PHARMACEUTICAL DRUG PRICING IN MALAYSIA: AN ASSESSMENT OF PERCEPTION, MECHANISMS, AND INTERNATIONAL COMPARISONS

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by

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LIST OF ABBREVIATIONS

AIFA	Agenzia Italiana del Farmaco
CTS	Commissione TecnicoScientifico
CPR	Comitato Prezzo e Rimborso
CTILD	Connective tissue disease-associated ILD
DMARD	Disease-modifying anti-rheumatic drugs
EPF	Employee Provident Funds
IIP	Idiopathic interstitial pneumonia
IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
MNMP	Malaysian National Medicines Policy
MEA	Managed entry agreement
MPU	Medicine Price Unit
PAS	Patient Access Scheme (PAS)
PSD	Pharmaceutical Service Division
PBS	Pharmaceutical Benefits Scheme
SOCSO	Social Security Organization

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PENENTUAN HARGA UBAT FARMASEUTIKAL DI MALAYSIA: PENILAIAN PERSEPSI, MEKANISME, DAN PERBANDINGAN ANTARABANGSA

ABSTRAK

Harga ubatan merupakan topik yang hangat di Malaysia. Tesis ini cuba menganalisa situasi semasa harga ubatan di Malaysia menggunakan kaedah kualitatif dan kuantitatif. Kajian ini dibahagikan kepada tujuh bahagian, melibatkan polisi dan strategi semasa, perbandingan dengan negara lain, persepsi masyarakat terhadap harga ubat, analisis polisi dan analisis farmakoekonomik. Bahagian Satu, Dua,Tiga Empat dan Enam adalah analisis kualitatif dan Bahagian Lima dan Tujuh adalah analisis kuantitatif. Bahagian Satu, Dua dan Tiga adalah tinjauan sistematik, dengan mencari artikel yang di dalam pengkalan data seperti PubMed, Scopus dan ScienceDirect. Bahagian Satu mengumpulkan informasi semasa tentang harga ubatan di Malaysia. Bahagian Dua menganalisa perbezaan antara polisi ubatan di Malaysia dan di Barat. Bahagian Tiga membandingkan perjanjian kewangan antara kerajaan Malaysia dan Itali dengan syarikat farmaseutikal. Bahagian Empat adalah kajian lapangan, menganalisa persepsi masyarakat tentang harga ubatan di Malaysia. Bahagian Lima membandingkan harga ubat di Malaysia dalam sektor kerajaan dan di Australia. Bahagian Enam ialah analisa polisi melibatkan Harga Rujukan Luaran (ERP) menggunakan perisian Reich PolicyMaker dan kerangka aliran pelbagai Kingdon untuk melihat minat dan pengaruh pihak berkepentingan serta kemungkinan halangan yang dihadapi. Bahagian Tujuh menyiasat impak bajet tocilizumab dalam penyakit paru-paru interstisial progresif dengan mendapatkan data dari institusi kerajaan dan pendapat pakar. Hasil kajian kualitatif menunjukkan bahwa harga ubatan di Malaysia untuk kerajaan dan swasta adalah tinggi berbanding harga rujukan antarabangsa. Polisi

ubatan di Malaysia juga berbeza dengan negara Barat. Negara di Eropah mengamalkan pasaran farmaseutikan yang terkawal. Dalam pasaran terkawal ini, harga ubatan ditentukan dengan harga rujukan antarabangsa. Harga ubatan dengan panduan dan bukan secara rawak. Perjanjian kewangan yang dilaksanan Malaysia adalah langkah tepat kerana ia mampu menurunkan perbelanjaan kesihatan. Walaubagaimanapun, ia mempunyai beberapa cabaran seperti beban administratif yang tinggi, modal yang tinggi dan memerlukan infrastruktur data yang baik. Hasil kajian kuantitatif menunjukkan masyarakat mempunyai persepsi yang buruk terhadap harga ubatan. Satu pertiga responden mempunyai praktis yang merbahaya akibat harga ubatan yang tinggi. 79.2% ubatan di Malaysia juga lebih mahal dari Australia. Impak bajet tocilizumab menunjukkan peningkatan RM384,613.44 selama tiga tahun, iaitu 0.01% peningkatan dalam bajet keseluruhan. Analisis ini menunjukkan: (a) harga ubatan di Malaysia lebih tinggi berbanding negara lain, (b) polisi farmaseutikal di Malaysia boleh ditambahbaik dengan belajar dari negara lain, (c) masyarakat mempunyai persepsi buruk terhadap harga ubatan, (d) harga ubatan di Malaysia lebih tinggi berbanding negara maju seperti Australia dan (e) tocilizumab mempunyai impak minima terhadap bajet keseluruhan. Oleh itu, terdapat pelbagai cara untuk Malaysia meningkatkan polisi harga. Pembuat polisi boleh menggunakan hasil kajian ini untuk menambahbaik polisi semasa dan membaiki strategi mereka bagi memastikan rakyat Malaysia akan terus menikmati sistem kesihatan yang berkualiti tinggi.

