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## Generic Substitution in Malaysia: Recommendations from a Systematic Review

Mohamed Azmi Hassali, Jayabalan Thambyappa, Fahad Saleem, Noman ul Haq and Hisham Aljadhey

**Mohamed Azmi Hassali,  
Jayabalan Thambyappa,  
Fahad Saleem, Noman ul Haq**  
*Discipline of Social and  
Administrative Pharmacy, School of  
Pharmaceutical Sciences, Universiti  
Sains Malaysia*

**Hisham Aljadhey**  
*College of Pharmacy,  
King Saud University,  
Riyadh, Saudi Arabia*

**For Correspondence**  
**Fahad Saleem**  
*Discipline of Social and  
Administrative Pharmacy,  
School of Pharmaceutical Sciences,  
Universiti Sains Malaysia.*

### ABSTRACT

Generic substitution is the act of switching from a branded drug to its therapeutically equivalent generic version. This study aims to systematically review the literature with regards to generic substitution around the globe. Studies compared generic and brand-name drugs for clinical efficacy and cost effectiveness. The current findings show that the new policies are aimed at supporting the development of the generics industry in the respective countries. Further investigation is needed to explore the implementation of the current generic substitution policies and how to increase their accessibility to the general population. Generic substitution policies comparison between countries were conducted among 9 countries, that is, Australia, Canada, Czech Republic, Ireland, Japan, Switzerland, Indonesia, United State and United Kingdom. From 27 journals that were reviewed, only 14 were selected based on the fulfilled criteria appropriate to the journals that we had searched. All these policies were then studied to propose recommendations for generic substitution.

**Keywords:** Generic substitution guideline, drug policy worldwide, generic drug, pharmaceutical policies, bioequivalent, quality assurance.

### INTRODUCTION

Generic substitution has been defined as an act of switching from a branded drug to its therapeutically equivalent generic version (Holmes *et al.*, 2011). The pharmaceutical equivalents between generic products and brand products should have identical amount of the same active ingredient in the same dosage form and route of administration, other than those that meet compendia requirements or other applicable standards of strength, quality, purity, and identity. Although they might differ in terms of shape, drug release mechanisms, scoring configurations, and shelf live/expiration time; they should produce equivalent drug concentration-time profiles in the blood (Holmes *et al.*, 2011, Johnston *et al.*, 2011). In order for a product to be considered as an acceptable generic substitute, generic drug manufacturers must comply with Good Manufacturing Practices (GMP) and it is mandatory to submit the following data for generic drug approval, including the bioequivalence study, stability testing as well as the specifications and test methods (Kobayashi *et al.*, 2011).

When the Food and Drug Administration (FDA) approves a new generic product, it implies that it can be substituted at the time of dispensing for the reference innovator or brand-name product on the expectation that the generic drug will produce the identical clinical response with a similar safety profile (Suh, 1999). Currently the concepts of generic substitution have received increasing attention in most developed countries. As healthcare costs rise, the practice of generic substitution is strongly supported by health authorities as they provide the same benefits and safety but with greatly reduced total prescription drug cost. Thus switching prescriptions from brand name drugs to identical generic drugs is becoming increasingly important for healthcare systems across the world in order to additional savings (Johnston *et al.*, 2011).

The growing confidence in generic quality by health care professionals, third parties, and patients help to promote the generic market at a faster rate in the pharmaceutical industry as a whole. Switching from the use of brand name to generic prescriptions is one of the most significant means of being cost effective because generic drugs are less expensive than brand name drugs, so they become the more preferred choice of drugs.

The period of time to create 'copy' is not too time consuming, and there is also greater flexibility for the generic manufacturer to determine the pricing of their product (Ward Health Strategies, 2007). However, pharmacists still play an important role in order to substitute a less expensive generic product for a brand name drug. Moreover, there are some factors that need to be considered by the pharmacists who deal with the selection of generic products such as regulatory issues, patients' medical and medication history, as well as the patient's opinion about generics. Besides, the factors that relate to the drug, which includes the drug class, cost, and bioequivalence information should also be considered (Kobayashi *et al.*, 2011, Suh, 1999).

## METHODOLOGY

### Search strategy

A systematic literature search with a computer-assisted literature search for relevant studies was performed using Science Direct, Google scholar, SpringerLink, BioMed Central and Elsevier. The following nine countries were reviewed: Australia, Canada, Czech Republic, Ireland, Japan, Switzerland, Indonesia, the United States and the United Kingdom. The analysis involved reviewing the journals on generics substitution policy. From 27 journal articles that were reviewed, only 14 were selected based on the fulfilled criteria.

