GENERIC MEDICINES: ASSESSMENT OF THE KNOWLEDGE AND PERCEPTIONS OF MEDICAL SPECIALISTS AND GENERAL PRACTITIONERS IN MALAYSIA

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GENERIC MEDICINES: ASSESSMENT OF THE KNOWLEDGE AND PERCEPTIONS OF MEDICAL SPECIALISTS AND GENERAL PRACTITIONERS IN MALAYSIA

By

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DEDICATED TO MY LORD KRISHNA, MY FAMILY
AND
ALL RESEARCHERS

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ABBREVIATIONS

%	Percentage
&	And
>	More Than
APHM	Association of Private Hospitals of Malaysia
API	Active Pharmaceutical Ingredient
APPL	Approved Products Price List
ASEAN	Association of South-East Asian Nations
AUC	Area Under Curve
BLA	Biologics License Application
BMI	Business Monitor International
bn	Billion
CAGR	Cumulative Annual Growth Rate
CCM	Chemical Company of Malaysia
cGMP	Current Good Manufacturing Practices
Cmax	Maximum Plasma Drug Concentration
CVS	Cardiovascular System
DALYs	Disability Adjusted Life Years
DCA	Drug Control Authority
DES	Drug-Eluting Stent
EC	European Commission
edn.	Edition
EGA	European Generic Medicines Association
EIU	Economic Intelligence Unit
EMA	European Medicines Agency
EPF	Employee Provident Funds
EPP	Entry Point Project
EU	European Union
FDA	Food and Drug Administration
GDP	Good Distribution Practices
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
GPhA	Generic Pharmaceutical Association

GPs	General Practitioners
GRAS	Generally Regarded as Safe
GS	Generic Substitution
HRD	Human Resources Department
IND	Investigational New Drug
INN	International Non-Proprietary Name
KNMP	The Royal Dutch Pharmacists Association
LDL	Low Density Lipoprotein
LHS	Left Hand Side
LMICs	Lower and Middle Income Countries
MAA	Marketing Authorization Application
MACCE	Major Adverse Cardiovascular and Cerebrovascular Event
MIDA	Malaysian Industrial Development Authority
MITI	Ministry of International Trade and Industry
mn	Million
MNCs	Multinational Companies
MNHAs	Malaysia National Health Accounts
MOH	Ministry of Health
MOPI	Malaysian Organization of Pharmaceutical Industries
MSQH	Malaysian Society for Quality of Health
NCEs	New Chemical Entities
NDA	New Drug Application
NEDL	National Essential Drugs List
NHMS	National Health Morbidity Surveys
NKEAs	National Key Economic Areas
NPCB	National Pharmaceutical Control Bureau
NTI	Narrow Therapeutic Index
OIC	Organization of the Islamic Conference
OOPPs	Out-of-Pocket Payments
OTC	Over-the-counter
PBS	Schedule of Pharmaceutical Benefits
PhAMA	Pharmaceutical Association of Malaysia
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

PPP	Purchasing Power Parity
PSD	Pharmaceutical Services Division
QD	Qualitative Descriptive
R&D	Research and Development
RHS	Right Hand Side
RM	Ringgit Malaysia
SHI	Social Health Insurance
SOCSO	Social Security Organization
TEH	Total Health Expenditure
TPPA	Trans-Pacific Partnership Agreement
USA	United States of America
USFDA	United States Food and Drug Administration
WHO	World Health Organization
WTO	World Trade Organization

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LIST OF PUBLICATIONS

1. **Kumar, R.**, Hassali, M. A. A., Kaur, N. and Kader, M. A. S. A. (2014) Perceptions of physicians from private medical centres in Malaysia about generic medicine usage: a qualitative study, Generics and Biosimilars Initiative Journal, 3(2), 63-70.

2. **Kumar, R.**, Hassali, M. A., Saleem, F., Alrasheedy, A. A., Kaur, N., Wong, Z. Y. and Kader, M. A. S. A. (2015) Knowledge and perceptions of physicians from private medical centres towards generic medicines: A nationwide survey from Malaysia, Journal of Pharmaceutical Policy and Practice (In Press).

UBAT-UBATAN GENERIK: PENILAIAN PENGETAHUAN DAN PERSEPSI PAKAR-PAKAR DAN PENGAMAL PERUBATAN DI MALAYSIA

ABSTRAK

Dalam tahun-tahun kebelakangan ini, perbelanjaan farmaseutikal telah berkembang lebih cepat berbanding komponen lain yang berkaitan perbelanjaan penjagaan kesihatan. Secara global, tekanan untuk menguruskan perbelanjaan farmaseutikal telah membolehkan kerajaan dan organisasi kesihatan bukan kerajaan untuk menggalakkan penggunaan ubat-ubatan generik. Pada tahun 2012, perbelanjaan out-of-poket (OOP) Malaysia terhadap penjagaan kesihatan adalah 79% daripada perbelanjaan sektor swasta dan ia adalah dua kali ganda tinggi bagi negara-negara berpendapatan tinggi out-of-poket pembayaran (OOPPs), yang purata 37% daripada perbelanjaan sektor swasta. Untuk menurunkan OOPPs dan mengurangkan beban kewangan terhadap pesakit dalam sektor penjagaan kesihatan swasta, ia amat disyorkan untuk menggalakkan penggunaan generik. Di Malaysia, preskripsi ubatan generik telah menjadi satu amalan biasa di hospital kerajaan. Walau bagaimanapun, trend di hospital perubatan swasta Malaysia keadaannya seolah-olah berbeza. Tujuan kajian ini adalah untuk menyiasat pengetahuan pusat perubatan swasta Malaysia physicians', dan persepsi berhubung penggantian ubat-ubatan generik bagi produk asas. Kaedah rekabentuk penyelidikan campuran telah diguna pakai untuk kerja-kerja ini. Di bawah kajian kualitatif, lapan belas pakar perubatan daripada bidang perubatan yang berbeza telah ditemuramah. Majoriti pakar memberikan pandangan positif tentang penggantian generik tetapi sinis tentang kualiti mereka dari segi keberkesanan dan keselamatan bagi beberapa kategori dadah. Doktor lebih