PHARMACEUTICAL DRUG PRICING IN MALAYSIA: AN ASSESSMENT OF PERCEPTION, MECHANISMS, AND INTERNATIONAL COMPARISONS

ABSTRACT

High drug price is a hot topic in Malaysia. This thesis attempts to analyze the nature of pharmaceutical pricing in Malaysia using qualitative and quantitative studies. The study was structured into seven workstreams, ranging from current policies and strategies, comparison with other countries, perception of the public on the drug price, policy analysis and pharmacoeconomic analysis. Workstream One, Two, Three, Five and Six are qualitative studies and Workstream Five and Seven are quantitative studies. Workstream One, Two, and Three are systematic reviews, conducted by searching for peer-reviewed articles in major electronic databases such as PubMed, Scopus, and ScienceDirect. Workstream One gathers information on the current medicine price in Malaysia. Workstream Two analyzed the difference between Malaysia's pharmaceutical policies and Western countries. Workstream Three compared Malaysia and Italy's financial agreements with pharmaceutical manufacturers. Workstream Four is a cross-sectional study, analyzing the perception of the public towards the drug price in Malaysia. Workstream Five compared the drug price in the Malaysian government sector with Australia by matching the drug database. Workstream Six is a policy analysis involving external reference pricing (ERP), performed using Reich's PolicyMaker tool and Kingdon's multiple stream framework to elucidate the stakeholders' interest and power, as well as potential challenges to the policy implementation. Workstream Seven investigates the budget impact of tocilizumab in progressive interstitial lung disease (PFILD) by obtaining

data from government institutions and expert opinions. The result of the qualitative studies found that the drug price in Malaysia for both government and private sectors was higher than international reference prices (IRP). Malaysian pharmaceutical policies are also different from those of Western countries. The European countries adopted a regulated pharmaceutical market. In this regulated market, the price of the drugs was determined using external reference pricing. The reimbursement and pricing of the drugs are also based on a set of guidelines rather than arbitrary nature. The financial agreement adopted by Malaysia is the right step forward as it was shown to reduce health expenditure. However, it also contains several challenges high administrative burden, high upfront cost, and the need for good data infrastructure. The result of the quantitative studies found that the public has a poor perception of drug prices. A third of the respondents also suffered from harmful practices due to the high prices. Additionally, 79.2% of the medicine in Malaysia has a higher price than in Australia. Meanwhile, the budget impact model for tocilizumab estimated an additional cost of RM384,613.44 over three years, corresponding to a 0.01 % increase in the overall budget. This analysis showed that: (a) the drug price in Malaysia is higher than in other countries, (b) Malaysian pharmaceutical policies may be improved by learning from other countries, (c) the public has a poor perception of the drug price, (d) the drug price in Malaysia is even higher than in another developed country (Australia), and (e) tocilizumab in PFILD has a minimum impact on the overall health budget. Hence, there are various avenues for Malaysia to improve its pricing mechanisms. Policymakers may use these findings to modify their current approaches and revamp their strategies to ensure that high-quality healthcare remains accessible for all Malaysians.

CHAPTER 1

INTRODUCTION

1.1 Global pharmaceutical pricing

Over the past half-century, pharmaceutical advancements have made it possible to treat and prevent a wide spectrum of disorders effectively. These advancements were so significant in modern healthcare that access to them was considered a fundamental human right. While exercising that right generates enormous social value, it presents a huge policy problem due to its associated costs. Despite the fact that demand for medications is one of the key drivers of pharmaceutical expenditure, growing costs are a primary source of concern for healthcare administrators since medicines are increasingly being priced at levels that appear to be unjust to consumers (Pollack, 2015).

Many stakeholders, including pharmaceutical industry executives, payers, healthcare providers, legislators, and patients, have expressed interest in the drug pricing strategies. As people's lives and general well-being depend on access to the medicines they require, this topic evokes strong feelings and diverse opinions.

Access to safe, effective, and "quality use of medications" is the focus of the pharmaceutical pricing strategy. There are various issues, challenges and barriers with access to novel treatments and the cost of expensive drugs on a global scale. Other issues related to the medicine access, trade and intellectual property rights are also central to the pharmaceutical policy discussion (Z.-U.-D. Babar, Jamshed, et al., 2013).

Pandemics like COVID-19 have once again emphasised the importance of developing novel, cost-effective therapies and vaccinations. The national pharmaceutical strategies have been successful in eliminating diseases and enhancing

the quality of life for patients. However, developing these policies is a difficult task that involves a number of capacity-building measures, such as effective governance and legislation, a skilled workforce and human knowledge, and a sustainable local pharmaceutical sector (Ayati et al., 2020).