### Inclusion and exclusion criteria

The selection of studies for this systematic review focused on the generic substitution or drug policy in countries that implemented a generic substitution policy. The study was selected if it was written in English language only. In addition to that, reviews on generic substitution guidelines designed worldwide were also included. Countries that did not implement generic substitution policy were excluded.

## RESULTS

### Generic substitution policy worldwide

#### *Developments of generic drugs policy in Australia*

A challenge to the originator brand-sector, in terms of supply of generics in the market, only began in the 1990s, but generic drugs have had an impact on the pricing of pharmaceuticals in Australia at least since the 1970s. Key policy stages include the Generic Pricing arrangements of the 1980s, the Minimum Pricing Policy (MPP) introduced in December 1990, the legalization of brand substitution in 1994, and the Therapeutic Group Premiums (TGP) policy from February 1998 (Lofgren, 2002).

The MPP was introduced into the Pharmaceutical Benefit Scheme (PBS) and it set the government subsidy for a drug at the level of the lowest priced brand otherwise known as the benchmark price (Chong *et al.*, 2011). The generic product had been accepted by the Therapeutic Good Administration (TGA) as bioequivalent, and then was identified in the Schedule of Pharmaceutical Benefits. However the major obstruction to the growth of the generics industry in Australia is that the PBS has provided no cost or other incentives for consumers, doctors, or pharmacists to choose generic products. In contrast, generics have been widely used in hospitals since the 1950s, where brand substitution has long been widely practiced. An explicit aim of the new policy was to support the development of an Australian generics industry. Most doctors continued to prescribe brand name products, and generic companies increased their PBS market share only marginally in the first few years after December 1990. However the effect of generic substitution at the pharmacist level, which was introduced in December 1994, resulted in a marked increase in the percentage of eligible PBS items dispensed at benchmark prices.

Five years later, in February 1998, the Brand Pricing Policy (MPP) model was extended to drugs with similar clinical effect in the form of the Therapeutic Group Premium (TGP) Policy, though pharmacists are unable to substitute between different chemical entities. This arrangement applies to four groups of products, where the lowest priced brand sets the benchmark price. About three years later, in mid-2001 the TGP policy included 190 brands at the benchmark level, 33 brands with a brand premium, and 22 with a therapeutic premium, ranging from \$1.40 to \$7.01 (Pharmaceutical Benefits Pricing Authority 2001). The effect then would seem to be for prices to converge at or be as close to the benchmark level as possible.

#### *Development of generic drugs policy in Canada*

The first phase of the Canadian generic drug development was completed in October 2007 and consisted of a detailed examination of each level of the Canadian generic drug sector, starting from the acquisition of ingredients for manufacturing generics and proceeding through their production, approval process, distribution and wholesale, dispensing and reimbursement or payment by public and private drug plans, and persons paying out-of-pocket. A draft of the report was circulated to over 100 sector participants and interested parties for fact-checking purposes. The final report found that more than ten generic drug

manufacturers were competing for shelf space in Canadian pharmacies by offering discounts to pharmacies averaging 40 per cent or more of the retail price. However, the benefits of this competition were not being passed on to provincial drug plans, consumers or private payers but contributed to the design of drug plans, which provided limited incentive for manufacturers to compete by offering competitive prices to end payers, or pharmacies (Competition Law & Policy OECD, 2009).

The second phase was benefiting from Generic Drug Competition in Canada: the Way Forward, released in November 2008, recommended a number of ways to make the generic drug market work better for the Canadian government, businesses and consumers. These included designing methods, such as a competitive tendering process; revealing to the end payers which framework to use to reimburse pharmacists directly for services they provided as well as for dispensing drugs; and also the removal of any unnecessary limits on advertising. Finally, the report encouraged the province to coordinate generic procurement, pricing and reimbursement policies to avoid or at best minimize unintended anticompetitive consequences (Competition Law & Policy OECD, 2009).

