ASSESSMENT OF POLICIES, DETERMINANTS AND CHARACTERISTICS OF GENERIC MEDICINES ENTRY INTO THE MALAYSIAN PHARMACEUTICAL MARKET

by

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STATEMENT OF ORIGINALITY

I declared that the work presented in this thesis contains no material which has been accepted for the reward of any other degree or diploma in any university or other institution. To the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text.

Fatokun Omotayo Oladuntoye

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LIST OF ABBREVIATIONS

APPL	Approved Products Price List
ATC	Anatomical Therapeutic Chemical
DCA	Drug Control Authority
EC	European Commission
EPF	Employee Provident Fund
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FOMCA	Federation of Malaysia Consumers Associations
FTA	Free Trade Agreement
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GRP	Generic Reference Pricing
HAI	Health Action International
ICTSD	International Centre for Trade and Sustainable Development
INN	International Non-proprietary Name
MAB	Medicine Advertisements Board
MDC	Malaysia Drug Codes
MIDA	Malaysian Industrial Development Authority
MITI	Ministry of International Trade and Industry
MMA	Malaysian Medical Association
MNMP	Malaysian National Medicines Policy

MOH	Ministry of Health
MOPI	Malaysian Organization of Pharmaceutical Industries
MyIPO	Malaysian Intellectual Property Office
MPS	Malaysian Pharmaceutical Society
NMUS	National Medicine Use Survey
NPCB	National Pharmaceutical Control Bureau
OECD	Organization for Economic Co-operation and Development
PEMANDU	Performance Management and Delivery Unit
PhAMA	Pharmaceutical Association of Malaysia
PSD	Pharmaceutical Services Division
R&D	Research and development
RM	Malaysia Ringgit
SOCSO	Social Security Organization
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TRP	Therapeutic Reference Pricing
UKIPO	United Kingdom Intellectual Property Office
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
USPTO	United States Patent and Trade Office
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

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LIST OF RESEARCH PUBLICATIONS AND COMMUNICATIONS

Published Articles

1. **Fatokun, O**., Ibrahim, M. I. M. and Hassali, M. A., 2013. Time-to-entry of generic medicines in Malaysia: implications for pharmaceutical cost containment. *Journal of Pharmaceutical Health Services Research*, 4(4) 203-210.

2. **Fatokun, O**., Ibrahim, M. I.M. and Hassali, M. A., 2013. Factors determining the post-patent entry of generic medicines in Malaysia: a survey of the Malaysian generic pharmaceutical industry. *Journal of Generic Medicines,* 10(1) 22-33.

3. **Fatokun, O**., Ibrahim, M. I.M. and Hassali, M. A., 2013. Generic industry's perceptions of generic medicines policies and practices in Malaysia. *Journal of Pharmacy Research,* 7(1), 80-84.

4. **Fatokun, O**., Ibrahim, M. I. M. and Hassali, M. A., 2011. Generic competition and drug prices in the Malaysian off-patent pharmaceutical market. *Journal of Applied Pharmaceutical Science,* 1(09), 33-37.

Published Conference Abstracts

1. **Fatokun, O**., Ibrahim, M. I. M. and Hassali, M. A., 2012. Entry barriers to generic medicines in Malaysia: policy implications for drug affordability and accessibility. Proceedings of the 17th International Social Pharmacy Workshop, 23rd- 26 July, 2012, Phuket. Thailand. *Research in Social and Administrative Pharmacy,* 8(6), e20. http://dx.doi.org/10.1016/j.sapharm.2012.08.047

2. **Fatokun O**., Ibrahim M.I.M. and Hassali M.A., 2012. Assessment of generic medicines development and entry decisions by the Malaysian generic pharmaceutical industries. Proceedings of the Asian Federation for Pharmaceutical Sciences Conference, 9th- 12th December, 2011, Kuala Lumpur, Malaysia. *Archives of Pharmacy Practice[print edition-ISSN 2045-080X]* 3(1);130

3. **Fatokun, O**., Ibrahim, M. I.M. and Hassali, M. A., 2011. Generic medicines promotion in Malaysia: views from the Malaysian generic pharmaceutical industry stakeholders. Proceedings of the Malaysian Pharmaceutical Society Pharmacy Scientific Conference, 21th -23rd October, 2011, Kuala Lumpur, Malaysia. *Malaysian Journal of Pharmacy,* 1(9), 409.

PENILAIAN DASAR, FAKTOR PENENTU DAN CIRI-CIRI KEMASUKAN UBAT GENERIK KE DALAM PASARAN FARMASEUTIKAL MALAYSIA

ABSTRAK

Sistem penjagaan kesihatan Malaysia bergantung ke atas ketersediaan ubat-ubatan generik yang setara dengan ubat-ubatan inovasi untuk mengurangkan perbelanjaan farmaseutikal yang semakin meningkat. Kajian ini menilai dimensi dan dinamik kemasukan ubat generik berikutan tamat paten pada produk-produk ubat inovasi di Malaysia. Ini adalah kajian kaedah-bercampur. Hasil kajian ini menunjukkan 14 kategori dasar-dasar dan langkah-langkah pengawalan dengan kesan berbeza-beza ke atas kemasukan generik di Malaysia. Kaji selidik melalui mel menghasilkan kadar respons yang boleh digunakan sebanyak 53.8% (14/26) berikutan empat mel berturut-turut. Pekali kebolehpercayaan pembolehubah keputusan kemasukan pelbagai item dan halangan kemasukan adalah 0.62 dan 0.82 masing-masing. Faktor-faktor utama yang memacu pembangunan generik dan keputusan kemasukan di Malaysia adalah pra-paten nilai pasaran tamat produk inovasi itu (Min-pangkat=3.75, M=4.14, SD=1.03), kos pembangunan generik dan kelulusan (Min-pangkat=3.04, M=3.50, SD=1.40) dan keserasian ubat generik baru dengan pelbagai produk firma yang sedia ada (Min-pangkat=2.79, M=3.64, SD=1.2). Pra-paten tamat nilai pasaran produk inovasi ini adalah factor kemasukan yang signifikan untuk firma-firma generik berorientasikan pasaran domestik berbanding dengan firma yang berorientasikan pasaran eksport (U= 0.00, Z=-2.36, p=0.01). Halangan utama kepada pembangunan ubat-ubatan generik dan kemasukan pasaran di Malaysia adalah kelompok paten oleh firma inovasi (Min-pangkat=7.96, M=4.07, SD=0.83) dan kemasukan awal ke dalam pasaran bagi ubat-