For many years, the cost of drugs has been a major concern around the world. The World Health Organization (WHO) estimates that one-third of the global population does not have reliable access to basic healthcare, and that number jumps to more than half in the poorest regions of Africa and Asia (World Health Organization, 2011). Essential medicines remain inaccessible to approximately 2 billion individuals worldwide (World Health Organization, 2017). According to the WHO technical report, the low-and middle-income countries (LMIC) have poorer access to the anticancer medicines, or only had access to medicines if they can afford higher out-of-pocket payments, especially for more expensive medications like targeted therapies. According to the report, patients in LMIC regions could only access 32.0% to 57.7% of the cancer medications on the essential medicine list if they were willing to pay for them in full (World Health Organization, 2018). Access to anticancer medicines in Malaysia was found to be good (Shafie and Chandriah, 2017).

However, in recent years, affordability of medicine has also increasingly becoming an issue for the high-income nations due to the introduction of newer expensive medicines. Even high-income countries whose publicly funded health-care systems routinely cover certain drugs struggle to provide access to medicines without jeopardising long-term viability. Hence there is a strong need to devise a policy to ensure that the price of medicine remains affordable.

1.2 Pharmaceutical pricing in Malaysia

Malaysia's healthcare system consists of two categories: public and private. The Ministry of Health (MOH) is responsible for the public sector, which is mostly funded through general taxation. The private sector is financed by private health insurance, consumers' out-of-pocket spending, non-profit agencies, and private entities (Malaysia Competition Commission, 2017). In the public sector, Malaysian pays RM1 for outpatient visit and RM5 for specialist visit. Malaysia does not have national health insurance scheme. There are two types of health insurance available: private and employee-based. Private insurance scheme is voluntary and mainly covers the private hospital cost. Examples of insurance companies are Allianz, Amgeneral Insurance and Great Eastern Insurance. Members are required to pay a predetermined monthly premium. As for employee-based insurance, these are provided by Social Security Organization (SOCSO) and the Employee Provident Funds (EPF). SOSCO provides employees protection in the event of an accident or occupational illness. (Jaafar et al., 2012).

Malaysia is a country with a high standard of living and a world-class healthcare system (BERNAMA, 2019). It has a health care worker-to-patient ratio of one to 186, above the World Health Organization's (WHO) target of 1:225. Malaysia now has 71,041 medical physicians working in the public and private sectors, which equates to one doctor for every 454 people, which is better than the 1:500 ratio (CodeBlue, 2020c). Nevertheless, the price of drugs in Malaysia has been steadily rising over the years (Hassali et al., 2012).

Pharmaceutical pricing strategies can be used to maximize medicine affordability. Various price-control programs have been implemented worldwide,

including the National Pharmaceutical Pricing Authority in the United Kingdom and social insurance plans in Germany and Japan (Hassali et al., 2012). Malaysia, however, has not established any pricing control policies in the private sector. The price of drugs in the private sector in Malaysia is unregulated and subject to market dynamics (Hassali et al., 2012). Hence, the private sector is free to set the price.

In 2005, the Pharmaceutical Service Division (PSD) of the Ministry of Health established the Medicine Price Unit (MPU) as a response to Malaysia's high drug prices. MPU has implemented a few measures based on the Malaysian National Medicines Policy (MNMP), such as encouraging voluntary disclosure of medicine prices by the manufacturer, establishing a task force to develop a concept paper on medicine prices, suggestion of External Reference Pricing (ERP) and reviewing existing laws pertaining to drug prices to provide equitable and prompt access to affordable, high-quality essential medicines. In Malaysia, the Medicine Prices Monitoring Survey, or Kajian Pemantauan Harga Ubat (KPHU), stands as a resolute commitment by the Pharmaceutical Services Program (PSP) to furnish a comprehensive overview of medicine availability, pricing, and affordability within the nation. Initiated back in 2006, this study necessitates a cooperative effort bridging Malaysia's public and private healthcare sectors. Notably, the selection of healthcare facilities and medicines for assessment adheres diligently to the guidelines set forth by the World Health Organization (WHO) and Health Action International (HAI). Consequently, the study effectively encompasses three distinct baskets of essential medicines, each with its unique implications: the WHO/HAI Basket, the Sustainable Development Goal (SDG) Basket, and the Single Product Registration Holder (PRH) Basket (Pharmaceutical Services Division, 2020).

International Reference Prices (IRPs) are a pricing mechanism used in the pharmaceutical industry, and they have been advocated and implemented by organizations like Management Sciences for Health (MSH) to guide drug pricing policies in different countries. IRPs are benchmark prices based on the prices of the same or similar medications in other countries. MSH, as a global health organization, facilitates the comparison of drug prices from various countries to establish a reference point for pricing negotiations and decisions. The price in the MSH database was latest updated in 2015 (Management Science for Health, 2015).