#### ***Development of generic drugs policy in Czech Republic***

Since 2008, generic substitution has been possible according to Act No. 48/1997 Coll. The substitution was introduced to offer quality and effective pharmaceuticals at lower prices to patients. Under Act No. 48/1997 Coll., generic substitution is possible if certain conditions are met. The substitution is possible only if the patient agrees and the prescribing doctor does not object. According to legislation the pharmacist has the right to offer a substitution; it is not an obligation but an option. The substitute must be the same active substance, dosage, strength and pharmaceutical form. Substitution for different active substances but equivalent is possible but only after consultation with the prescribing doctor and only if the pharmaceutical is urgently needed. More than rationalizing health care system expenditures such as insurance companies' costs, generic substitution is very helpful for patients as it can lower their co-payments. The aim of generic substitution as implemented in the Czech Republic was to decrease the cost of public health insurance in the form of charge for medicines (Competition Law & Policy OECD, 2009).

#### ***Development of generic drugs policy in Ireland***

In Ireland, generic medicines are sold in low volumes. The Department of Health and Children in Ireland supports the increased use of generics where this is appropriate and achievable in the market. The generic and branded medicines industry in Ireland is highly regulated. Manufacturers are required to comply with licensing requirements and must adhere to the agreement with the country's policies. Wholesalers as well as retailers must also adhere to the licensing requirements. Although the prescribing of newer and more expensive medication is essential for crucial treatments, it is appreciated that enhanced generic prescribing with

appropriate pricing has the potential to produce significant savings. In this regard, it is likely that Ireland will seek an increased use in generic medicines in return for a reduction in the price of these medicines in the next series of agreements, which will last from 2010 until 2015 (Competition Law & Policy OECD, 2009).

#### ***Development of generic drugs policy in Japan***

Generic drugs means pharmaceutical products equivalent to corresponding approved drugs in terms of active ingredients, dosage and indications except those products produced by the same manufacturers of the approved drug. The requirements for marketing authorization are as follows:

- a. The applicant has a license for manufacturing and marketing
- b. The factory has a license or accreditation for manufacturing the item
- c. The name, ingredients, quantity, dosage and indications of the item are appropriate
- d. The item fulfils the requirement for compliance with the GMP

The Japan Fair Trade Commission (JFTC), an agency involved in the use and promotion of generic products published "The Report of the Fact Finding Survey on the Distribution of Pharmaceuticals," in September 2006. The report exposes the trade practices related to generic pharmaceuticals and evaluates them from the viewpoint of competition policy. In addition, the Ministry of Health, Labour and Welfare has set some numerical targets to boost up the share of generic drugs to over 30% in volume which is double the current share by FY 2012. They also established the "Action Programme for Promoting the Safe Use of Generic Drugs" in October 2007 to promote the use of generic pharmaceuticals.

Generic substitution policy is still new in Japan and it is not commonly practiced by community pharmacies despite the pharmacists' positive attitudes toward generic substitution. The Japanese government encourages dispensing of generic substitution drugs since it results in higher reduction of cost of total drug prescription. The market share of generic drugs by volume was 20.2% in 2009 (Ministry of Health, Labour and Welfare 2010) which is still low compared to European countries (Germany, Netherlands and United Kingdom) where the reported market share was 40% and 69.7% in Denmark (Yves *et al.*, 2011).

The Ministry of Health, Labour and Welfare proposed a guideline for bioequivalence studies for generic manufacturers and made it possible for generic products to be registered on the reimbursement list every 6 months rather than once a year since 2007 to accelerate registration of generic drugs. For the substitution of brand drug to generic drug, it is necessary for either physician to prescribe the generic drug in the hospital or the pharmacist to switch the originally prescribed drug to a generic drug in the pharmacy (Yves *et al.*, 2011).

#### ***Development of generic drugs policy in Switzerland***

In a recent generic medicine policy implemented in Switzerland in January 2001, pharmacists have been authorized to

substitute original drugs with generics provided that they have the agreement of the patient and have informed the prescribing physician. Since July of the same year pharmacists have received a fixed fee when dispensing a generic drug, independent of the price of the dispensed drug, which avoids financial penalization.

There is no reference pricing scheme that requires the patient to pay the difference between the actual price of the medicine and the reference price. However, since 2006, patient copayments for brand drugs have been raised from 10% to 20%. To be admitted to the reimbursed drugs list, generics need to be priced lower than the branded drug. This means a minimal saving in comparison with the originator being requested since 2005 (in 2009, -20% to -50%, depending on market size). Besides that, Switzerland has no other mechanisms used like mandatory guidelines and expenditure targets to regulate physicians' generic prescription practices (Yves *et al.*, 2011).

