



Relevance of variation in use of terminology to define generic pharmaceutical products

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Suggested citation: Fonseca EM. Relevance of variation in use of terminology to define generic pharmaceutical products. *Rev Panam Salud Publica.* 2015;37(2):113–7.

ABSTRACT

The World Health Organization (WHO) promotes the use of generic drug policies to foster competition in the pharmaceutical sector, reduce drug prices, and increase access to therapeutic drugs. However, little is known about how countries implement these policies. This article describes different terminology adopted by national regulatory authorities to define generic versus proprietary drug products in developing countries, including those in Latin America, and challenges that arise in their application of WHO guidelines, such as labeling issues. The author concludes that variation in generics terminology in these countries is a result of institutional context (i.e., the public sector setting as well as the body of laws and regulations that exists in the country) and policy legacies, such as intellectual property regimes, and highlights the need for further analysis of pharmaceutical regulations to improve understanding of the barriers and political implications of generic drug policies.

Key words: drugs, generic; generic drug policy; drug industry; drug labeling; legislation, drug; drug costs; Brazil; Latin America.

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WHAT IS A GENERIC DRUG POLICY?

According to the World Health Organization (WHO), a generic medicine is a pharmaceutical product that is no longer protected by a patent, is interchangeable with an innovator drug, and can be copied by other companies (1). WHO suggests generic drug substitution as a key component of a national drug policy to address what economists define as “market failure” in the pharmaceutical sector (1: 33). In perfect market conditions, buyers and sellers should be able to trade and negotiate without government interference, for an optimal solution. However, in the pharmaceutical sector this equilibrium does not exist for two main reasons. First, the consumer (or patient) does not, for the most part, choose the product, relying instead on doctors’ expertise and preferences for product selection. In turn, doctors rely on information from pharmaceutical companies, medical journals, or medical school. Economists call this type of information “asymmetric” (when one party in a transaction has more or superior information than the other). Second, there is a lack of competition, created by patent protection, brand loyalty, or market segmentation (1). For example, brand loyalty promoted by marketing strategies can lead to market monopoly even after a patent expires. Therefore, the use of generic drugs is usually promoted in both the public and private sector to foster market competition while reducing drug costs and increasing drug availability and patient access (1).

This article describes different terminology adopted by national regulatory authorities to define generic versus proprietary drug products in developing countries, including those in Latin America, and challenges that arise in the application of WHO guidelines, such as labeling issues. The first section defines generic drug policy instruments and why some may prove controversial. The second section describes the different terminology used in certain Latin American countries, based on secondary sources, and efforts to harmonize it across countries. The last section suggests reasons for the variation in generic drug terminology and future avenues for policy analysis and research.

The development of a common regulatory environment for the movement of pharmaceutical products requires consistency across policies. While the guidelines proposed by WHO represent a credible model on which to base such regional policies, a better understanding of how these guidelines might be disseminated across countries is required. Details on pharmaceutical policies are provided elsewhere (2), along with current discussions of the terminology used to define the generic names of biosimilar prod-

ucts (i.e., drugs that are structurally and functionally different from the innovator products) (3).

For public health practice, generic drug regulation can have far-reaching implications on the price and supply of medicines. Generic drug regulations can either limit or promote the supply of affordable drugs. Conversely, if poorly regulated, products causing spontaneous abortion, congenital malformation, or even death may enter the market. Therefore, understanding how such generic drug regulations are applied is crucial for promoting the sustainability of these interventions over time.

GENERIC DRUG POLICY INSTRUMENTS AND CONTROVERSIES

Analysis of “market failure” helps identify situations in which government should intervene in the pharmaceutical sector and is thus frequently used by policy-makers as a diagnostic approach. Used by WHO as a normative rationale, the concept of “market failure” guides member countries on how to identify problems in this sector and which solutions should be taken to regulate it. These policy investigations are vital but are only one side of the problem.

Two generic drug policy instruments are used to stimulate market competition: international non-proprietary names (INNs), and bioequivalence tests. All drugs have three different names: 1) the chemical name, which describes the product’s molecular structure to scientists; 2) the generic name or INN, a shorter, simpler version of the chemical name; and 3) the brand name, assigned by the manufacturer and given trademark protection, and usually shorter and easier to remember than the INN (4). Each INN is a unique name that is globally recognized and is public property. WHO suggests the use of INNs to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients worldwide (5). For example, the simvastatin developed by Merck is marketed as Zocor[®], Simlup[®], Simcard[®], or Simvacor[®]. The use of an INN facilitates the drug’s clear identification, safe prescription, and dispensing as medicine to patients, as well as communication and exchange of information about it among health professionals and scientists (6). It also allows both patients and institutional buyers to shop for the lowest price by using one common name for a drug that may be made by different suppliers. Some countries have defined a minimum size for the characters of a printed INN vis-à-vis the product trademark and advertising (e.g., 30%–50% of the brand name size, with some countries requiring equal size for both), while other countries have taken more radical approach by abolishing trademarks for any product used in the public sector (1).

