is possible to better understand the creation of regulatory norm. Thus, to provide valuable inputs to understand why and how large-scale pharmaceutical regulatory norms are created (beyond the narrow assumption that they serve the interests of particular groups) and how these norms reshape (or not) the regulatory environment.

In this sense, Vogel (1996) also questions the capture model of regulatory policy analysis. Particularly problematic, he argues, is its distorted view of public versus private interests. Because there is no unique public interest (government officials

might disagree on how to define this in ways that cannot be understood in terms of their capture by private interests), it is not possible to explain variation in regulatory policy until we understand how government officials in different countries define public interest. Additionally, the author points out that governments themselves can change the preference of interest groups, manipulate their demands, put one group against the other. The narrow models of interest group preference ignore the role of the state as an autonomous actor/structure in the policy process. Looking at public institutions rather than private interests explained better these variations.

This book challenges narrow assumptions of pharmaceutical regulatory process, such as generic drug regulation, as a function of the lobbying activity of self-interested corporations. Instead, an alternative model, developed in this study, starts by looking at the context in which this regulatory policy is proposed and takes the preferences of interests groups (whether firms, decision makers or patient advocacy groups) as problematic instead of given. In other words, it supports the argument that actors' preferences are socially constructed within the regulatory process.

Preference Formation

This study proposes that it is necessary to understand how regulatory policy legacies shape an actor's preference to be able to understand the extent to which international guidelines and interests groups (e.g. industries) activities matter for pharmaceutical policy development. This longitudinal perspective allows for an assessment of the actors participating in the pharmaceutical regulatory process, an understanding of the content of their demands and how they behaved in the pursuit of these claims, and in turn, an assessment of how and why the pharmaceutical regulation's reform and development came about.

This book draws on a historical institutional approach that posits that the behaviour of political actors is affected by the institutional context in which they interact [cf. 92]. The claim that institutions matter is not new but it needs to be qualified. I emphasise the importance of observing how regulatory concepts are being framed. This is consistent with arguments that political structures determine not just how much influence groups have but also what policies they demand in the first place [93, 94].

Institutions are defined as "formal rules, compliance procedures, and standard operating practices that structure the relationship between individuals in various units of the polity and economy" [95, p. 19]. They understand actors' preferences as endogenous, i.e. the institutional arrangement defines where, when and how interest groups matter for the policy agenda/implementation process. This definition embraces the pharmaceutical regulation studied in this book. Parameters that regulate generic medicines are at the same time a formal institution (e.g. Federal Law); a public policy as this law defines the role of the Ministry of Health in promoting its implementation; but also a regulatory regime as its technical standards are designed, implemented and enforced by the National Regulatory Agency.

The choice for historical institutional approach is because it provides an overarching analytical framework to investigate the interactions of government, firms, and patient advocacy groups in the making of pharmaceutical regulation. Since it does not limit the analysis into particular groups or deduced interests, it allows me to investigate the possible different groups engaged with the regulatory process and whose participation might have not been predicted previously.

Roughly, there are two ways in which actors' preferences can be understood⁴; one group of scholars deduce from theory or previous studies the interests for the relevant actors (rational choice theory) as the previous section demonstrated, while another group of scholars understand that preferences result from the historical process, i.e. they are socially constructed (historical institutionalism and sociological institutionalism⁵) [99, 100]. This ontological distinction makes all the difference when assessing the regulatory policy reform as the theoretical parameters and methodological choices also differ according to the nature of the causal relation [cf. 101].

Preference formation is then understood as the "process by which social actors decide what they want and how to pursue" it [94, p. 129]. It is necessary to look at the policy path before the political events/decisions taken and its subsequent period to trace the evolution of preferences. For example, this parameter would require looking at the participants of the policy process before a given reform, what their policy demands were and strategies they adopted to pursue them; and compare these with the subsequent period. Preferences are not driven by strategic interactions; instead they evolve as events unfold (e.g. past decisions) [94].

Therefore, "actors' preferences are not just an input to the policy process but a product of it" [102, p. 429]. This not to say that actors are not utility maximizers but their utility is flexible [cf. 103]. These scholars argue that actors make sense of their interests through a dependence on the political process and regulatory context, i.e. the content of the rationality is socially constructed [cf. 93]. To understand how preferences evolve, Hall (2005) suggests that political actors have multiple preferences (even for a single issue), which can have multiple effects. By attaching more weight to one variable over another, the actor emphasizes one dimension more strongly⁶. For instance, government must balance the rights of patent protection of pharmaceutical products and access to medicines.

Another important part of this process is framing: how an issue is publicly portrayed. Elster (1983) argues that actors must pay some lip service to the common good as it is impossible to express selfish arguments in public debates. It is impossible to express a preference for the common good without acquiring it: "by speaking the voice of reason, one also exposes oneself to reason" (Elster 1983, p. 36). When a generic drug firm asserts its preference for producing affordable medicines

⁴ Not all scholars accept this dichotomous approach to rationality, and efforts have been made to clarify the intersections between them [96–98].

⁵ There is a slight variation between these two. I aligned both as they focus on comparative historical analysis and also both understand preference as a socially constructed phenomenon.