#### ***Development of generic drugs policy in Indonesia***

A Generic Drug Policy was launched in Indonesia in 1989-in principle to expand drug coverage for the community. This was to ensure availability of essential drugs by assuring the safety, quality and efficacy, and affordable prices to the public. Intensification of communication and information related to the benefits of using generic drugs to health professionals was carried out efficiently and in a planned, systemic, and sustainable manner. Generic drug use in public health care facilities is mandatory. Pharmacists are allowed to substitute a brand name drug for its generic with physician and/or patient approval. Thus, when the use of generic drugs increases, the drug coverage can be improved significantly.

#### ***Development of generic drugs policy in the United States***

Before brand products can be substituted with generic products, it is compulsory to undergo testing and meet US Food and Drug Administration (FDA) requirements. Over the years, various acts and regulations have been developed in order to guide generic substitution. Unfortunately, in 1937, more than 100 people died after ingesting sulphonamide elixir containing toxic solvent of diethylene glycol. This phenomenon happened as a result of no requirement for the drug to be tested prior to distribution to the public (Johnston *et al.*, 2011).

In 1962, the Kefauver-Harris Amendment included other aspects to the manufacturer in providing data that demonstrate the efficacy in treating a particular indication and the drugs required to be manufactured according to Good Manufacturing Practice (GMP) (Johnston *et al.*, 2011).

There are certain requirements for prescribing any substituting drugs. The requirements are divided into several sections as follows:

- I. If the medical practitioner prescribes a brand name drug without indicating an intention to prevent substitution, a pharmacist may dispense a generic equivalent drug.

- II. Pharmacy personnel should inform the person who presents the prescription of the price difference between the brand name drug and the generic substitution drug.
- III. The pharmacist should label the container with the name of the drug dispensed followed by the words "generic equivalent for" followed by trade or brand name of product that has been replaced by the generic product.
- IV. Prescription should be dispensed as written only if the prescriber writes "DAW", "Dispense as written", "do not substitute", "medically necessary" or any statement that does not allow the pharmacist to substitute the medication.
- V. This section applies to all prescriptions including those presented by or on behalf of persons receiving state or federal assistance payments.
- VI. The labeling and oral requirements of this section are not related to the pharmacist that serves patients in a health care institution. Formulary should be prepared in hospitals in order to apply this exemption to hospitals and for inspection by the board.
- VII. A list of drugs that shall not be used as generic substitution by dispensing pharmacists should be established by the board.
- VIII. This section provides a glossary of several terms like brand name, formulary and generic equivalent.

#### ***Development of generic drugs policy in the United Kingdom***

Generic substitution is a standard practice in secondary care in UK but there is a proposal to implement it in primary care. The UK has the highest prescription of generic drugs in the world (83% in the community in England in 2008). However, sometimes generic substitution is inappropriate and in such cases, brand name drugs should be prescribed to ensure continuity of supply of particular product and to avoid potential adverse effects due to toxicity.

Generic substitution policy in the UK includes the following (Duerden and Hughes, 2010):

- I. National Health Service (NHS) states that it is a priority to give people more choices. The choices include the right to be involved in decision making about health care and information that should be given to make such decision.
- II. Two medicines may be said to be bioequivalent if the 90% confidence intervals for the ratios of the geometric means (generic:innovator) of the area under the plasma drug concentration versus time curve (AUC) and the maximum plasma concentration (C<sub>max</sub>) fall between 0.8 and 1.25 (80% and 125%).
- III. The generic manufacturer should submit an application to the regulatory authorities based on the safety and efficacy data of the equivalent branded product. They have to show that the pharmacokinetics of the same molar dose of their product is within acceptable, predefined limits.

IV. Although most generic manufacturers try to produce a drug that is similar to the proprietary product, there is no requirement of a drug to have a similar appearance. As a result, generic drugs often differ from the brand product and vice versa in case of packaging.

### RECOMMENDATION OF GENERIC SUBSTITUTION

Obstacles to the market entry of generics in most instances are not technical, but derived from institutional arrangements, including the prescription practices of doctors, brand loyalties, and regulatory and reimbursement systems, including retail pharmacy regulation and practices.