suka untuk melihat keputusan biokesetaraan dijalankan oleh pengilang generik dan juga mereka lebih suka untuk menghias dengan beberapa kajian farmakodinamik berasaskan komuniti kecil. Kajian kuantitatif adalah satu kajian di seluruh negara yang melibatkan pakar-pakar perubatan dari pusat perubatan swasta di Malaysia. Secara keseluruhan, 263 jawapan diterima daripada hospital berbeza di Semenanjung dan Malaysia Timur. Respon yang telah diterima terdiri daripada penyertaan dari hospital kecil ke hospital besar dalam rantaian Malaysia. Pelbagai persatuan yang ketara telah diperhatikan mengikut butir-butir demografi dan pengetahuan dan persepsi doktor mengenai generik. Selanjutnya, kajian intervensi pendidikan telah dijalankan untuk menilai kesan ke atas pengetahuan dan persepsi doktor tarhadap ubat-ubatan generik. Terdapat sedikit peningkatan dalam pengetahuan diperhatikan selepas intervensi, yang disokong oleh pelbagai kajian, memastikan perubahan dalam tingkah laku, setiap kali pengetahuan mengenai generik telah disediakan. Kejayaan generik di pusat-pusat perubatan swasta di Malaysia bergantung kepada perubahan persepsi doktor mengenai ubat-ubatan generik. Selain pelaksanaan dasar penggunaan ubat generik untuk hospital swasta di Malaysia, ini juga boleh dicapai melalui pembaikan dalam pemasaran dan promosi produk generik yang lebih baik. Para doktor yang berkhidmat di hospital-hospital awam di Malaysia mungkin mempunyai pemahaman yang lebih baik mengenai ubat-ubatan generik, daripada mereka yang menjalankan amalan perubatan di sektor swasta, kerana kebanyakan ubat-ubatan yang diberi oleh hospital kerajaan adalah generik. Dalam sektor swasta, maklumat akademik boleh membantu meningkatkan pengetahuan doktor mengenai ubat-ubatan generik.

GENERIC MEDICINES: ASSESSMENT OF THE KNOWLEDGE AND PERCEPTIONS OF MEDICAL SPECIALISTS AND GENERAL PRACTITIONERS IN MALAYSIA

ABSTRACT

In recent years, pharmaceutical expenditure has grown faster than many of the other components of healthcare spending. Globally, pressure to manage pharmaceutical spending has led governments and non-governmental health organizations to promote the use of generic drugs. In 2012, Malaysia's out-of-pocket (OOP) expenditure on healthcare was 79% of private sector spending and it was twice the high income countries out-of-pocket payments (OOPPs), which average at 37% of private sector expenses. To bring down the OOPPs and reduce financial burden on patients in private healthcare sector, it is highly recommended to promote the use of generics. In Malaysia, generic drug prescribing has become a common practice in public hospitals. However, the trend in private medical centres of Malaysia seems to be different. The aim of this study was to investigate Malaysian private medical centers physicians´ knowledge, and perceptions regarding substituting generic medications for originator products. Mix methods research design was adopted for this work. Under qualitative study, eighteen medical specialists from different medical fields were interviewed. The majority of specialists were positive about generic substitution but cynical about their quality in terms of efficacy and safety for some drug categories. Physicians preferred to see the results of bioequivalence conducted by generic manufacturers and also preferred them to garnish it with some small scale community based pharmacodynamic studies. The quantitative study was

a nationwide survey involving physicians from private medical centres in Malaysia. In total, 263 responses were received from different hospitals of Peninsula and East Malaysia. The responses received comprised of participation from small to big hospitals chains of Malaysia. Various significant associations were observed among physicians´ demographic particulars and their knowledge and perceptions about generics. Further, an educational interventional study was carried out to evaluate the impact on the knowledge and the perceptions of physicians towards generic medicines. A slight improvement in knowledge was observed after the intervention, which was supported by various studies, assuring a change in behaviour, whenever the knowledge about generics was provided. The success of generics in private medical centres in Malaysia depends on changing the perceptions of these physicians about generic drugs. In addition to implementation of generic drug usage policy for private hospitals in Malaysia, this can also be achieved through improved marketing and promotion of generic products. The doctors serving in the public hospitals in Malaysia might have a better understanding about generic medications, than those who are practising in the private sector, since most of the medications dispensed by government hospitals are generics. In the private sector, academic detailing can help to improve the knowledge of physicians about generic medicines.

CHAPTER ONE: GENERAL INTRODUCTION

1.1 Background

The expenditure on healthcare is steadily increasing in many countries around the globe. The World Health Organization (WHO) reported that 5.3 trillion dollars were spent on healthcare in 2007, which amounted to a sum of 6.5 trillion dollars in a recent fact sheet published by the agency (Xu, et al., 2010; WHO, 2012a). Although higher health expenditures cannot necessarily be linked with better health outcomes, a minimum level of resources are required for a healthcare system to fulfil its vital functions adequately. Moreover, with the increment in lifestyle diseases, such as hypertension, cardiovascular (CVS) diseases, cancer, and diabetes etc., national healthcare costs are increasing noticeably. In recent years, it has been reported that pharmaceutical expenditure is growing faster than many of the other components of healthcare spending (Henriksson, et al., 1999; Schneeweiss, et al., 2002; Ess, et al., 2003; Thorpe, K. E., 2005; Zuvekas, et al., 2007; Coma, et al., 2009; Leng, et al., 2011; Godman, et al., 2012a; Hoffman, et al., 2012; Hermansyah, A., 2013; Hoffman, et al., 2013). In the United States of America (USA), total spending on medicines in 2010 was $307 billion (bn), an increase of around $60bn since 2005 and $135bn since 2001 (Figure 1.1).

Across Europe, healthcare is scarcely managing to cover its expenses. The rise in pharmaceutical expenditure is typically between 4% and 13% per annum (Heikkilä, et al., 2007; Simoens, S., 2009; Sermet, et al., 2010; Vandoros, et al., 2013). This rise is similar to the USA in its pace, especially when compared to the growth of other parts of healthcare expenditure (Schneeweiss, et al., 2002; Schneeweiss, et al., 2004).

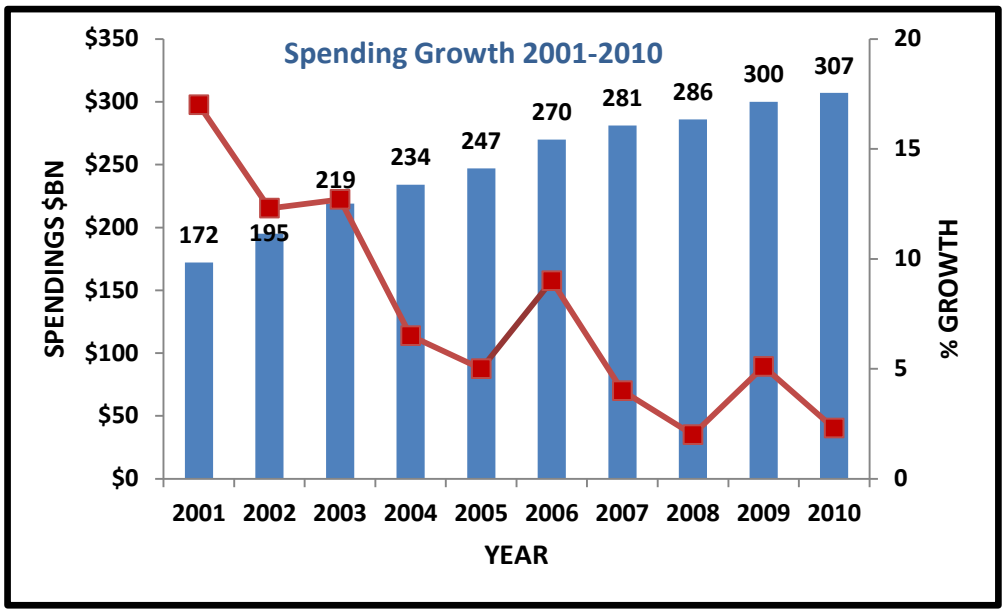

Figure 1.1 Spending on Medicines in the US (2001-2010)
[Adapted and Modified from IMS Database, 2012]