ubatan generik yang diimport (Min-pangkat=7.75, M=4.07, SD=0.73). Dasar-dasar dan peraturan-peraturan kerajaan dilihat sebagai agak berkesan dalam mempromosikan ubat-ubatan generik di Malaysia. Majoriti daripada responden, 64.3% dan 69.2% masing-masing tidak berpuas hati dengan aktiviti mempreskripsi ubat generik dan pendidikan dan pemberian maklumat ubat-ubatan generik kepada professional penjagaan kesihatan. Separuh daripada responden tidak puas hati dengan kesedaran orang awam terhadap ubat generik. Majoriti daripada responden (57.1%) berpuas hati dengan pendispensan ubat generik di Malaysia. Dalam kajian ini, sejumlah 154 kemasukan ubat generik (M=12.83, SD=9.61) yang berlaku selama tempoh data 8 tahun bagi seluruh 12 sampel ubat dan proses kemasukan dicirikan dengan tren garis melengkuk kuadratik berurutan (*sequential quadratic curvilinear trend*) yang signifikan (R^2=0.83, *p*=<0.001). Masa kemasukan (dalam hari) ubat generik adalah jelas lewat melampaui masa kemasukan satu hari sepertimana yang dihipotesiskan selepas tamat tempoh paten asas produk inovator (median=125, M=396.92, SD=507.49, Z=-2.284, *p*=0.02). Analisis sekunder persaingan generik dalam kalangan 28 ubat-ubatan yang tamat paten yang mana majority telah berada dalam pasaran untuk beberapa tahun menunjukkan peningkatan ketersediaan ubat generik telah menurunkan keseluruhan harga ubat dalam pasaran farmaseutikal tamat paten. Dapatan kajian ini menunjukkan kepentingan kemasukan bilangan ubat generik yang cukup dan memastikan tanpa halangan selepas tamat paten produk-produk ubat inovator. Secara keseluruhan, kajian ini mendedahkan kehadiran pelbagai dasar dengan pelbagai kesan ke atas kemasukan ubat-ubatan generik di Malaysia. Kemasukan ubat-ubatan generik di Malaysia didapati ditentukan oleh nilai jualan pra-paten produk inovator, kos pembangunan generik,

persaingan kemasukan pasaran dan kewujudan halangan kemasukan berkaitan dengan paten. Sekiranya berlaku kemasukan, corak kemasukan generik dicirikan oleh satu trend garis melengkung berurutan, tetapi masa untuk kemasukan generik didapati ditangguhkan dengan ketara selepas tarikh habis tempoh paten asas ke atas produk inovasi di Malaysia.

ASSESSMENT OF POLICIES, DETERMINANTS AND CHARACTERISTICS OF GENERIC MEDICINES ENTRY INTO THE MALAYSIAN PHARMACEUTICAL MARKET

ABSTRACT

The Malaysia healthcare system relies on the availability of generic equivalents of innovator medicines to curtail the rising pharmaceutical expenditure. This study assesses the dimensions and dynamics of generic medicines entry following patent expiration on the innovator drug products in Malaysia. This was a mixed-methods study. The findings of this research revealed 14 categories of policies and regulatory measures with varying effects on generic entry in Malaysia. The mail survey yielded a usable response rate of 53.8% (14/26) following four successive mailings. Reliability coefficients for the multi-item entry decisions and entry barriers variables were 0.62 and 0.82 respectively. The major factors driving generic development and entry decisions in Malaysia were pre-patent expiration market value of innovator's products (Mean-rank=3.75, M=4.14, SD=1.03), cost of generic development and approval (Mean-rank= 3.04, M=3.50, SD=1.40) and compatibility of the new generic medicine with firms' existing products range (Mean-rank=2.79, M=3.64, SD=1.2). The innovator product's pre-patent expiration market value was a significant entry driver for domestic-market oriented generic firms as compared with export-market oriented firms (U=0.00, Z=-2.36, p=0.01). The Major barriers to generic medicines development and market entry in Malaysia were patent clustering by innovator firms (Mean-rank=7.96, M=4.07, SD=0.83) and earlier market entry of imported generics (Mean-rank=7.75, M=4.07, SD=0.73). Government policies and regulations were perceived to be fairly effective in

promoting generic medicines in Malaysia. Majority of the respondents, 64.3% and 69.2% were dissatisfied with generic prescribing and generic medicines education and information to healthcare professionals respectively. A majority of the respondents (57.1%) were satisfied with generic dispensing in Malaysia. In this study, a total 154 generic entries (M=12.83, SD=9.61) occurred over an 8-year data period for the entire 12 drug sample, and entry occurrence is significantly characterized by a sequential quadratic curvilinear trend (R^2=0.83, p=<0.001). The time to entry (in days) of generic entrants is significantly delayed beyond the hypothesized time to entry of one day following basic patent expiration on innovator products (Mdn=125, M=396.92, SD=507.49, Z = -2.284, p=0.02). Secondary analysis of generic competition among the 28 off-patent drugs, majority of which have been in the market for several years shows that increased generics availability reduces the overall drug price in the off-patent pharmaceutical market, a finding that illustrates the importance of ensuring unhindered and sufficient entry of generic medicines following patent expiration on the innovator drug products. Overall, this research revealed the presence of a variety of policies with varying effects on the entry of generic medicines in Malaysia. The entry of generic medicines in Malaysia was found to be determined by the pre-patent sales value of the innovator products, cost of generic development, market entry competition and the existence patent-related entry barriers. In the event of entry, the pattern of generic entry is characterized by a sequential curvilinear trend, but the time to generic entry is found to be significantly delayed beyond the date of basic patent expiration on innovator product in Malaysia.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Background

The rising pharmaceutical expenditure in many countries around the world, including Malaysia, has led governments and non-governmental health organizations to advocate the use of generic medicines (World Health Organization [WHO], 2001; De Joncheere, Rietveld and Huttin, 2002; Ford, 2004; Kanavos, Costa-Font and Seeley, 2008; Ministry of Health [MOH], Malaysia, 2009a). A generic medicine is a "pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after the expiry of patented or other exclusivity rights" (WHO, 2011, p.41); and innovator product "is generally that which first was authorized for marketing on the basis of documentation of efficacy, safety and quality" (WHO, 2011, p.41).