IRP by MSH and External Reference Pricing (ERP) are two distinct approaches used for pharmaceutical pricing comparisons. IRP by MSH involves collecting and analyzing drug price information from different countries to establish a reference price based on the lowest or average price observed among the selected countries. Its objective is to support pricing strategies in low- and middle-income countries, enabling fair prices and accessibility for essential medicines (Management Science for Health, 2015). On the other hand, ERP is a policy implemented by individual countries to compare and determine drug prices based on prices in other countries, often aiming to adopt a price closer to the lowest observed price in the external reference countries. While IRP by MSH focuses on equitable access to medications, ERP is used by high-income countries to manage pharmaceutical expenditures and promote cost-effective healthcare spending (Rémuzat et al., 2015).

A study conducted in Malaysia in 2019, found that the price of innovator drugs used in the ischemic heart disease are 24 times higher than the international reference price, whereas the generic drugs are 11 times higher (You et al., 2019). Another study conducted in the private sector found that 26 out of 28 drugs included in their analysis are 31 times higher than the international reference price (Ud din Babar et al., 2005).

Meanwhile in the public sector, the government procurement price is also found to be higher than the international average (Hamzah et al., 2020a). Hence, Malaysia needs a strong policy, preferably a combination of several pricing strategies, to ensure that the price of medicine remain sustainable.

1.3 Pharmaceutical strategy in Australia

The provision of medical care in Australia is financed in a hybrid manner by both public and private sources (Biggs and Cook, 2018). As a federation, Australia is made up of six states and two territories. According to the Constitution, providing medical care falls under the purview of the individual states (Wheelwright, 1995). Nevertheless, a significant portion of the funding comes from the federal government. The federal government and the states share health policy and health-care service responsibilities. Public hospitals, which account for the greatest single portion of overall health care costs, are managed by the respective state governments. However, a significant portion of the funding for the public hospital system comes from the federal government based on the agreement with each state and territory (Biggs and Cook, 2018). Australian citizens, permanent residents, refugees, and foreign nationals covered under a reciprocal healthcare coverage agreement are all covered by Medicare, the country's mandatory public insurance scheme. Medicare is comprised of two parts: payments to public hospitals through the states and territories and direct payments to physicians and other health professionals. Medicare is funded for by taxes, which are levied at either 1.5% of each person's income or 2.5% of the income of those who do not have private insurance but make more than a certain amount of income (Dixit and Sambasivan, 2018).

The Pharmaceutical Benefits Scheme (PBS) is an important part of the Australian healthcare system and is considered to be one of its main pillars. PBS was initially conceived of as a means of supplying medicines to returning service members during the Second World War (WWII). During the war, the Curtin Government (which was in power from 1939 to 1945) recognised the importance of ensuring that Australians had access to innovative antibiotics like penicillin, streptomycin, and sulphonamides. The goal of the Curtin government, which was part of a larger plan to establish a tax-funded national welfare programme, was to make it possible for all Australians, including war veterans, to purchase not only antibiotics but also a more comprehensive list of essential medicines. After overcoming numerous political obstacles and general ideological opposition to a welfare state, the wartime government of Curtin and Chifley passed the Pharmaceutical Benefits Act in 1944 with this vision in mind. Residents of Australia were eligible to receive free prescription medicines from community pharmacies under the plan proposed by Curtin and Chifley, provided that the medicines were included in a "formulary" drafted by an expert committee (Goddard, 2014). Fast forward, PBS today operates under Australia's National Medicines Policy (NMP), which has been in place since 2000 (Shaw and Chisholm, 2019). The NMP outlines four objectives that should be accomplished through cooperative effort:

- Australians should have prompt and affordable access to the medicines they require.

- medicines that are of appropriate quality, safety, and effectiveness

- quality use of medicines

- preserving an ethical and thriving pharmaceutical industry

Today, the PBS makes it possible to obtain subsidised medications in a timely manner. This enables patients to obtain prescribed medications from a licenced pharmacist by merely paying a co-payment, which is AUD 42.50 as of 1 January 2022, or AUD 6.80 for those with concession card (Department of Health, 2022). Concession cardholders include elderly and disabled pensioners, unemployed and sick people, and low-income earners. For highly specialised drugs, there is a separate formulary (section 100), with supply limited to public and private hospitals. There are also special arrangements for indigenous groups, palliative care patients, and funding for human growth hormone (Department of Health, 2022). Australia was chosen in this study due to the availability of high-quality public data (medicine price, associated fees, method of pricing calculation) on the internet and ease of use.