The different ways of raising funds to cover healthcare costs are inadequate, but, of even greater concern, the costs themselves are set to ascend. According to World Bank statistics, public spending on healthcare in the European Union (EU) could shoot up from 8% of the gross domestic product (GDP) in 2000 to 14% in 2030 and keep on growing beyond that date. The dominant anxiety of the European healthcare sector is to discover new ways to balance its budgets and control spending. If that is not achieved, the resources to pay for healthcare will soon fall short of demand (The Future of Healthcare in Europe, 2011). All European governments are facing the same basic challenge: how to fund their own health-care systems without demanding too many sacrifices from the public. A survey conducted in 6 European healthcare systems: Switzerland, France, Germany, Italy, Spain and United Kingdom, reveals that overall healthcare expenditure has grown on average by about 80% in these countries since 1990, while the GDP of the group has grown by only about 25%

(Beyer, et al., 2007). This divergence is expected to continue during the coming decades (Figure 1.2).

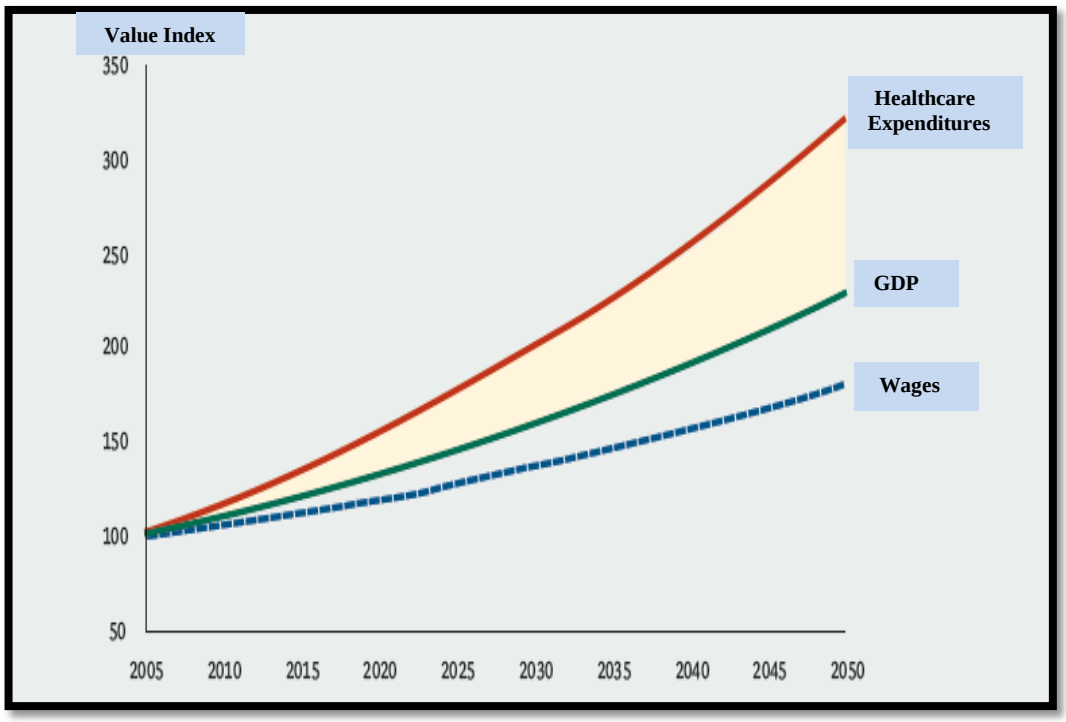

Figure 1.2 Healthcare Expenditure will Continue to Outpace GDP and Wages [Adapted and Modified from Beyer, et al., 2007]

In the lower and middle income countries (LMICs), this expenditure ranges from 20% - 60% of the total spending on healthcare (Cameron, et al., 2009; Godman, et al., 2010a). In these countries, patented medicines generally cost considerably higher than their generic counter parts, and by example, they can go up 10 fold (WHO, 2010a; Cameron, et al., 2012; GaBI Online, 2014). Overall, insurance coverage in the LMICs remains poor and many schemes do not cover expenses on medicines. Hence, medicines are still mainly purchased through out-of-pocket payments (OOPPs) in the private sector. Globally, pressure to manage pharmaceutical spending has led governments and non-governmental health organizations to promote the use

of generic drugs (De Joncheere, et al., 2002; Simoens, et al., 2006; Simoens, S., 2007; Araszkiewicz, et al., 2008; Sermet, et al., 2010; Godman, et al., 2012b). European health authorities, and health insurance companies, have instigated a number of reforms and initiatives in recent years to deal with this unsustainable growth. Among the many efforts made by them include a focus on the policies surrounding generics, to result in providing high quality treatment at lower prices, with considerable savings (Seeley, E. 2008; Seeley, et al., 2008; Figueiras, et al., 2009; Ministry of Health, Labour and Welfare of Japan, 2012).

1.2 Generic Medicines

A generic medicine can be defined in different ways (Birkett, D. J., 2003; Davit, et al., 2013; Dunne, et al., 2013). However, the term is easy to understand as defined by the WHO as "a pharmaceutical product, usually intended to be interchangeable with an innovator product, which is manufactured without a license from the innovator company and is marketed after the expiry date of the patent or other exclusive rights" (WHO, 2012b). The United States Food and Drug Administration (USFDA) define a generic drug product as "a drug product which is comparable to a reference (brand) listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use". Before registration, similar to all medicinal products including originator, generic drug products must pass through a rigorous registration process and stringent requirements to ensure their quality, safety and efficacy (USFDA, 2012).