However, because generic medicines typically incur comparatively lower developmental costs, they are offered at a lower price (Reiffen and Ward, 2005; Simoens, 2009; Brems, Seville and Baeyens, 2011). Thus, generic medicines play a key role in ensuring drug affordability and containment of pharmaceutical costs, since the prices of medicines on the market is a major component of pharmaceutical expenditure (Ess, Schneeweiss and Szucs, 2003; Dukes, et al., 2003; World Health Organization and Health Action International[WHO and HAI], 2008; Doloresco, et al., 2011). For example, a recent study (Cameron et al., 2012) showed that up to 89% of drug cost

could be saved in the private health sector of low-to-medium income countries if lowest-priced generic equivalents of innovator brands are used. Similar cost saving advantages from the use of generic medicines has been reported in high and middle-income countries (Chan, 2011). For instance, in the USA, savings from the use of generics for the US healthcare system was around US$139.6 billion in 2009 (U.S. Department of Health and Human Services, 2010). In Europe, it has been estimated that generic medicines generate savings of more than €25 billion per annum (Simoens, 2010). Likewise in Malaysia, a study by Shafie and Hassali (2008) estimated that consumers could potentially save up to 90% of the cost of their drugs by using generic products. In general, literature indicates that as more generic medicines become available, price competition in the off-patent pharmaceutical market ensues and the overall drug price falls (Caves, Whinston and Hurwitz, 1991; Reiffen and Ward, 2005; Saha, et al., 2006; Nguyen, Kaplan and Laing, 2008). Therefore, from the viewpoint of pharmaceutical cost containment and accessibility, it has been argued that "competition provided by generic medicines, is essential to keep public budgets under control and to maintain widespread access to medicines to the benefit of consumers" (European Commission [EC], 2009a, p.12).

However, in order to maximize the cost-saving benefits from generic medicines, their availability need to be ensured and sustained through prompt market entry following patent expiration of the innovator drug products (Kanavos, Costa-Font and Seeley, 2008; EC, 2009a; b; Sheppard, 2010). For instance, it was noted that: "efficient" and "timely" market entry of generic medicines ensures access to affordable medicines and

contributes significantly to the sustainability of the Australian Pharmaceutical Benefits Scheme (PBS) (Generic Medicines Industry Association, 2011). Conversely, substantial loss of savings could result if entry of generic medicines is delayed or hindered (Kesselheim, Fischer and Avorn, 2006; EC, 2009b). For example, European Commission in its study (EC, 2009b) that analysed the extent of post-patent entry of generic equivalents of top-selling prescription medicines in 27 member countries of the European Union between 2000 and 2007, estimated a loss of about €3 billion in savings for the European healthcare system as a result of delay in immediate entry of generic equivalents, following loss of patent and exclusivity of the innovator products.

Furthermore, given the generic industry dependence on the development and production of generic equivalents of highly priced off-patent innovator products (Scott-Morton, 2000; Prasnikar and Skerlj, 2006; EC, 2009b; Borkowski, 2010), the ability to achieved entry in a prompt manner with less impediments, improves efficiency in the generic industry (Brundtland, 1999; United Nations Conference on Trade and Development-International Centre for Trade and Sustainable Development [UNCTAD-ICTSD], 2005; Bianchi and Labory, 2006; Prasnikar and Skerlj, 2006; Lutz, Kemp and Dijkstra, 2010). This in turn result in benefits to the consumers and the health care system, as most drug expenditure are for drugs for which generic equivalents may not be available or insufficiently available to effect price-lowering competition (King and Kanavos, 2002; (Nguyen, Kaplan and Laing, 2008; Doloresco, et al., 2011). Thus, once generic equivalents of patent expired innovator products are available, the consumers and the healthcare payers can avail themselves of the resultant price advantages. As Bianchi and

Labory (2006, p.306) remarked, “promoting competition in the drug market has the main effect of promoting efficiency, but the resulting lower prices also improve access to medicines”.

In summary, the availability and use of generic medicines provide opportunities for the containment of pharmaceutical costs and the sustenance of the health care system. But in order to derive the maximum benefits from generic medicines, their prompt entry following patent expiration of innovator products need to be ensured (Department of Health, UK, 2002; EC, 2009b; Iizuka, 2009). However, a number of interdependent factors influence the dynamics of post-patent entry of generic medicines in the pharmaceutical industry (Driouchi and Zouag, 2012). These factors, which are the primary subject of this research, and which will be given a detailed review in Chapter 2 are pharmaceutical policy and regulatory environment; existence and strength of entry barriers; and the level of competition in the pharmaceutical market (Scott-Morton, 1999, 2000; Hudson, 2000; Magazzini, Pammolli and Riccaboni, 2004; Competition Bureau, Canada, 2007; Kanavos, Costa-Font and Seeley, 2008; EC, 2009b; Brems, Seville and Baeyens, 2011).

Meanwhile, given the intrinsic linkage between the healthcare system and the pharmaceutical industry (Homedes, Ugalde and Forns, 2005; Mukherjee, 2007), the following sections present an overview of the Malaysia healthcare system and pharmaceutical industry, and thus provide the background for the research problem.