1.4 Pharmaceutical financial analysis in progressive interstitial lung disease

Interstitial lung disease (ILD) is a heterogeneous group of diseases characterized by inflammation and fibrosis of the lung parenchyma, sharing pathophysiological, clinical and radiological manifestation (Travis et al., 2013). ILD can be broadly classified based on the aetiology, one category with those that the cause is known such as environmental exposure, drugs and systemic diseases, and those of which the cause is unknown, such as idiopathic interstitial pneumonia (IIP) (Ryu et al., 2007). The American Thoracic Society/European Respiratory Society (ATS/ERS) revised the classification of IIP in 2013, into major, rare and unclassifiable (Figure 1.4-A) (Travis et al., 2013). The most common and severe type of IIP is idiopathic pulmonary fibrosis (IPF), a chronic progressive lung fibrosis with poor prognosis. IPF disease progression varies from slow progression to rapid loss of lung function and eventually death (Ley et al., 2011)

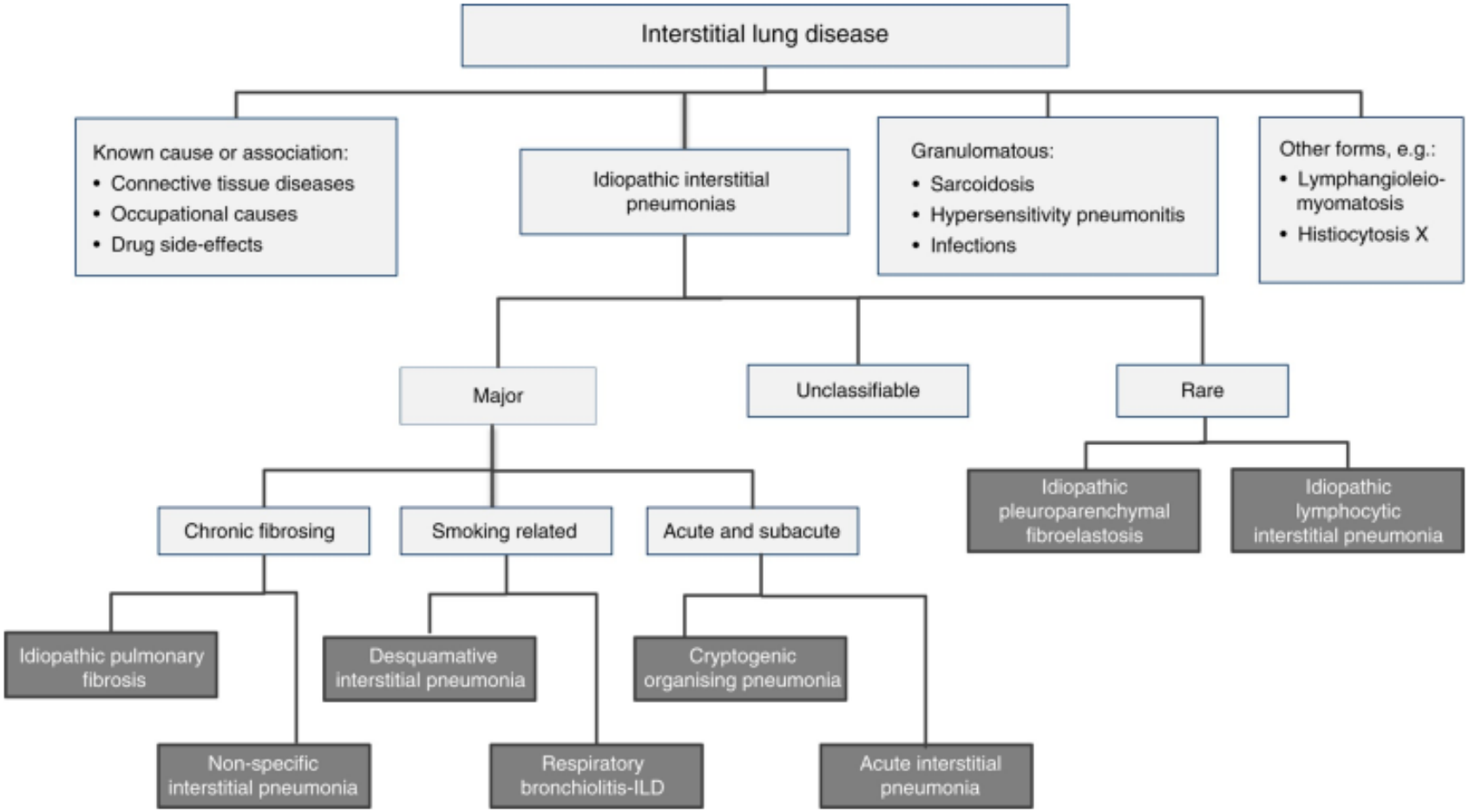

Figure 1.4-A: Classification of ILD. Adapted from The American Thoracic Society/European Respiratory Society

IPF is the most common form of fibrotic ILD, affecting nearly three million people all over the world. In Europe and Northern America, the incidence is estimated to be between 3 and 9 cases per 100,000 people per year, and it has been progressively rising over time. Asia, with a reported incidence of 1.2 - 4.16 per 100,000 people, and Scandinavia, with an incidence between 1.3 and 4.3 per 100,000, appear to have the lowest rates in the world (Hutchinson et al., 2015). Men are more likely to be affected by IPF than women, and older adults are more likely to be diagnosed with the condition; in the UK, 85 percent of newly diagnosed cases are found in those older than 70 years (Martinez et al., 2017). In patients who do not get antifibrotic medication, the median survival time from the time of diagnosis is typically three to five years. Many of these patients pass away as a result of gradual respiratory failure (Navaratnam et al., 2011).