In addition to these controls, the concept of bioequivalence is an essential requirement for any generic registration in many countries including Malaysia (Galgatte, et al., 2013). A bioequivalence study is performed to demonstrate a clinical equivalence between a generic product and its reference drug product to allow a bridging with the clinical studies conducted on the originator product. Hence, a repetition of preclinical or clinical studies is not required (European Medicines Agency, [EMA], 2010). A generic drug is expected to have the same clinical effect i.e. therapeutically equivalent and have a similar safety profile as the branded product when administered under the conditions specified in the labelling. Hence, generic drugs can be substituted for originator products by physicians and pharmacists (Levinson, D. R., 2008). Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name. Generic drugs are as effective as branded drugs and are much more economical than originator brands (Matin, Y., 1999; Simoens, et al., 2006; Shafie, et al., 2008; WHO, 2011; Vogler, S., 2012a; European Generic Medicines Association [EGA], 2013a). Generic medicines are available as a standard therapy for many acute and chronic diseases (Sheppard, A., 2011; EGA, 2013a).

The Hatch-Waxman Act (1984) allows the entry of generic drugs into the market for trade, without conducting the expensive clinical trials, unlike their originator counterparts (Lewek, et al., 2010; Davit, et al., 2009; Bera, et al., 2012; Perkins, et al). Hence, generic development costs are much lower; furthermore, they are being sold at a lower price when compared to originator brands. Generic drug manufacturers also have to follow similar strict quality standards with respect to identity, strength, quality, purity and potency. However, some variability can and

does occur during manufacturing, for both the originator and the generic products. When a drug product, generic or referenced, is mass-produced, very small variations in purity, size, strength, and other parameters are permitted. The USFDA limits the amount of variability that is acceptable. Both generic and branded products are being manufactured under similar cGMP conditions as those required for the innovator companies. All generic manufacturing, packaging, and testing sites, must pass the same quality standards as those of the branded drugs, and the generic products must meet the same specifications as any brand name product. In fact, many generic drugs are made in the same manufacturing plants as the brand name drug products. Hence, these low priced generics do not essentially construe to be of a lower quality. Generally, generics do not spend on costly advertising, marketing, and promotion. In addition, the availability of a single product, from multiple generic companies, creates competition in the market place, often resulting in price erosion (USFDA, 2012). The USFDA requirements for a bioequivalent generic drug product are as follows:

a. It should have the same active ingredients and strength as the originator product.
b. It should have the same dosage form and route of administration.
c. It should be bioequivalent i.e. the same amount of the drug should be delivered in the same amount of time as that of the reference product.
d. It should have the same labelling except for the name of the medication.
e. It should have a documented chemistry, manufacturing steps, and quality control measures. The raw materials and finished product specifications should meet the United States Pharmacopoeia specifications.
f. The potency and the shelf-life should be comparable to the reference product.

g. The facilities used to manufacture, process, test, package and label the generic product should meet good manufacturing practices (GMP).

Thus, generics offer a simple and important solution to these expenditure issues, resulting in drug affordability, and the containment of pharmaceutical costs, since the price of medicines is a major component of healthcare costs (King, et al., 2002; Dukes, et al., 2003; Wallack, et al., 2004; Hassali, et al., 2009a; Godman, et al., 2010b; Hassali, et al., 2010; Simoens, S., 2010; Doloresco, et al., 2011; Al-Tamimi, et al., 2013; Hermansyah, A., 2013). Generic pharmaceuticals have now been cited as being a dependable lever to decrease healthcare costs and have continued to deliver outstanding savings to many developed countries. Genazzani, et al., stated that generic drugs are a major asset to national projects through the reduction of pharmaceutical expenses (Genazzani, et al., 2008). Apart from reducing healthcare costs, generic medication benefits include the reduction of a patient´s out-of-pocket costs, and most importantly, to an increased adherence to the treatment regime (Shrank, et al., 2006; Shrank, et al., 2009a; Brems, et al., 2011; Iizuka, et al., 2011). With the use of generics, healthcare systems can save substantial amount of money which can be utilized to pay for more expensive patented and new innovative products that are required to treat some diseases where generics are not available (EGA, 2007). The savings from generics can also be utilized by policy makers or government to finance the research and development (R&D) and reimbursement of newer, expensive innovative medicines (Simoens, et al., 2006).

The advantages of generic medications can be listed as below:

a. Reduction of the overall treatment cost for patients, resulting in the affordability and the containment of healthcare costs for governments.
b. Increased adherence to therapy due to lower medicine costs.
c. Stimulates innovation and the development of new drugs.
d. Creates access to essential medicines and the continuity of supply.
e. Economic development and employment.

Despite the above advantages of generic medicines, their use worldwide is lacking (Kirking, et al., 2001). The World Health Report (Chisholm, et al., 2010) has identified the following ten leading causes for health system inefficiency:

a. Medicines - the use of sub standard medicine and counterfeits
b. Medicines - inappropriate and ineffective use
c. Medicines - underuse of generics
d. Healthcare products & services - overuse
e. Health workers - inappropriate or costly staff mix
f. Healthcare services - inappropriate hospital admissions and length of stay
g. Healthcare services - inappropriate hospital size
h. Healthcare services - medical errors and suboptimal quality of care
i. Health system leakages - waste, corruption & fraud
j. Health interventions - inefficient strategies

Under use of generics was listed as one of the main reasons for healthcare system inefficiency.

Over the period 2003 to 2012, the USA has saved more than $1.2 trillion from the healthcare system by using generics. In 2012 itself, the U. S. health system has saved $217bn, up from $188bn in 2011, due to the usage of generic medicines (Johnson, L. A., 2012; Generic Pharmaceutical Association, 2013). In 2012, savings, only from newer generic products (entering the market in the past 10 years), represent more than half of the total savings; which means that the use of generics in newer drugs will result in an exponential growth in savings (Figure 1.3).