1. 2 Overview of the Malaysian Healthcare System

Malaysia is a developing country situated in the Southeast Asia region of the Asia continent. The country covers an area of about 330,290 square kilometres and has a total population (2010) of 28.25 million (Department of Statistics, Malaysia, 2011), with an annual population growth rate of 2.1% (MOH, Malaysia, 2010). Malaysia consists of two land masses separated by the South China Sea: West Malaysia (Peninsular Malaysia) and East Malaysia comprising of the Federal Territory Labuan, and States of Sabah and Sarawak (Figure 1). Peninsular Malaysia has its frontiers with Thailand in the north and Singapore in the south, while Sabah and Sarawak borders the territory of Kalimantan, Indonesia (Department of Statistics, Malaysia, 2011). Malaysia is made of five regions: the *Northern region* consisting the states of Perak, Penang, Kedah and Perlis; the *Central region* consisting the states of Kuala Lumpur, Selangor and Putrajaya; the *Southern region* consisting the states of Negeri Sembilan, Melaka and Johor; and the *East coast region* consisting the states of Pahang, Terengganu and Kelantan; and the *East Malaysia region* consisting the states of Sabah, Sarawak and Labuan (Tourism Malaysia, 2012).

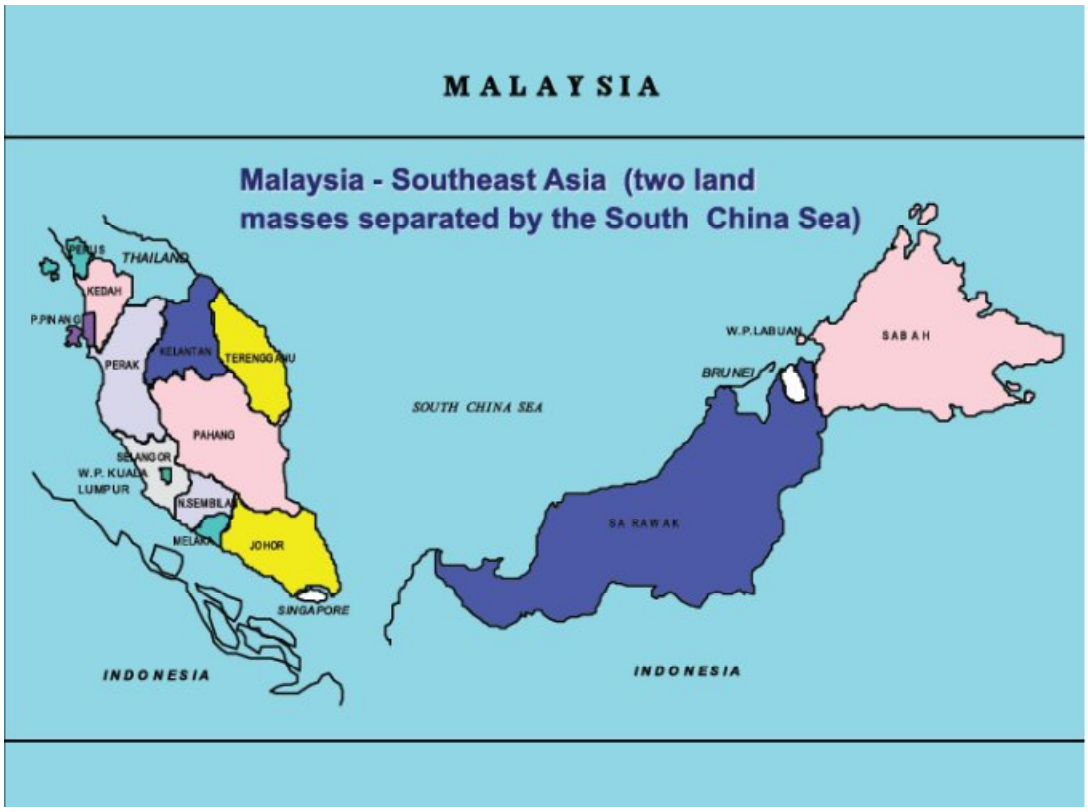

Figure 1.1 Geographical location of Malaysia (Hamidy, 2010)

Malaysia overall GDP (2010) was US$237.797 million (Ringgit Malaysia [RM] 765.965 million) (Department of Statistics, Malaysia, 2011; United Nations, 2012) and GDP per capita (2010) was US$8.373 (United Nations, 2012). In 2009, the economically-productive population which consists of population aged 15 to 64 years was 18.0 million or 63.6% of the total population, while the economically dependent, that is aged below 15 years, and 65 years and above, was 10.3 million or 36.4% of the total population (MOH, Malaysia, 2009b). The three leading causes of deaths in the Malaysia public health sector in 2010 were diseases of the circulatory system (25.35%); diseases of the respiratory system (18.46%); and certain infectious and parasitic diseases (17.81%) (MOH, Malaysia, 2011a). While pregnancy, childbirth and the

puerperium (25.72%); diseases of the respiratory systems (9.56%); and injury, poisoning and other consequences of external causes (8.98%) constitutes the three leading causes of hospitalization (MOH, Malaysia, 2011a).

1.2.1 Structure of the Malaysian Healthcare System

The Malaysian healthcare system is divided into the public and private sectors. The public sector is government-led and provides healthcare services through hospitals, special medical institutions, and health clinics (Yu, Whynes and Sach, 2008; MOH, Malaysia, 2010). The private sector provides healthcare services through clinics, hospitals and medical centers (Yu, Whynes and Sach, 2008). The public health services are highly subsidized and funded by the government (Yu, Whynes and Sach, 2008; Rasiah, Abdullah and Tumin, 2011) primarily through general taxation, and from contributions to the employee provident fund (EPF) and the social security organization (SOSCO) (Ramesh, 2007; Yu, Whynes and Sach, 2008). The private sector health services are essentially fee-for-service system, where services are paid for out-of-pocket by patients or through private health insurance scheme (Yu, Whynes and Sach, 2006; Ramesh, 2007). In 2008, the total health expenditure in Malaysia was RM31.869 billion, out of which government health expenditure was 44.1 % and the private health expenditure was 55.9 % (WHO, 2010a). The main source of financing for private health expenditure in Malaysia is out-of-pocket payments (73.2%), followed by private health insurance with 14.4% (WHO, 2010a). At present, there is no compulsory insurance or National Health Insurance scheme in Malaysia (MOH, Malaysia, 2008; Yu, Whynes and Sach, 2011).