A subset of ILD, which is called progressive fibrosing interstitial lung disease (PFILD), develop severe and progressive fibrosing phenotype (George et al., 2020; Kolb and Vašáková, 2019). Due to the diverse aetiology and challenging diagnosis, the epidemiology of PFILD is less well understood.

Current treatment options offer limited clinical benefits for PFILD patients (Makino, 2021). Tocilizumab has demonstrated clinical improvement in the faSScinate trial, improving patients' pulmonary function (Khanna et al., 2016). Tocilizumab was also approved in the United States in 2021 to treat systemic-sclerosis associated interstitial lung disease (SSC-ILD) (Genentech, 2021).

The rationale for conducting a budget impact analysis of tocilizumab in the context of pharmaceutical pricing study for PFILD stems from its potential significance in healthcare resource allocation and budget planning. Given the

considerable economic burden associated with managing PFILD, the introduction of tocilizumab as a potential treatment option could have substantial implications for healthcare budgets. As such, a budget impact analysis becomes imperative to estimate the financial impact of adopting tocilizumab in the treatment landscape. It allows decision-makers to assess the feasibility of its inclusion and make evidence-based pricing decisions. Notably, it should be emphasized that the budget impact analysis of tocilizumab in PFILD is yet to be studied in Malaysia, warranting further research to inform policy and healthcare decision-making in the country.

1.5 Problem statement

Previously, several studies showed that medicine prices in Malaysia are excessive. Medicine price in the private sector is also unregulated. The spending on medicine in Malaysia has increased substantially since 1997 (Malaysia Competition Commission, 2017). However, the amount of evidence presented in this area is currently limited. The factors influencing medicine prices and their impact on society are widely documented in Europe and other Western countries. Similar research is scarce in Malaysia.

Therefore, there is a solid need to evaluate what the previous studies have shown regarding the pharmaceutical price in Malaysia. This will help to set a foundation and ascertain whether there is a prevailing trend regarding pharmaceutical prices in Malaysia. The amount of information available on the current pharmaceutical policies in Malaysia is also limited. The dearth of information will make it challenging for policymakers to determine if there are any areas for improvement. Hence, it is crucial to compare this country's policies with others and extract potential room for optimization.

Furthermore, the public's perception of the medicine price has yet to be investigated. It is critical to understand what the public thinks about the drug price as it helps to shape the policies being developed afterward. The recent introduction of ERP policy has also necessitated further analysis of how it affects the stakeholders involved and if there is any potential hindrance to the nationwide implementation.

The cost-effectiveness of tocilizumab in PFILD has yet to be studied. As a result, the financial value of tocilizumab as a treatment option for PFILD remains uncertain, necessitating a comprehensive budget impact assessment. By providing a comprehensive overview of the economic ramifications associated with tocilizumab adoption, decision-makers can make informed choices regarding the drug's inclusion in treatment protocols. Furthermore, physicians will gain critical insights into the balance between treatment efficacy and financial burden, enabling them to tailor individualized therapeutic plans for PFILD patients.

These observations establish the need for an in-depth study on how pharmaceutical pricing in Malaysia works, the intricacies and convolutions, and, therefore, highlight the sources and prospects for changes.

1.6 Study significance

The results of this study will help to determine the current state of pharmaceutical prices in Malaysia. This will help to establish a consensus on Malaysia's medicine price and become a foundation from which more research can be done. It will also help to demonstrate the importance of understanding how pharmaceutical pricing works, their impact on the health budget, and consequently finding strategies to optimize it.

Comparing Malaysia's pharmaceutical strategies with other countries is beneficial as it helps to identify discrepancies and peculiarities of Malaysia's strategies. This will assist policy learning and transfers and provide new perspectives on reforming the healthcare system. Additionally, the country will be able to save time and gain valuable insight from other nations' experiences, achievements, and setbacks.

Furthermore, the result of the study will assist the policymakers in identifying the public's perception towards the current medicine price and help them revamp the system. Other parties, such as think tanks and advocacy groups, may utilize the finding to comprehend the existing pricing method better. It is hoped that the result of the study will serve as a springboard for further research on pharmaceutical pricing, not only in Malaysia but also across the ASEAN region.

1.7 Research objectives

General Objective:

To evaluate the characteristics of pharmaceutical pricing in Malaysia in terms of the current policies and strategies, comparison with other countries, perception of the public on the drug price, policy analysis and pharmacoeconomic analysis.

Specific Objectives:

1. To provide a synthesis of literature on pharmaceutical prices in Malaysia and their pricing mechanisms using systematic review.

2. To investigate and compare the pharmaceutical pricing policies in Malaysia and other countries.

3. To assess the knowledge, attitude and perception of Malaysian on medicine price in Malaysia.

4. To compare the price of medicine in Malaysia's government sector with other country (Australia).

5. To investigate the policymaking process of External Reference Pricing in Malaysia.

` 6. To conduct a budget impact analysis of tocilizumab in PFILD.