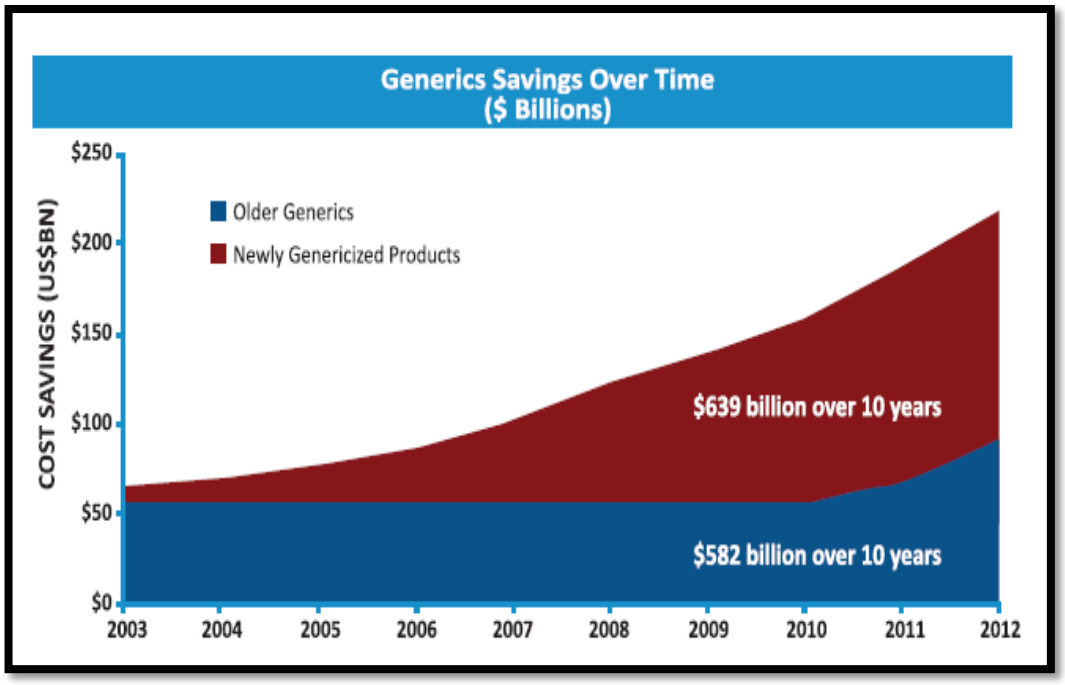

Figure 1.3 Generics Savings over the Course of Time in the USA [Adapted from the Generic Pharmaceutical Association, GPhA, USA]

In the US, generics account for approximately 75% of prescriptions, and this only incurs 13% of the total cost of newer, innovative, and generally more expensive medications (Kohl, et al., 2007). In Europe, it has been estimated that the use of generics is contributing almost €30bn every year to the healthcare system (Sheppard

A., 2011). Figure 1.4 depicts the market share of generics which differs a lot among the different European countries (Vogler S., 2012b).

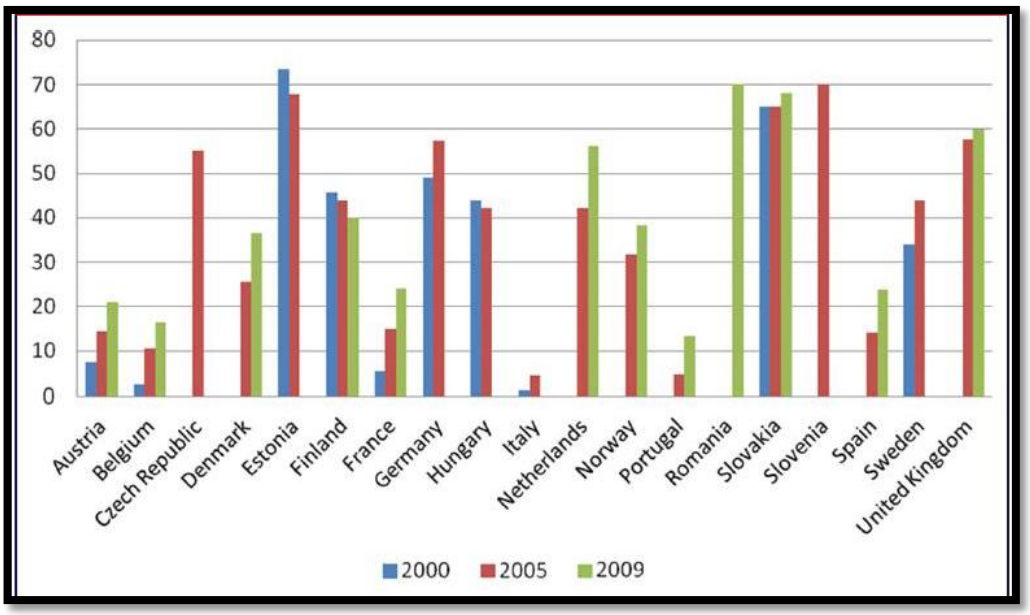

Figure 1.4 Generics Market Share of the Outpatient Market in the EU (% Volume) [Adapted from Vogler S., 2012b]

The study conducted by Vogler, (2012b) in 16 European countries to discover the price differences between the originators and generics, for a selected basket of molecules, showed that an investment in generics tends to pay off (Vogler, S., 2012b). As per a recent WHO report, in the private sector of 17 countries, an average of 9% - 89% could be saved, by individual medicines, incurring a switch from the originator brand to the lowest priced generic equivalent (WHO, 2010a; Brems, et al., 2011; Kaplan, et al., 2012). In 2006, generics accounted for 42% of dispensed packs among 27 countries across Europe, but this cost was only 18% of the total pharmaceutical expenditure (Simoens, S., 2008a).

However, in order to get the maximum benefits from generics, it is really important to ensure that their availability, and immediate market entry, follows the patent expiration of the originator (Kanavos, et al., 2008; Fatokun, et al., 2011; Sheppard, A., 2011). The objective of generic medicines can be lost, or the results can be devastated, by a delayed or hindered entry into the market (Kesselheim, et al., 2006). In a study conducted by the European Commission (EC), it was estimated that almost €3bn was lost in 27 member countries, due to the delayed entry of generic versions of the top selling products between 2000 and 2007 (EC, 2009a).

Globally, governments across many countries have taken various initiatives to bring down their healthcare costs, which has led to lower reimbursed prices for generics and originators, as well as interchangeable brands, within the pharmacological or therapeutic classes (Godman, et al., 2008; Godman, et al., 2009a; Ferner, et al., 2010; McGinn, et al., 2010; Godman, et al., 2012a). The dispensing of generics was seen as a standard treatment, and this was planned through encouraging or mandating pharmacists, to substitute less expensive generic products, in place of the more expensive originators, wherever relevant, unless prohibited by physicians or the health authorities (Figueiras, et al., 2008; Seeley, et al., 2008; Simoens, S., 2008a). Preferential co-payment policies for generics in the US, among the insured population and seniors, have also resulted in a high utilisation of generics. As a result, generics account for approximately two thirds of prescriptions, but only 13% of costs (Kohl, et al., 2007; Shrank, et al., 2009a). Similar situations also occur in Asia. As an example, physicians working in government hospitals in Indonesia will soon be required to only prescribe generic drugs, unless there are no generic alternatives available (Bland, B., 2010).