1.2.2 The Malaysian Pharmaceutical Industry

The Malaysian pharmaceutical industry is broadly categorized into three groups: the multinational pharmaceutical companies, domestic pharmaceutical manufacturing firms and generic pharmaceutical importers (Hassali, et al., 2009). Other players in the distributive sector of the industry are pharmaceutical wholesalers and retail pharmacies. The multinational pharmaceutical firms, which are represented by the Pharmaceutical Association of Malaysia (PhAMA) operate in Malaysia as subsidiaries or representatives of foreign research-based pharmaceutical manufacturers and are largely engaged in importation and distribution of branded innovative pharmaceutical products (Azmi and Alavi, 2001; Business Monitor International, 2010). The domestic pharmaceutical manufacturing industry, which is represented by the Malaysian Organization of Pharmaceutical Industries (MOPI), is mainly a generic pharmaceutical formulating industry (Hassali, et al., 2009; Malaysian Industrial Development Authority [MIDA], 2009; Business Monitor International, 2010).

As at 2011, there were 87 firms licensed to manufacture pharmaceuticals in Malaysia (Malaysian Organisation of Pharmaceutical Industries [MOPI], 2011). However, only a fraction of these firms are active local producers of prescription pharmaceuticals. For example, as at the end of 2007, only about 30 firms were licensed to manufacture prescription pharmaceuticals, while the rest produce over-the-counter medicines (Business Monitor International, 2010). Generic pharmaceuticals importers in Malaysia are very diverse and the players are not easily distinguishable. According to the Malaysian drug registration database, licensed importers of prescriptions

pharmaceuticals comprise of a mix of independent domestic companies, representatives of foreign-based firms and some licensed domestic manufacturers (National Pharmaceutical Control Bureau, Malaysia, 2010). The number of licensed community pharmacies in Malaysia as at 2009, were 2,047 (Pharmaceutical Services Division [PSD], Malaysia, 2009a). In Malaysia, the Pharmaceutical distribution and supply follows the typical chain of distribution from the manufacturers to the final consumers via one to several intermediaries (Mustaffa and Potter, 2009), except in the public health sector where a concession firm procures and distributes drugs on the 'approved products price list' (APPL) to all government hospitals and clinics (Babar and Izham, 2009; PSD, Malaysia, 2009a; Business Monitor International, 2010), while non-APPL drugs are obtained through Ministry of Health tender or by direct purchase (PSD, Malaysia, 2009a).

The pharmaceutical industry in Malaysia is regulated by the National Pharmaceutical Control Bureau (NPCB) under the purview of the Drug Control Authority (DCA). Patent protection on pharmaceutical products and process in Malaysia is governed by the Patents Act 1983 (as amended) and the Patents Regulations 1986 (as amended) (Azmi, 2003); and these legislations are in compliant the World Trade Organization (WTO) agreement on trade-related intellectual property rights. (Gee, Azmi and Alavi, 2009).

1.3 Problem Statement

Although the Malaysian healthcare system is generally seen as a 'model' for other developing countries in terms of overall health system performance (Smith, Correa and Oh, 2009), the rising healthcare expenditure in general, and pharmaceutical expenditure in particular has become increasingly challenging to the Malaysian government and consumers (MOH, Malaysia, 2005; Babar, et al., 2007; MOH, Malaysia, 2008; Babar and Izham, 2009; Smith, Correa and Oh, 2009; Yu, Whynes and Sach, 2011). For instance, the total expenditure on drug procurement for use in the government hospitals and clinics increased from RM 303.80 million in 1998 to RM 1510 million in 2008, representing a 397% change in pharmaceutical spending over a ten year period (PSD, Malaysia, 2008a). Furthermore, in 2009, the overall national pharmaceutical expenditure in Malaysia was around RM4.29 billion (14% of total health expenditure), with a substantial part accounted for by branded and patented drug products (Business Monitor International, 2010; Babar, Ibrahim and Hassali, 2011). For example in 2007, the total spending on the "top 150 drugs by expenditure" in Malaysia, was around RM2.18 billion (Faridah et al., 2010), many of which are newer prescription drug molecules for which generic equivalents may not be available (Babar, et al., 2007; Smith, Correa and Oh, 2009).

This situation evidently has implications for drug affordability and accessibility, especially in the private sector where consumers have to pay for their medicines out-of-pocket (Babar, et al., 2007; Shafie and Hassali, 2008; Business Monitor International, 2010). Though, the local pharmaceutical industry has a strong capacity to manufacture

generic medicines (Hassali, et al., 2009, MIDA, 2009), the Malaysian pharmaceutical market continue to be dominated by patented and imported drugs (Azmi and Alavi, 2001; Ministry of International Trade and Industry [MITI], Malaysia, 2006; Hassali, et al., 2009; Smith, Correa and Oh, 2009; Business Monitor International, 2010). For instance, in 2005, the Malaysian pharmaceutical market was estimated at RM 2.7 billion, of which about 80% were accounted for by imported drugs (MITI, Malaysia, 2006). Accordingly, the growth of domestic pharmaceutical industry is constrained (Azmi and Alavi, 2001; Tham and Yahya, 2008; Performance Management and Delivery Unit [PEMANDU], Malaysia, 2010) and drug prices in Malaysia remain disproportionately high (Babar, et al., 2007; Babar and Izham, 2009; Smith, Correa and Oh, 2009), with a consequent rise in pharmaceutical expenditure.