CHAPTER 2

LITERATURE REVIEW

2.1 Pharmaceutical pricing in Malaysia

The healthcare system in Malaysia, consist of two sectors, the public and the private sectors. The public sector, is controlled by Ministry of Health (MOH), and is mainly financed through general taxation. Whereas the private sector, are funded by commercial health insurance, out-of-pocket payments by consumers, nonprofit and private institutions (Malaysia Competition Commission, 2017). Malaysia is an upper-middle income country with world-class healthcare system (BERNAMA, 2019). However, the cost of drug price in Malaysia has been increasing substantially over the years. Drug price in Malaysia in the private sector is unregulated like free market and is left entirely to market forces. Hence, the manufacturer may hike the price at will, as long as the market can bear it.

The pharmaceutical industry in Malaysia rose at an annualised rate of 8.3 percent from RM 3.4 billion in 2006 to RM 8.6 billion in 2016, owing to higher wages, changing demographics, and an increase in non-communicable diseases. Between 2006 and 2016, spending on prescription pharmaceuticals increased by almost 75%, while spending on over-the-counter (OTC) drugs decreased by 21%. (Malaysia Competition Commission, 2017).

In 2017, MOH spent the most on health care, accounting for 43 percent of total expenditures, followed by out-of-pocket (OOP) spending at 38 percent, and private insurance at 7%. (Figure 2.1-A). From 1997 to 2017, OOP spending accounted for between 29 and 38 percent of total health spending (Ministry of Health Malaysia, 2019). According to the World Health Organization (WHO), OOP of 30 to 40% of total

spending indicates that people are not adequately covered. In practice, an OOP of 15–20 percent of overall health expenditures greatly decreases a country's financial disaster (World Health Organization, 2017). From 1997 to 2017, OOP remained the largest source of private sector financing in Malaysia, accounting for roughly 77 percent of total financing. Furthermore, between 1997 and 2017, pharmaceutical spending surged by almost ninefold from RM325 million in 1997 to RM2.9 billion in 2017. In 1997, pharmaceutical spending accounted for 10% of OOP spending and increased to 14.94% in 2015 before decreasing to 13.55% in 2017 (Ministry of Health Malaysia, 2019).

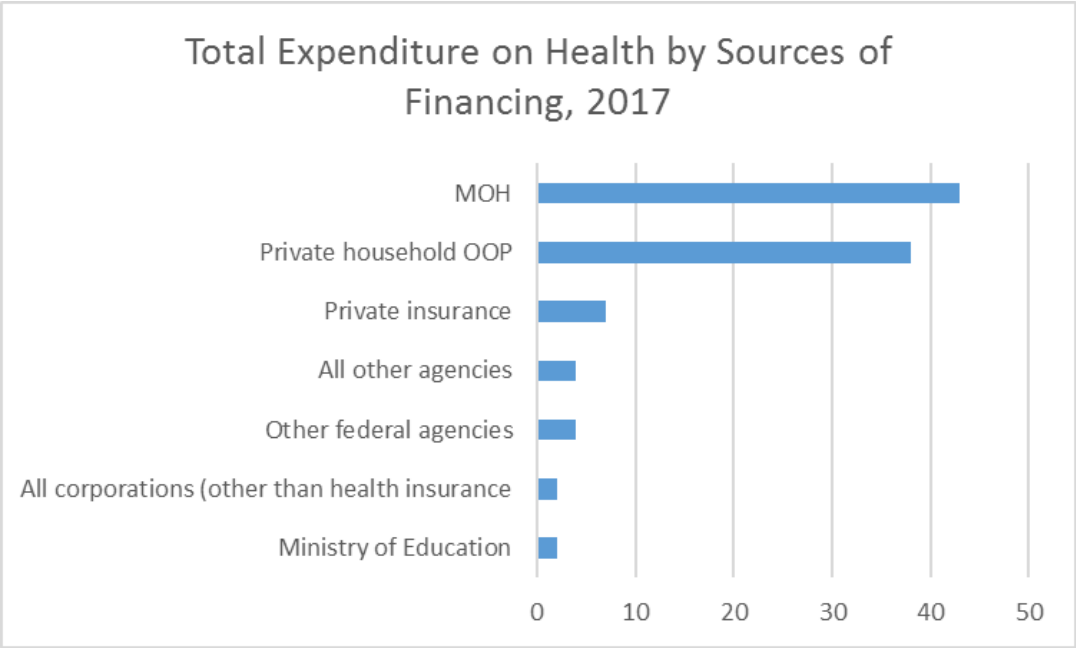

Figure 2.1-A:Total Expenditure on Health by Sources of Financing, 2017. Adopted from (Ministry of Health Malaysia, 2019)

Malaysian pharmaceutical products are broadly classified into four categories: prescription medicines, over-the-counter (OTC) products, traditional medicines, and health/food supplements. Domestic pharmaceutical firms manufacture generic drugs, traditional medicines, and herbal supplements, as well as contract manufacturing for foreign multinational corporations (MNCs) (Malaysia Investment Development Authority, 2020). According to the National Pharmaceutical Regulatory Authority (NPRA), currently there are 292 prescriptions, 63 non-prescriptions and 438 health supplements registered in Malaysia (National Pharmaceutical Regulatory Agency, 2021).