1.2.1 Overview of Generic Drug Product Development Processes

The above brief discussion about generics describes a situation whereby generic medication refers to products that are no longer under patent protection. The entry of a generic drug product, following the patent expiration of originator, begins with the development of the generic drug product (Prasnikar, et al., 2006; Lionberger, R. A., 2008; Genazzani, et al., 2008). Different markets understand and use the term ¨generic drug¨ or ¨generic medicine¨, however, it is commonly understood to be as per the definition provided by the WHO to mean a pharmaceutical product which is:

a. usually intended to be interchangeable with an innovator product
b. manufactured without a license from the originator company, and
c. marketed after the expiration date of the patent or other exclusive rights (Generic drugs, WHO).

Prasnikar, et al., explained that the generic development process initiation completes the manufacturing with a market entry of the product and is classified into 6 phases: phase 0 (generation of an idea), phase 1 (preliminary assessment), phase 2 (laboratory development), phase 3 (development of the technology), phase 4 (product registration), phase 5 (market launch).

Phase 0 represents the selection of the probable generic candidates based upon many factors. Generally, large scale generic pharmaceutical companies will have a dedicated expert team, which will propose a list of potential generic molecules every year, as a proposal to initiate the next phase of activities (Prasnikar, et al., 2006).

Phase 1 is a preliminary assessment phase, where drug molecules are assessed roughly for their market potential, patent expiry, complexities, the expenses involved, budgets, regulatory and intellectual property concerns, R&D and regulatory strategies, production feasibility and other commercial factors. This phase is the 'desk research' stage, involving all relevant documentation about the potential drug molecule, prior to the initiation of any practical activities in a laboratory (WHO, 2011). A risk based analysis is also conducted in order to introduce the new molecule in the development pipeline.

Phase 2 starts in the development laboratory, with experimental work, which includes pre-formulation studies, formulation development, analytical method development, innovator characterisation, comparative dissolution studies, accelerated stability study work, pilot bioequivalence, and primary packaging development studies. At this stage, the scale up from the laboratorial to the semi-industrial scale is achieved (Prasnikar, et al., 2006; WHO, 2011).

Phase 3 is the process or technology development phase. This phase includes the transference of product technology, to industry measurement, and the preparation of registration documentation. It includes clinical studies, toxicological studies, bioequivalence studies, and the completion of stability studies. This phase ends with the manufacturing of 3 registration or submission batches (Prasnikar, et al., 2006).

Phase 4 is the registration of the product with a regulatory agency. The manufacturer files all of the documentation related to the product in a dossier, and replies to any

queries if any are raised by the regulatory agency during the course of the evaluation. This phase aims for obtaining marketing authorisation (Prasnikar, et al., 2006).

Phase 5 is related to activities to be completed for the market launch of the product, which includes a launch requirement calculation, the ordering of raw materials and packaging materials, toolings etc., and ends with a final launch of the product (Prasnikar, et al., 2006).

As discussed earlier, generic drug product related registrations do not involve pre-clinical and clinical studies as required for the originator product. Alternatively, generics have to go through bioequivalence studies only, which are much cheaper than the clinical trials that are undertaken by the originators.

Figure 1.5 depicts that the main reason for generics being cheaper products is primarily due to their much lower investments when they are compared to the innovator products (Dunne, et al., 2013). However, the market price of a generic product can be considerably driven by the end-user and the prescription perception, local regulations, and reimbursement models (Simoens, S., 2007). Keeping in view the manufacturing costs, it should probably not differ significantly, as they (the generic and originator products) are both manufactured under the same standards, conditions, and the regulations in force as stated by the regulatory authorities. It should be noted that an originator product, can turn into a generic product, when the patent has expired, and this is very common these days. Since, the branded product becomes open to generic competition, after the patent expiry, and noticeable price erosions can be observed (Birkett, D. J., 2003).

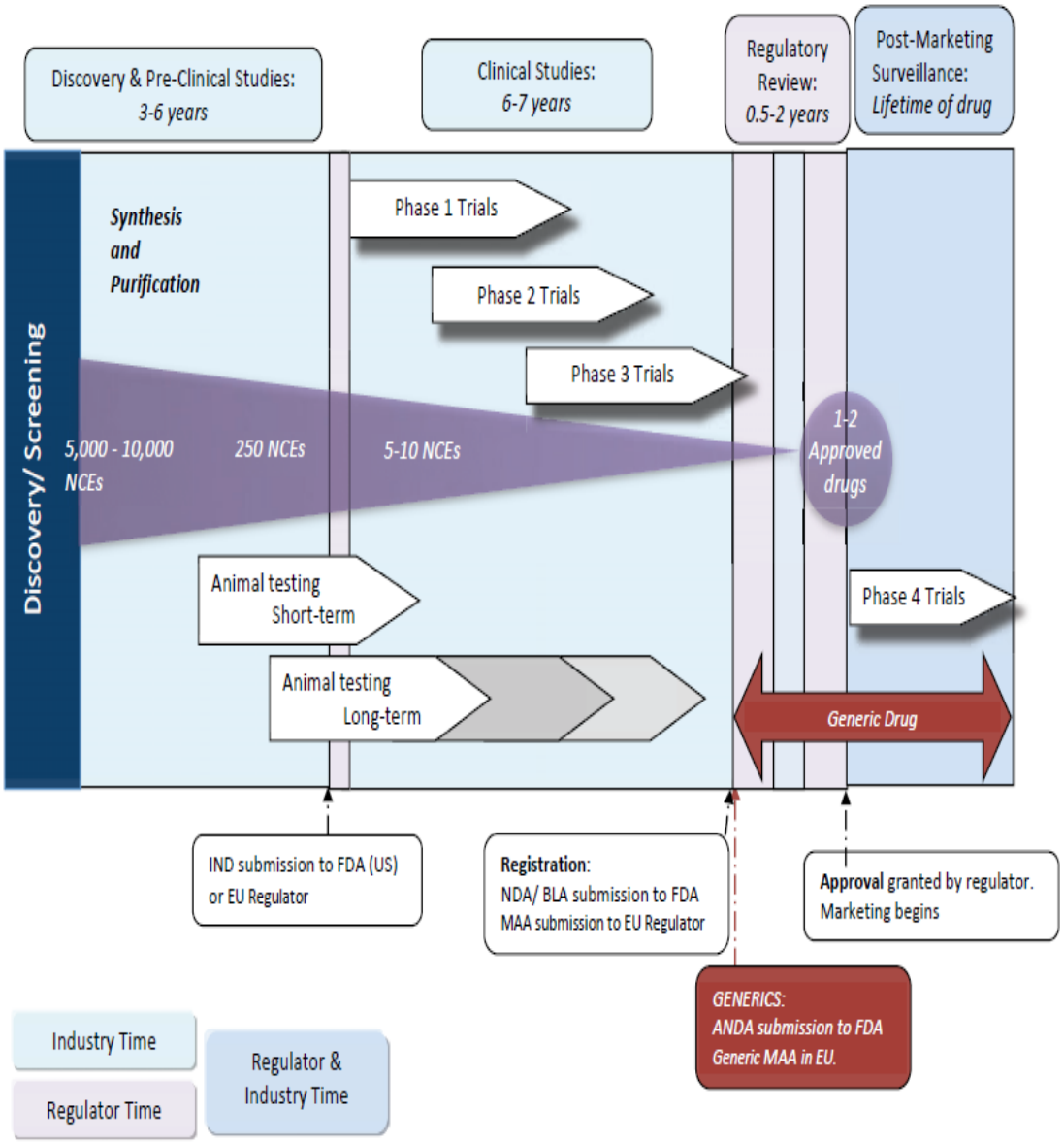

Figure 1.5 Schematic of the Drug Development Process
[Adapted from Dunne, et al., 2013]