One factor that creates opportunity for drug affordability and containment of pharmaceutical expenditure is the ability for generic medicines producers to develop and make prompt market entry with generic equivalents of innovator product following patent expiration (Azmi and Alavi, 2001; Jaeger, 2006; Davies, 2008; EC, 2009b; Sheppard, 2010). Prompt and sufficient generic entry helps sustain the supply continuity of generic medicines, improves efficiency in the generic industry, and ensures the availability of affordable medicines and a consequent reduction of drug expenditure (Brundtland, 1999; UNCTAD-ICTSD, 2005; Bianchi and Labory, 2006; Jaeger, 2006; EC, 2009b; Brems, Seville and Baeyens, 2011; Doloresco, et al., 2011). However, in Malaysia, efficiency in the domestic generic industry remained a challenge (Shafie and Hassali, 2008; PEMANDU, Malaysia, 2010) and high drug prices and escalating drug

expenditure has become burdensome (Babar et al., 2007; MOH, Malaysia, 2008; Babar and Izham, 2009; Smith, Correa and Oh, 2009), thus indicative of some impediments, structural or strategic to the development, prompt and sufficient market entry of generic medicines in Malaysia.

Therefore, this study aims to explore the aforementioned problem and provide empirical evidence on the dimensions and dynamics of the post-patent entry of generic medicines in Malaysia, with a view to contribute to policy recommendations on the attenuation of pharmaceutical expenditure and improvement of the competitiveness of the generic medicines industry in Malaysia.

1.4 Justification of Research

In Malaysia, the introduction of highly priced new innovator medicines has become a major driver of the rising healthcare expenditure (MOH, Malaysia, 2008). Hence, in the pursuit of drug affordability, pharmaceutical cost containment and improvement in the competitiveness of the generic industry, the Malaysian government has put in place policies and regulatory measures aimed at encouraging the development, sufficient production of generic medicines and expedited market entry of newly off-patent drug products (MITI, Malaysia, 2006; MOH, Malaysia, 2009a). Additionally, the government viewed that "the anticipated expiry of several brand drugs, offers vast opportunity for the production of patent expired generic drugs, for both the local and export markets" (MITI, Malaysia, 2006, p. 413) and does not want "the introduction of generic drugs to be obstructed and delayed" (MOH, Malaysia, 2011b).

Yet, to date, little studies have been carried out on post-patent entry of generic medicines in Malaysia, particularly with respect to the phenomenon of patent expiration and the dynamics of entry of new generic medicines following patent expiration of innovator products. Conversely, some studies (De Run and Felix, 2006; Al-Gedadi, Hassali and Shafie, 2008; Babar and Awaisu, 2008; Thomas and Vitry, 2009; Chua, et al., 2010; Chong, et al., 2010a; b; 2011) have only looked at the knowledge, attitude and perception of practitioners and consumers on issues related to uptake of generic medicines in Malaysia. However, literature suggests that to fully understand the implications of pharmaceutical patents on introduction of generic medicines and pharmaceutical expenditure, studies on the generic entry process is crucial (Frank and Salkever, 1992; EC, 2009b). Therefore, empirical studies on the dimensions and dynamics of the post-patent entry of generic medicines in Malaysia are needed to provide information to guide the policy objectives of the government. This is particularly important, given the strong patent protection system and proliferation of innovators' pharmaceutical patents in Malaysia (Azmi and Alavi, 2001; Gee, Azmi and Alavi, 2009), with the propensity to impede entry of generic medicines and the likelihood of limiting drug affordability and accessibility (Correa, 2011). For instance, it has been reported that the highest number of patents granted in Malaysia between 1989 and 2006 was to the pharmaceutical sector, with granted pharmaceutical patents described as having a "phenomenal" growth rate of 3,110% (Gee, Azmi and Alavi, 2009, p. 332). Furthermore, over 90% of these patent applications and patent grants in Malaysia are foreign-owned (Gee, Azmi and Alavi, 2009; Smith, Correa and Oh, 2009;

Govindaraju and Wong, 2011). In view of this, Smith, Correa and Oh (2009, p. 689) remarked:

> "Malaysia provides a good example of how patent protection can create inequalities in pharmaceutical trade between developed and developing countries; with developed countries exporting high-value patented drugs, and developing countries prevented from producing them, compelled to import them, with consequent issues for access to affordable medicines".

Therefore, given the country's health system reliance on the potential cost-lowering benefits of generic medicines and the generic industry dependence on expiration of patent on innovator products, with the opportunities for growth and pharmaceutical cost containment in the healthcare system, the availability of empirical information on post-patent entry, its determinants and role of generic competition will be vital to the provision of policy recommendations and help contribute to government effort in pharmaceutical cost containment, ensuring access to affordable medicines and improving the competitiveness of the generic industry.

1.5 Research Objectives

The general aim of this research was to study the dimensions and dynamics of the post-patent entry of generic medicines in Malaysia, with a view to providing empirical evidence that is vital to generating informed policy decisions on containment of pharmaceutical expenditure and improvement in competitiveness of the Malaysia generic industry. To achieve this aim therefore, the following specific objectives were set forth:

1. To identify the existing policy and regulatory measures influencing the entry of generic medicines in Malaysia.
2. To explore the extent to which the identified policies and regulatory measures can potentially promote or impede the entry of generic medicines following patent expiration on innovator products in Malaysia.
3. To assess the factors influencing decisions to develop and introduce a new generic medicine into the Malaysian pharmaceutical market.
4. To identify the barriers to post-patent entry of generic medicines in Malaysia
5. To assess the views of Malaysian generic drug manufacturers on promotion of generic medicines in Malaysia.
6. To examine the pattern of generic entry into the Malaysian pharmaceutical market
7. To evaluate the time to entry of generic medicines into the Malaysian pharmaceutical market following patent expiration of innovator products in Malaysia.
8. To assess the potential effects of generic entry and competition on the prices of off-patent drug products in the Malaysian pharmaceutical market.

1.6 General Overview of Research Methodology

This section provides in brief, the methodologies utilized in this thesis. The detailed methods followed for each of the objectives were given in subsequent Chapters of the thesis.