The development and implementation of INNs has proved to be a highly contested effort. Past studies have suggested that marketing budgets for pharmaceutical products can be as much as two to four times larger than those for research and development (7). Therefore, many companies are reluctant to give

up the substantial investment they have made in the brand name of their product. In addition, because of brand loyalty and the credibility associated with the original product name, health professionals, consumers, and retailers might be skeptical about the quality of drugs commercialized under generic names. Successful substitution of generic drugs for brand-name drugs requires that doctors, pharmacists, and patients be informed and willing to exchange one product for another (8). If they have doubts about the production standards or quality of generic medicines, they are often in a position to refuse them.

Another relevant component of a generic drug policy is the interchangeability/bioequivalence requirement. According to WHO, generic drugs must be therapeutically equivalent to their innovator version (i.e., their rates and extents of absorption can not differ significantly from those of their original version). The concept of “bioequivalence” can give legitimacy to generic drugs by implying that one commodity can be replaced by another and establishing the parameters for a market transaction based on price (9: 2). Discussion on testing for interchangeability/bioequivalence is relatively technical and complex. Detailed information on the technical parameters can be found elsewhere (10, 11). To summarize, a bioequivalence test establishes whether or not a generic drug will have a clinical effect equal to a brand-name drug with no difference in the potential for adverse effects. A bioavailability test, on the other hand, establishes the rate/extent to which the active pharmaceutical ingredient is absorbed from a pharmaceutical dosage and becomes available in general circulation (12). While the former test helps establish equality between two products, the latter refers to the medicines’ performance in the human body (a parameter that is not required for intravenous drugs, which are 100% bioavailable or directly introduced into general circulation). The bioequivalence regulatory concept and scientific parameter was first developed by the U.S. Food and Drug Administration (FDA) and a network of experts engaged in the generic drug sector during the 1980s to facilitate the entry of these products into the market after patent protection expired (9, 13). Until then, generic drug companies had to go through an approval process that was similar to (and as lengthy as) the one required for innovator companies and usually duplicated clinical trials carried out previously.

Some studies conducted by international agencies argue that current bioequivalence requirements for certain medicines (e.g., antiretroviral drugs such as ritonavir) are too stringent, unnecessary, and can lead to reduced supply by domestic pharmaceutical companies, limiting access to medicines in developing countries (14, 15). For example, a study by the United Kingdom’s Department of International Development (DFID) (15) described the case of Sri Lanka and how its local regulatory agency did not have 1) the capacity to carry out bioequivalent tests (e.g., the ability to conduct controlled trials in humans) or 2) staff sufficiently trained in statistics and pharmacology. The

authors suggested that even when bioequivalence data are available to domestic pharmaceutical producers, innovator products should not be commercialized in the local market, to avoid creating a market barrier for domestic pharmaceutical companies that produce medicines no longer protected by a patent.

On the other hand, there are some successful cases of this type of policy, such as in Brazil, where generic drug regulation was followed by the development and implementation of policies to help domestic pharmaceutical companies adapt to the new requirements. For example, Brazil's 1999 "Generics Law," which based marketing approval for generic drugs on demonstration of bioequivalence, created gaps between the requirements for participating in the recently created generic drug sector and domestic drug companies' capacity to adapt their production and delivery processes and/or their industrial plants (16). In response, the government established a set of policies to help build domestic drug companies' production capabilities and help them fill these gaps (17).

Generic drug policies can be implemented at various stages of the pharmaceutical product production and distribution channels—from the supply chain to the point of purchase (1). The goal of the policy is to encourage the target groups to supply and demand generic drugs. For example, a government can carry out a mass media campaign to encourage doctors to prescribe generic drugs or patients to request them (when available). On the supply side, a government can incentivize companies by facilitating registration of generic drugs with national regulatory agencies or by committing to allotting preference to generics in the procurement of medicines for its public health system.