⁶ This is not nested games as rational scholars propose, but a constitutive element of who the group is and what they want. Nested game are independent situations, while for the historical perspective, events are sequent and dependent on one another.

and increasing access to medicines, these are not fabricated rationales but part of the firm's identity⁷.

Introducing new elements to the regulatory regime and the magnitude of change creates uncertainty and actors can pursue different and at times conflicting interests, as it is not possible to predict the outcome. For example, the scandal of thalidomide in Europe caused many children to be born with malformations led several states to create National Regulatory Authorities [cf. 104]. Periods of uncertainty can create discrepancies from expected behaviour making it impossible to predict what political actors want, without knowing the content and structure of social relations [93]. Preferences are developed through a process of gradually understanding the situation/options available. As actors adapt to the new regulation, they push the path further along the way. I demonstrate this pathway with a qualitative analysis of the Brazilian case.

What all these theoretical discussions tell us is that to analyse the process of generic drug regulation in Brazil, it is necessary to begin by looking at the circumstances by which this policy emerged on the policy agenda. It then proceeds to identify the interest groups participating in the policy process, understanding their multiple demands and strategies (e.g. preferences over international non-proprietary name (INN), bioequivalence tests or other alternative solution), how they perceive the Generic Drug Act, and where (which government departments) they voiced these claims. In sum, the political struggle. This provides a base line to compare the content of their demands in the aftermath of reform and seeks groups that support the policy path (how they feedback the generic drug regulation) or those who are dissatisfied with this regulatory arrangement (on what grounds, how and where they complain). Investigating these requires looking at the generic policy process from a historical perspective.

This analysis is grounded in empirical data collected between 2007 and 2013, including more than 57 in-depth interviews with key informants, reviews of historical documents related to Bioequivalence (BE) and INN (from Brazil and from international agencies like the WHO) and thousands of newspaper articles. I used a process-tracing approach (chronological narrative backed by the analytical parameters described in this section) to explain how and why Brazil promoted this large-scale regulatory reform in the pharmaceutical sector and to highlight its evolving implications. The research protocol can be found in the appendix.

The Brazilian Context

Brazil's relevance in the study of pharmaceutical regulation is manifold. First, the country has had an unusual, remarkable and widely discussed intervention in this sector. As part of these interventions, in 1999, the Brazilian government created a

⁷ The process is not to look at the causal role of ideas as distinct from interests but rather in the constitutive role of ideas. The former implies a methodological analysis of the causal arguments/variable testing, the latter requires process tracing.

new independent pharmaceutical regulatory agency, began a vehement price negotiation of AIDS medicines with research-based pharmaceutical industries, shepherded an international movement to clarify the TRIPS agreement and approved the Generic Drug Act in 1999 [1, cf. 2, 3]. In addition, Brazil is one of the few countries in the world with state-owned pharmaceutical industries competing with local and multinational pharmaceutical firms [cf. 105]. Brazil has a vibrant HIV/AIDS activism that has, since the 1990s, held the government accountable to its Constitutional commitment of providing free and universal access to medicines [106].

Lastly, Brazil has one of the most stringent generic drug policies among Latin American countries. This is evidenced by the number of products that must provide bioequivalence, the mandatory use of INN or the Brazilian non-proprietary name (BNN) and by the fact Brazil is one of the few countries that has a law binding these rules⁸ [cf. 70]. All these elements and remarkable policy achievements offer a complex setting where it is possible to test, compare and posit different explanatory variables. For instance, the multiplicity of actors in the pharmaceutical sector in Brazil (public and private firms, national and multinational, government officials, AIDS advocacy) and the possibility of comparing their preferences in different temporal dimensions enrich the study design.

Similar to the current state of the international literature on generic drugs, Brazilian scholars have focused extensively on the economic efficiency of this policy enacted in 1999 and the attitudes of health professionals and consumers to it. Several studies analysed the economic outcomes of generic drug competition in Brazil⁹. For example, the study of Vieira and Zucchi [6] suggests that generic drugs enter the market in Brazil costing 40% less (on average) than its innovator version; in addition, this difference increases over time. Similar findings were also reported by other economists [107–109]. Other authors have found that generic drug competition is particularly important to lower the price of treatment for chronic illnesses such as diabetes and heart conditions, but also noticed that the best-selling generic drugs in Brazil are those in the antibiotics therapeutic class [6, 11, 12, 110].

In Brazil, because a great deal of drug consumption is out-of-pocket, the perception of consumers in demanding, and health professionals in offering/prescribing these products, is crucial to fostering market penetration of these products. A survey conducted by Bertoldi et al. [111] of a population-based sample of adults from a southern Brazilian city suggests that, although the population was aware of these products, there was still little consumption of generics (and also a relative misunderstanding of different types of pharmaceutical products, whether similar, generic or innovator products). In addition, the study of Rosenberg [12], who surveyed nearly 550 physicians in the city of Rio de Janeiro in 2008, found that doctors are suspicious of the quality of generic drugs and also demonstrate concerns about whether the pharmacists/drug store will substitute medicines correctly.

⁸ Apart from Brazil, only Ecuador has one but it is not as stringent as the Brazilian; for example, there is no bioequivalence requirement.

⁹ Detailed information about this will be provided in Chap. 5 of this book.

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