1.2.2 Are Generics Really the Same as the Originator Products?

There have been, although, concerns with the effectiveness and the safety of generics (Himmel, et al., 2005; Kjoenniksen, et al., 2006; Heikkilä, et al,. 2007; Kanavos, P., 2008; Simoens, S., 2008b; Figueiras, et al., 2009; Tsiantou, et al., 2009; Shrank, et

al., 2009a; Shrank, et al., 2009b; Chua, et al., 2010; Ferner, et al., 2010; McCartney, M., 2010; Sermet, et al., 2010), with some originator companies questioning the quality of generics, as part of their marketing strategies, to reduce the post-patent erosion of lost sales (EC, 2009b). However, concerns regarding generics generally only apply to a minority of situations (Kjoenniksen, et al., 2006; Shrank, et al., 2009a; Tsiantou, et al., 2009). There have been a substantial number of clinical studies conducted comparing a generic product with a reference product. Most of these studies have demonstrated the therapeutic equivalency between the generic and the branded drug product. In a recent review article, researchers reported the clinical data of 47 studies, which compared generic and reference products, for the treatment of heart and artery disease. These studies included some of the most frequently used medications that are globally available, like beta-blockers, diuretics, statins, and warfarin. These findings suggested that there is no evidence of a superiority of branded products, when compared to generic drugs, in measured clinical outcomes conducted in these studies (Kesselheim, et al., 2008).

In another study, 428 patients underwent implantation with a drug-eluting stent (DES) for coronary artery disease and were enrolled and then completed >1 year of clinical follow-up. Patients were divided into the following 2 groups, based on the treatment formulation, Platless® (test formulation, n=211), or Plavix® (reference formulation, n=217). The incidence of 1-year major adverse CVS, and cerebrovascular events (MACCEs), and stent thrombosis, were retrospectively reviewed. The result of the study proved that the two preparations of Clopidogrel showed similar rates of MACCEs (Park, et al., 2012).

Another multicenter study, which assessed the efficacy of a generic form of Atorvastatin in 119 patients, showed that Low Density Lipoprotein (LDL)-Cholesterol was reduced by 36.6% at four weeks and by 37.5% at eight weeks from the baseline. Total cholesterol and triglycerides were significantly reduced. There were no serious drug-related adverse events. It was concluded that the generic product Atorvastatin was safe and effective in the treatment of primary hypercholesterolemia (Punithavathi, et al., 2009).

Hence, there are many studies available, to prove this equivalency between generic and branded medicines. However, in spite of these studies, some physicians are concerned, because the bioequivalence studies, that predicate generics to be the equivalent, are not made public. They also have no access to find out about the differences in fillers, and other additives, which might change the rates of release. So it comes as no surprise that only 12 of 43 medical journal commentaries, on the subject of generic vs. brand medicines, encouraged the use of generics (Wegmann, J., 2010). Various reasons have been identified by researchers about the under utilisation of generics. Some physicians, pharmacists, and consumers, have expressed that bioequivalent generics, and branded medicines, may not be equivalent in their effects on various clinical parameters, including physiological measures, such as heart rate, or blood pressure, on important laboratory measurements, and various outcomes, such as health system utilisation, or mortality (Gaither, et al., 2001; Shrank, et al., 2009a). Narrow Therapeutic Index (NTI) drugs are of particular concern, where minor differences in plasma levels, can be less effective, or lead to toxicity (Banahan, et al., 1998). Originators have suggested that generics may be less effective or/and less safe than their branded counterparts. Anecdotes have appeared

in the lay press raising doubts about the efficacy and the safety of certain generic drugs (Saul, et al., 2007; Beck, M., 2008; Rockoff, J., 2008). There have also been concerns related to confusion, when patients are dispensed multiple branded generics, each with different names and appearance, which can potentially lead to medical errors (Godman, et al., 2009b; Decollogny, et al; 2011; Kesselheim, et al., 2014; Oyetunde, et al., 2014).

1.2.2.1 Generic Substitution

Generic medicines offer same health outcomes as they are clinically equivalent interchangeable medicines with originator products, but at a much cheaper cost (Godman, et al., 2010b). Generics are considered to be a cost-effective, first line or standard therapy for many diseases and conditions, such as hypertension, diabetes, hyperlipidaemia, hypercholesterolaemia, allergies, depression, gastrointestinal disorders, osteoporosis, infections, skin diseases etc. (Sheppard, A., 2011; EGA, 2013b). However, there has been concerned raised with some NTI drugs, specifically due to switching or substituting them but not prescribing or dispensing them for the first time, currently there is no evidence of inferiority of generics. Currently, generic medicines are promoted as an integral part of healthcare systems (Al-Tamimi, et al., 2013), not only due to their affordability but also for sustainability of healthcare systems (Alrasheedy, et al., 2013). In order to promote generic medications, generic substitution (GS) and generic prescribing has been adopted by many healthcare systems (Vogler, S., 2012b). GS can be defined as an act of dispensing an equivalent generic medicine when an originator brand is prescribed (i.e. switching the patient from an originator product to an equivalent generic product), while generic

prescribing is defined as prescribing by the approved international non-proprietary name (INN) of the medicines (Ferner, et al., 2010). There are two aspects to consider regarding the use of generics: the 'prescribability' or 'dispensability' of generics (i.e. prescribing or dispensing generics for the first or initial patient prescription) and the 'switchability' or substitution (Rani, et al., 2004; Thiessen, J. J., 2005).