GEOGRAPHIC VARIATIONS IN GENERIC DRUG REGULATION IN LATIN AMERICA

Market competition in the pharmaceutical sector differs substantially between developed and developing countries. In European countries and the United States, intellectual property law was consolidated in the 1950s (18). In these countries, competition begins once the patent expires. In this scenario, the introduction of bioequivalence parameters accelerated the market entry of pharmaceutical products whose patent had expired (i.e., it became unnecessary to perform lengthy clinical trials to register a product that had gone off-patent). In contrast, in Latin American and Caribbean countries, for example, intellectual property rights were introduced (or in some countries, reintroduced) in 1995, with the creation of the World Trade Organization (WTO) and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (19). Consequently, market competition in these countries began before the adoption of a patent system. In Brazil, for example, until 1996, any pharmaceutical company could manufacture innovator medicines without paying royalties to the research-based company that developed the drug. Medicines that were copied were not classified as generic drugs

as there was no such regulation during this period; they were classified as "similar" products (or "multi-source" products, in current WHO terminology).

The introduction of mandatory bioequivalence tests in these countries expanded the normative standards for registering pharmaceutical products no longer under patent, regulating existing market competition. There is wide variation across countries in the requirements for bioequivalence tests and how the tests should be implemented (20). For example, Brazil, Canada, Mexico, and the United States usually adopt bioequivalence requirements for drugs with a narrow therapeutic range (NTR) and those that are highly toxic. As small differences in the amount of a NTR drug that is administered can result in more serious consequences compared to less toxic drugs, the required degree of assurance of equality with the original product is greater for the former type of the drug than for the latter. From a list of 96 drugs, based on the WHO Essential Medicine List requirements for bioequivalence tests, 87 products require bioequivalence tests in Brazil, compared to 59 in Mexico, 21 in Venezuela, and 15 in Argentina (21). To the best of the author's knowledge, no studies have been conducted that compare the pharmaceutical products that require these tests across countries and/or determine whether they are NTR products. These are important research questions that warrant the attention of international health agencies.

Three studies carried out by the World Bank and Pan American Health Organization (PAHO) advisors in 2003 and 2005 highlighted differences and similarities in generic drug policy in Latin America (18–20). In Argentina, Brazil, and Mexico, a generic is an off-patent drug therapeutically interchangeable with an innovator product and is identified by an INN (or a Brazilian nonproprietary name (BNN)), and pharmaceutical products are divided into three types: 1) innovator drugs (patent products); 2) generic drugs (therapeutically equivalent to an innovator drug); and 3) similar or multisource drugs (not bioequivalent to any innovator drug, due to different form, size, or shelf life). In Bolivia, Chile, Colombia, Costa Rica, Ecuador, Nicaragua, and Peru, pharmaceuticals are classified as 1) brand-name products (patent or off-patent) and 2) generics (off-patent, identified by an INN). According to Homedes & Ugalde (18), only Brazil and Ecuador have legislation regulating the use of generic drugs. In Argentina, Chile, Colombia, Costa Rica, Mexico, Nicaragua, Peru, and Uruguay, while there is no specific legislation on the use of generics, national laws address it to some extent.

Table 1 provides a summary of different types of pharmaceuticals. In Latin American countries there is no consensus about labeling (for brand-name or INN products) or technical requirements (bioequivalence and bioavailability) for registering generic drug products.

The market for generic drug products ranges from newly off-patent products (e.g., pravastatin, a medicine to lower cholesterol) to a broad range of

TABLE 1. Types of pharmaceutical products in selected Latin American countries

Country	Type of pharmaceutical product
Argentina	<p>Innovative drugs</p> <p>Similar drugs (or copies). These have the same active ingredient, concentration, pharmaceutical form, and dosage and are used for the same indication as the innovative products. They are equivalent to the innovative product but might differ in size, shape, packaging, and period of activity. They are pharmaceutically equivalent to the innovative drug. They may use a brand name.</p> <p>Generic drugs. These are drugs that have been proven to be bioequivalent to the innovative drug. They are off-patent and tend to be identified by an International Nonproprietary Name (INN).</p>
Brazil	<p>Innovative or reference drugs</p> <p>Similar drugs. These have the same active ingredient, concentration, dosage, and pharmaceutical form as the reference drug. They are used for the same indications. They are equivalent to the reference drug but may have different size, shape, packaging, and excipients. Need to be identified with a brand name.</p> <p>Generic drugs. These are interchangeable with the reference drug and have been proven to have the same efficacy, security, and quality. They are produced after patent expiration and are identified with an INN or Brazilian nonproprietary name.</p>
Mexico	<p>Innovative or reference drugs</p> <p>Generic interchangeable. These are interchangeable with a reference product as certified by the Health Secretariat. They are off-patent and are identified by an INN.</p> <p>Similar drug. These drugs have the same active ingredient as the reference product and may be identified with a brand name or an INN.</p>
Bolivia, Chile, Colombia, Costa Rica, Ecuador, Nicaragua, Peru	<p>Branded drugs. These are proprietary drugs and similar or copy drugs.</p> <p>Generic drugs. These use an INN or other internationally recognized names. They are off-patent.</p>