In general, a combination of qualitative and quantitative methods were used to meet the research objectives and address the research questions (see Section 2.6) Mixed methods approach is commonly recommended in health policy and services research (O'Cathain, Murphy and Nicholl, 2007; Almarsdottir and Traulsen, 2009; Gilson, 2012; Mills, 2012), as it broadens and deepens investigation of health policy and systems issues (Gilson, et al., 2011). Mixed research methods also served the purpose of "complementarity", where each method addressed a different but overlapping aspect of the research objectives in order to achieve an "enriched, elaborated understanding of the phenomenon" under study (Greene, Caracelli and Graham, 1989; Smith, 2002; Gray, 2009).

Research objectives 1 and 2, which were examined in Chapter 3 employed qualitative policy documents analysis and key informant survey. Relevant key informants were surveyed through a combination of semi-structured interviews and structured self-completed qualitative questionnaire. Data obtained were analysed using a deductive content analysis (Hsieh and Shannon, 2005; Elo and Kyngas, 2008). A detailed description of the methodology and data analysis is provided in Chapter 3.

A cross-sectional mail survey approach was implemented to address the *research objectives 3, 4 and 5.* These objectives were examined in Chapter 4. The survey participants comprised of the members of the Malaysian Organization of Pharmaceutical Industries (MOPI). The questionnaire consisted of items on factors

influencing decisions to develop and introduce a new generic medicine into the Malaysian pharmaceutical market; entry barriers to new generic medicines into Malaysian pharmaceutical market; effectiveness of government regulations and policies in promoting generic medicines; satisfaction regarding the level of generic prescribing, dispensing, public awareness and education to healthcare professional about generic medicines in Malaysia. Data analysis included descriptive measures and inferential statistical tests. Detailed description of the methodology and data analysis is provided in Chapter 4.

Research objectives 6 and 7 examined in Chapter 5 utilized a dataset of 'best-selling' single entity prescription drug products in Malaysia that loss of basic patent protection and experienced generic entry between January 2001 and December 2009. Best-selling medicines were used on the basis of the empirical conclusion that entry of new generic medicines is predicted on the sales value of the drug molecule facing patent expiration (Bae, 1997; Hudson, 2000; Magazzini, Pammolli and Riccaboni, 2004; Saha, et al., 2006; Iizuka, 2009). The basket of drugs for assessment was selected from 3 different sources in order to obtain a robust set of drug products with the highest market value ('best-selling'). The characteristics and extent of generic entry were assessed using the following variables; therapeutic class of drug molecule; date of first marketing approval of innovator INN drug molecule; date of expiration of basic patent of innovator INN drug molecule; date of marketing approvals of all generics of the drug molecule; manufacturing sources of all generics of INN molecule i.e. local or imported; date of first generic entrants and number of generic entrants from January 2001-December

2009. Data were analysed descriptively and inferentially. Detailed description of the methodology and data analysis is provided in Chapter 5.

Research objective 8 was addressed through secondary analysis of the prices of off-patent pharmaceutical products in Malaysia. Data were sourced from the results of national surveys on medicines prices in Malaysia. The retail price data of 28 prescription off-patent multisource medicines collected in a national medicines price survey in Malaysia was utilized to examine the effects of generic competition as measured by the relationship between number of registered brands of the multisource medicines and their proportional prices. Detailed description of the methodology and data analysis is provided in Chapter 6.

1.7 Outline of the Research

In examining the phenomenon pharmaceutical patent expiration and the entry of generic medicines in Malaysia, this research provides novel insights into the dynamics and determinants of post-patent entry of generic medicines in Malaysia; and the potential effects of generic competition in the Malaysian off-patent pharmaceutical market.

Chapter 1 contained the introduction which sets out the context and scope of the research, provides background information on the Malaysian health systems and the importance of generic entry and availability in the pharmaceutical market. It announced the research problems and provided justifications for the study. Finally, it presents the research objectives to be addressed and outlines the methodology of the research.

Chapter 2 provided an extensive review of the extant literature on policies and regulatory measures influencing generic entry, the determinants and characteristics of entry and the effects of post-patent entry of generic medicines on pharmaceutical prices. Finally, it described the conceptual framework of the research.

Chapter 3 examined the prevailing the policy and regulatory environment relating to generic medicines in Malaysia; and analyses the extent to which these policies can potentially promotes or hinders the entry of generic medicines following patent expiration of innovator drug products. The policy analysis is crucial and necessary to appreciate the entry determinants, characteristics, and potential effects of post-patent generic entry addressed in Chapters 4, 5 and 6 respectively.

Chapter 4 provided an examination of the various determinants of market entry of generic medicines in Malaysia, from the perspective of the generic drug industry. The examined determinants range from issues related to the strategic behaviour of the innovator firms, pharmaceutical market characteristics, regulatory measures, and the demand-side drivers of generic entry.

Chapter 5 characterized the pattern of post-patent entry of generic medicines in Malaysia and assessed the extent of generic entry in Malaysia, in terms of the speed of

entry following patent expiration and the number of entrants for a given patent-expired innovator drug products.

Chapter 6 demonstrated the importance of prompt and sufficient entry and availability of generic medicines following patent expiration of innovator products in Malaysia by providing information on the potential effects of generic entry and competition on pharmaceutical prices in Malaysia.

Chapter 7 provided the summary of the major findings of this research along with conclusions reached regarding the thesis research questions. It then provided the limitations encountered in the research and suggestions for further studies. Finally, it presented the concluding remarks and outlined the research recommendations.

CHAPTER 2

LITERATURE REVIEW AND CONCEPTUAL FRAMEWORK

2.1 Introduction

This Chapter provides a detailed review of the extant literature relevant to the present research and presents the conceptual framework of the research issues mentioned in Chapter 1. The Chapter begins with an overview of generic medicines development process. Next, it discusses the extant literature on policies and regulatory framework impacting on post-patent entry of generic medicines; the determinants and characteristics of generic entry; and potential effects of post-patent entry of generic medicines on pharmaceutical prices. Finally, it presents, on the basis of empirical evidence, the conceptual framework on post-patent entry and diffusion of generic medicines in the pharmaceutical market. A major focus of this Chapter is the provision of comprehensive background information that will subsequently guide the examination of the research objectives and research questions in Chapters 3, 4, 5 and 6.