### THE PROPOSED GENERIC SUBSTITUTION POLICY

- I. Pharmacists and patients should always communicate to know the safety and suitability of the alternate brands for patients before using the generic drugs to minimize the patient's misunderstanding and confusion about the drugs and improve patient acceptability of a generic product. Acceptability of the patients might stimulate the motivation, behaviour, and knowledge about the generic products of the practitioner.
- II. In order to give proper guidance on generic substitution, a formulary of interchangeable medicines must be developed. The requirements for marketing authorization of the generic products are:
  - The applicant must have a license for manufacturing and marketing.
  - The factory must have a license or accreditation for manufacturing the item.
  - The name, ingredients, quantity, dosage and indications of the item should be appropriate.
  - The items must fulfill the requirement for compliance with the country's GMP.
- III. Generic substitution is aimed at cost savings for patients. This leads to the replacement of expensive original pharmaceuticals prescribed by the doctor with cheaper generics having the same active substance or equivalent effect with the original.
- IV. The supply chain should be reduced by avoiding unnecessary distribution level between manufacturers and patients to ensure the price offer is affordable to the patients.
- V. Strict quality standards should be issued. The generic substitution drugs should be safe and effective, pharmaceutically equivalent, bioequivalent, adequately labeled and manufactured in compliance with current GMP regulation.
- VI. The National Pharmaceutical Control Bureau (NPCB) is the regulatory body for approval and registration of the generic drug. It is important for the generic product to meet its crucial criteria such as safety, efficacy and efficiency.

- VII. The generic drug products must be manufactured under the FDA's approval under its same standard as good manufacturing practice regulations.
- VIII. Education is an important factor. The government and general practitioners are responsible for disseminating the information about the generic drugs to the consumers in order to avoid misunderstanding.
- IX. Pharmacists and medical practitioners should have positive perceptions toward generic substitution products as it can affect consumer or patient choice.
- X. Labeling of medicine should be based on the international non-proprietary name (INN) as it can help the patients to identify their medication and avoid misunderstanding when substitutions occur (Chua *et al.*, 2010).
- XI. Collaboration between general practitioners (GPs) and pharmacists should be established in order to increase the usage of generic drugs by the public (Chua *et al.*, 2010).
- XII. Pharmacists should have a system where they can access relevant information about the generic medicines before dispensing them.
- XIII. A list of branded products that cannot be substituted with generic drugs should be established, such as non-bioequivalent generic products and Narrow Therapeutic index (NTI) medicines in which small variations in bioavailability may be clinically significant. This can help the general practitioners to identify the drugs in the list that cannot be substituted with the generic product.
- XIV. The lists can aid the pharmacists to assess the generic equivalence of the products chosen as a substitution for the patients.
- XV. If the substituted drugs are included in the lists, pharmacists have the authority to change to the generic drug unless the patient demands the brand name drug. However, if the prescriber puts an initial or sign (e.g. do not substitute), the dispensing pharmacist should dispense according to the prescribed medication. Pharmacist cannot replace it with the generic substituted drug or other brand name drug.
- XVI. Reference-pricing system should be implemented.
- XVII. Education to increase awareness and confidence towards generic medicines need to be targeted among medical doctors and consumers alike.

### CONCLUSION

This article shows that many countries are aware of the advantages of generic substitution especially in reducing cost and increasing patient compliance. However, the fact that generic drugs do not have to undergo large, expensive clinical trials that are required for approval of brand-name drugs give rise to questions about the quality and safety of generics. Furthermore, there is also an issue on the pricing and reimbursement status of generic drugs. It is compulsory for generic drugs to undergo various tests to meet the requirements and to ensure that the authorization procedures of

generic drugs are equally efficient, safe and equivalent to the corresponding originator product. It is also important to implement a Reference-pricing system as a solution in the pricing issue (Chua *et al.*, 2010).

This article highlights the importance of educating general practitioners about the generic products approval system concerning bioequivalence, quality, and safety. Both pharmacists and medical practitioners should have positive perceptions toward generic substitution products since it can affect the choice of the consumers and patients. Good communication between pharmacists and physicians are expected to improve the generic substitution process. Besides, regulatory bodies for approval and registration of the generic drug should play their role to ensure the generic product meets its crucial criteria such as safety, efficacy and efficiency while the government and general practitioners are responsible for disseminating information about the generic drugs to the consumers in order to increase understanding, acceptance and ability to make choices. Lastly, this article is an urgent call for our country to establish a policy regarding generic substitution practice. In addition, several suggestions from the reviewed content can be used to improve the practice of generic substitution in Malaysia.

## DISCLOSURE

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