Source: Homedes & Ugalde (18). Reproduced with permission from the World Health Organization.

older medicines (e.g., acetylsalicylic acid). Contestation can be extensive in the first case and may limit or delay generic drug competition. For example, innovator companies can use loopholes in regulatory rules to delay entry of generic medicines (22, 23). There are also cases of incremental innovation, such as a new therapeutic use of a medicine (also called second medical use) or an improvement in a pharmaceutical product already patented, both of which could (arguably) receive a new patent (24). These types of intellectual property regimes are also important in generic drug regulation as they determine which medicines can be legally copied and when.

Over the past decade, PAHO and its member countries have worked closely to establish harmonized procedures to improve the quality, safety, and efficacy of pharmaceutical products marketed in the region. At a regional meeting of PAHO's Working Group on Bioequivalence in 2005, participants 1) raised concerns about how WHO guidelines for pharmaceuticals could limit access to medicine and 2) noted the need for testing of off-patent medicines already on the market (25). Meeting participants also agreed that political and commercial components related to the application of the WHO recommendations should be explored in future Working Group sessions and at ministries of health in the region (25, 26).

FINAL REMARKS AND AVENUES FOR INVESTIGATION

Variation in generics terminology in developing countries is a result of institutional context (i.e., the public sector setting as well as the body of laws and

regulations that exists in the country) and policy legacies, such as intellectual property regimes. There is consensus among international agencies that generic drug policy is a crucial instrument for increasing access to medicines, and its application requires the acquiescence of a constellation of domestic agents and institutions. Therefore, national policy-makers should examine their own domestic structures to better understand how the policies recommended by international experts, and the generic and non-generic drug terminology used in their implementation, would be best be applied. In the field of pharmaceutical drug policy-making, which is largely dominated by economists and pharmacists, in-depth policy analysis studies of pharmaceutical regulations are imperative for elucidating the challenges inherent in policy harmonization efforts as well as their political implications. Possible avenues for investigation include 1) potential conflicts of interest in applying generic drug policies, 2) variations in public policy between countries with domestic pharmaceutical production capacity and those largely dependent on imports, and 3) how social and political actors engage in regulatory policy discussions based on their own preferences and strategies.

Acknowledgments. This manuscript was adapted from the author's doctoral thesis in Social Policy at the University of Edinburgh (United Kingdom). Further research and data collection was conducted during her postdoctoral fellowship at the Fundação Getulio Vargas in São Paulo, Brazil. The author thanks Daniel Clegg, Jeff Collin, Scott Greer, Amy Nunn, and Regina Pacheco for their contributions to this study.

Funding. Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) grant no. # 2014/07725-3.

Conflicts of interest. None.

RESUMEN

Relevancia de la variación en el uso de la terminología para definir los medicamentos genéricos

La Organización Mundial de la Salud (OMS) promueve el uso de políticas de medicamentos genéricos para estimular la competencia en el sector farmacéutico, reducir los precios y aumentar el acceso a los medicamentos. Sin embargo, hay poca información sobre la aplicación de dichas políticas por parte de los países. Este artículo describe la terminología empleada por los organismos regulatorios nacionales para definir los medicamentos genéricos frente a las

especialidades farmacéuticas de marca en los países en desarrollo, incluidos los de América Latina, así como las dificultades que se encuentran en la aplicación de las directrices de la OMS, como por ejemplo en el etiquetado. El autor llega a la conclusión de que la variación en la terminología de los medicamentos genéricos en estos países es resultado del contexto institucional (es decir, el sector público y el ordenamiento jurídico-administrativo del país) y de los legados de las políticas, como los regímenes de propiedad intelectual, y destaca la necesidad de analizar más a fondo los reglamentos farmacéuticos a fin de conocer mejor los obstáculos y las implicaciones de las políticas en materia de medicamentos genéricos.

Palabras clave: medicamentos genéricos; política de medicamentos genéricos; industria farmacéutica; etiquetado de medicamentos; legislación de medicamentos; costos en drogas; Brasil, América Latina.

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Manuscript received on 8 October 2014. Revised version accepted for publication on 27 February 2015.