During a GS, there are many aspects that must be taken into consideration. The physician's attitude towards GS is most often related to their general prescribing behaviour, their perception of therapeutic efficacy, their beliefs about generics, and their previous experience using generic alternatives, including any negative effects. Pharmacists may consider other kinds of issues like regulatory matters, the therapeutic class of the drug, the cost, and the bioequivalence information, when dispensing generic medication, as well as a patient's medical and medication history, together with their acceptance to a change of brand. Also one need to consider patient's preference, their consent, prescriber's approval (if needed), patient's understanding of the difference between the medicine brands to prevent any confusion due to brand changing (especially for elderly patients), consistency in the selection of the brand, especially for chronic and long-term therapy, the assessment of allergy history to any excipient, whether the new brand needs different instructions to be understood, and the patient's familiarity with the brand (e.g. metered-dose dry-powder inhalers etc.) (International Society of Drug Bulletins, 2006; National Prescribing Service Limited, 2006; National Prescribing Service Limited, 2007; Duerden, et al., 2010). A patient's concerns can be the drug's efficacy, their overall satisfaction, the side effects, its appearance, in addition to their willingness to take medication, and every concern about managing their health

condition. Old aged patients do generally not prefer a change in their medicine or its appearance (Banahan, et al., 1997; Suh, D. C., 1999; Mott, et al., 2002; Kjoenniksen, et al., 2006; Best Practice Journal, 2007).

In addition, it is needed to educate patients about quality, safety, efficacy of generics and their bioequivalence, the similarities and differences between them against the originator product. The issues related with the usage of generics can be categorized with respect to the user as:

i. Consumers: Major barriers to acceptance include:

a. Preference for a doctor's prescribed brand of medicine,
b. Concern over the safety and the efficacy of generic medicine,
c. Concern about the adverse effects from generic brands, and the confusion that may arise from different brands of the same medicine.

ii. Prescribers/Pharmacists: Major barriers to acceptance include:

a. A possibility of patient confusion and a low level of confidence with generic medicine.
b. Loyalty to the companies involved in R&D.
c. A lack of knowledge on the issues surrounding bioequivalence testing for generic medicines.

Therefore, healthcare professionals need to assess the suitability of GS based on their professional judgment (USFDA, 2014). However, it is more important to note that the generic product must be bioequivalent and therapeutically equivalent to the

originator while GS. Thus, unlike other factors that need to be considered when performing GS, therapeutic equivalence should be based on scientific evidence rather than the professional judgement of individual healthcare professionals, as GS is not appropriate for some medicines (Duerden, et al., 2010; Ferner, et al., 2010; Lewek, et al., 2010; Holmes, et al., 2011). For example, NTI drugs such as antiarrhythmic drugs (e.g. digoxin), anti-epileptic drugs (e.g. carbamazepine), anticoagulant drugs (e.g. warfarin), and immunosuppressants (e.g. tacrolimus). Other examples include solid oral modified-release dosage forms of drugs like carbamazepine, diltiazem, morphine and oxycodone etc., medicines containing more than one active ingredient (e.g. oral contraceptives, antacid preparations containing simethicone), different products of the same active ingredient that have different licensed indications [e.g. sildenafil (Viagra® or Revatio®], and products using different salts to form the active ingredients (e.g. nortriptyline) (Duerden, et al., 2010; Ferner, et al., 2010; Lewek, et al., 2010; Holmes, et al., 2011).

To avoid such situations, many countries have implemented regulatory guidelines to ensure that prescribing and substitution of generic products are appropriate. One such example is the *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the 'Orange Book', which is a useful guide for pharmacists and other healthcare professionals with regards to therapeutic equivalence and approved generic products in the United States (USFDA, 2014). In Orange book, products that are therapeutically equivalent, where there is adequate evidence supporting bioequivalence, are designated with a code 'A', and products that are not therapeutically equivalent, where there is no adequate evidence supporting bioequivalence, are designated with a code 'B'.

Another example is from Australia, the *Schedule of Pharmaceutical Benefits (PBS)*, which is a useful guide for healthcare professionals and consumers regarding therapeutic equivalence between medicines (Department of Health and Ageing - Australia, 2007; Department of Health and Ageing - Australia, 2013). In this schedule, 'a' precedes the names of therapeutically equivalent and interchangeable medicine brands, whereas 'b' is attached to brands of medicines that are equivalent to the original brand but there is no evidence of equivalency between them. For other medicines not marked with 'a' or 'b', their therapeutic equivalence is not known; hence, caution should be exercised when GS is done. *British National Formulary* of United Kingdom is a useful tool for healthcare professionals when GS is not suitable for some medicines (Duerden, et al., 2010; Ferner, et al., 2010; Joint Formulary Committee, 2011). *The Royal Dutch Pharmacists Association* (KNMP) of The Netherlands has produced a professional guideline for community pharmacists regarding GS. This guideline provides principles and guidance to community pharmacists to perform GS appropriately. It also addresses the issue of NTI drugs and other drugs for which GS is not appropriate. Furthermore, it addresses random substitution and the general considerations and factors that need to be taken into account, such as the factors related to patients, prescribers and legal issues (Grandia, et al., 2012; KNMP, 2012).

There is ample evidence in literature for the necessity of having a formulary of interchangeable medicines to facilitate appropriate GS (Chong, et al., 2010a; Chua, et al., 2010; Johnston, et al., 2011; Hassali, et al., 2012a). Johnston, et al., (2011) recommended that evidence regarding therapeutic equivalence should be made available to the public and that best practice guidelines are required for GS

(Johnston, et al., 2011). Furthermore, Hassali, et al., (2012a) concluded that a formulary of interchangeable medicines must be developed to promote responsible GS. The formulary should also contain the list of the products that are not suitable for GS. Such a formulary would help both pharmacists and prescribers to assess the generic equivalence of the products offered as alternative substitutes (Hassali, et al., 2012a). In conclusion, it is essential to have a formulary of interchangeable products to guide responsible GS, to help healthcare professionals to be more confident when providing GS and to avoid situations where GS is inappropriate.

Many studies are available in the literature promoting the use of generics (Amit, et al., 2004; Araszkiewicz, et al., 2008; Kesselheim, et al., 2008; Davit, et al., 2009; Punithavathi, et al., 2009; Kesselheim, et al., 2010; Park, et al., 2012), and are also reporting positively about the safety and the efficacy associated with the switching of products (Alessi-Severini, et al., 2006; Paton, C., 2006). On the contrary, there have been reports about a patient's concerns relating to generic medicine. These studies range from the qualitative assessment of the perceptions in specific patient populations (Bulsara, et al., 2010), to general consumer knowledge (Hassali, et al., 2009a; Figueiras, et al., 2010), versus the knowledge of professionals, which includes pharmacists and physicians (Babar, et al., 2011; Qunital, et al., 2012). Many of these studies focus on the influence of a relatively cheaper price of any prescriptions and the use of generic products (Heikkilä, et al., 2011a; Heikkilä, et al., 2011b; Heikkilä, et al., 2012). On the other hand, there have been many studies depicting the facts that consumers feel that a generic drug product is less effective when compared to the originator's medicine. There have also been studies reporting that the consumer responded well and then advanced in treatment when switched