2. 2 Overview of Generic Medicines Development Process

The entry of generic medicines following patent expiration of innovator drug product begins with the development of the generic drug entity (Prasnikar and Skerlj, 2006; Lionberger, 2008). This process is multifaceted, varied and sometimes overlaps, depending on the drug molecule and other regulatory requirements (Lionberger, 2008). However, for illustrative purpose, this thesis adopted the model proposed by Prasnikar and Skerlj (2006) (Figure 1).

The process of the development until market launch of a new generic product is classified into: Phases 0 (generation of idea), 1 (preliminary assessment), 2 (laboratory development), 3 (development of technology), 4 (registration) and 5 (launch) (Prasnikar and Skerlj, 2006). *Phase 0* is the period of selection of the potential generic drug candidate worthy of development by the generic manufacturers.

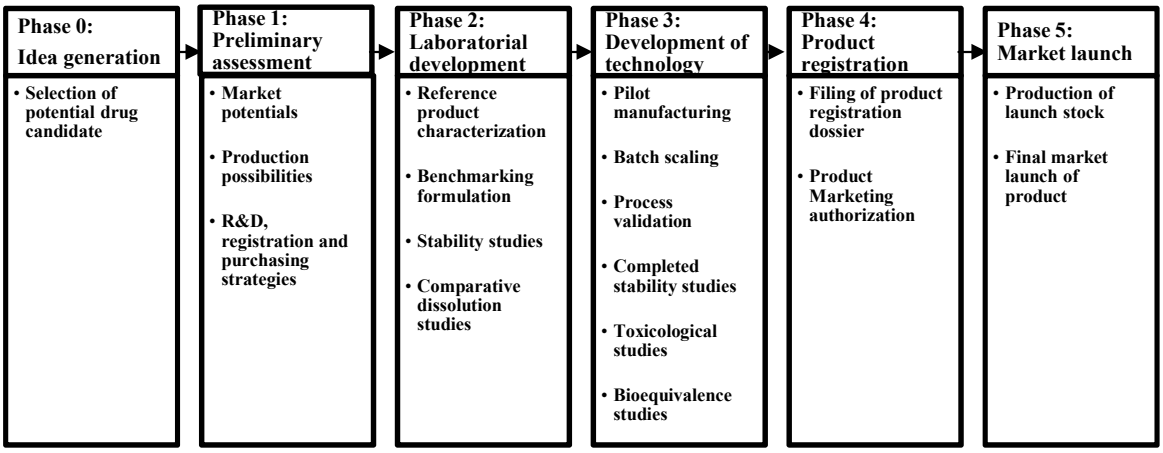

Figure 2.1 Schematic view of the development and market entry process of a new generic medicine Source: adapted from Prasnikar and Skerlj (2006) and Lionberger (2008)

Phase 1 represents the 'desk research' stage, where the manufacturer takes into consideration potential research and development commitments, manufacturing capabilities, regulatory and intellectual property concerns, marketing potentials and other commercial factors (Prasnikar and Skerlj, 2006). This phase also include the collection of all relevant documentation about the potential drug molecule prior to initiation of any laboratory activities and identification of possible quality risks arising

from the active pharmaceutical ingredient prior to the development of a generic drug product (WHO, 2011). At *phase 2*, the manufacturer undertakes various preliminary laboratory tests depending on the nature and characteristics of the generic drug candidate. This includes selection and characterization of innovators comparator product, benchmarking for formulation experiments and stability studies, formulation selection experiments, pilot-bioequivalence and comparative dissolution studies and development of primary packaging (Prasnikar and Skerlj, 2006; WHO, 2011). *Phase 3* is the development stage, when the drug formulation undergoes clinical studies, toxicological studies, bio-equivalent studies and completed stability studies. This phase ends with the production of registration batches (Prasnikar and Skerlj, 2006). *Phase 4* is the registration stage. At this phase the manufacturer files the product registration dossier with the drug regulatory authority for marketing authorization. The phase ends when the marketing authorization is issued by the authority (Prasnikar and Skerlj, 2006). *Phase 5* comprises of the pre-launch activities (e.g., production of the launch stock, ordering of raw materials, packaging materials etc.) and final market launch of the product (Prasnikar and Skerlj, 2006). In general, the above outlined process takes an average of 5 years (Prasnikar and Skerlj, 2006). For innovator products, the time taken from research and development, including filing for patent to market lunch is about 10 years (EC, 2009b).

In brief, the process of generic drug development and entry comprises of pre-development stage (phases 0 and 1) and development stage (Phases 2 and 3). Marketing authorization stage (Phase 4) and market entry stage (Phase 5). However, the

development and the eventual market entry of generic pharmaceuticals are affected by a number of variables. These variables which are evidenced from previous work, are discussed in the following sections.

2.3 Review of Literature

The review of the related literature covers three broad areas. First, the known findings on the impact of pharmaceutical policies and regulatory measures on generic entry were discussed. Second, the large literature on the determinants and characteristics of post-patent entry of generic medicines were discussed. Third, the literature findings on the effects of post-patent entry of generic medicines and potential contributions to pharmaceutical cost containment and competitiveness of the generic pharmaceutical market were provided.

2.3.1 Generic Medicines Policies

In broad terms, generic medicines policies are pharmaceutical policies, including regulatory measures that are intended to promote the entry, availability and uptake of generic medicines in the pharmaceutical market (Hawkins, 2011). Although these policies are generally documented, however, like other health policies, generic medicines policies may include informal and unwritten practices of policy stakeholders and actors (Gilson, 2012). Policies related to generic medicines are highly diverse in nature with various policy measures implemented to meet the overall objectives of drug