The pharmaceutical industry in Malaysia can be classified into three categories; manufacturing, importation and distribution. There are 253 licensed manufacturers, 477 licensed importers and 1084 licensed wholesalers in Malaysia as of 2021 (National Pharmaceutical Regulatory Agency, 2021). The importation and distribution sectors are monopolised by multinational corporations (MNC), whereas the manufacturing sector is made up of domestic generic manufacturers and foreign-owned companies with manufacturing sites in Malaysia. The vast majority of local businesses are either small or medium-sized enterprises, and they are engaged in the production of traditional remedies, herbal products, and generic pharmaceuticals (Malaysia Investment Development Authority, 2020).

Recent studies have shown that the drug price in Malaysia, both in the public and the private sector is higher than other countries (You et al., 2019). Hence it is important to search for the possible factors contributing to the high prices and the mechanism that can be adopted to improve it.

2.2 External reference pricing (ERP) in Malaysia

In May 2019, the then Minister of Health, Dr Dzulkefly Ahmad, announced that the proposal for the adoption of external reference pricing (ERP) has been approved by the Cabinet. MOH would work with the Ministry of Domestic Trade and Consumer Affairs (KPDNHEP) to control drug price and gazette regulations under the Price Control and Anti-Profiteering Act 2011, in which price control would be placed under KPDNHEP (Boo Su-Lyn, 2019). ERP is a method in which a country uses the prices of drugs from other countries to determine the price of drugs in its own country. ERP generally uses four criteria to select the reference country: geographic proximity, equivalent gross domestic product (GDP), comparable socioeconomic status, and other special considerations such as the price level (Kanavos et al., 2020). ERP is common in developed European countries, where 29 out of 31 countries (except the United Kingdom and Sweden) apply ERP (Rémuzat et al., 2015). It is also gaining popularity in low- and middle-income countries. ERP is a straightforward approach that is adaptable and is simple to implement.

Emphasizing on the increasing patient congestion in the public sector, Dr Dzulkefly mentioned that ERP would ensure that services provided by the private sector remain affordable, providing more options for the people. ERP would use the average of the three lowest prices, to be imposed at both wholesale and retail levels, including clinics, pharmacies, and hospitals. The implementation would take place in stages, beginning with single-source drugs and gradually progressing to more expensive new drugs (Boo Su-Lyn, 2019).

This announcement has elicited mixed reactions, in which it has gained support from the public sector and citizens, but has been opposed by the private sector.

The private sector's opposition to the implementation of ERP is rooted in several factors. Firstly, prices in different markets are not directly comparable due to variations in the burden of disease, specific medical indications, differences in patients' preferences and ability to pay, diverse market structures, and variations in components included in pricing, such as distributor margins and sales taxes. Moreover, medicines may be at different stages of their life cycle across countries, potentially enjoying distinct levels of intellectual property protection. Additionally, discrepancies in pack sizes and presentation further complicate price comparisons. Secondly, the private sector argues that controlling medicine prices alone will not significantly impact the objective of reducing overall healthcare costs, as pharmaceuticals account for a modest proportion of out-of-pocket expenses. Lastly, the private sector expresses concern that ERP implementation may jeopardize patient access to critical medications, potentially leading to delays in medicine availability and access, thereby posing a risk to patient well-being (PhAMA, 2019).

In the recent report, MOH has adopted ERP) as a pricing policy, utilizing a comparison of drug selling prices with reference countries, including Australia, Taiwan, South Korea, Thailand, and South Africa. The selection of these reference countries was based on specific criteria such as being developed countries, having a similar GDP, belonging to the same region, or possessing established pricing policiesb(Pharmaceutical Services Division, 2020). The pricing information for the reference countries was sourced from the Pharmaceutical Pricing & Reimbursement database (PharmOnline International (POLI), 2021). This approach enables MOH to benchmark drug prices against those in comparable countries, allowing for more informed pricing decisions and enhancing cost-effectiveness in healthcare management.

2.3 Patient Access Scheme (PAS) in Malaysia

In 2018, Malaysia introduced the Patient Access Scheme (PAS) to facilitate access to expensive drugs. PAS or also known as managed entry agreement (MEA) is a type of conditional agreement between the payer and the manufacturer (Lim et al., 2018). There are many forms of MEA such as price-volume capping, outcome-based agreements, rebates, discounts, paybacks, risk-sharing agreements, or performance-based agreements. For example, in price-volume capping, the manufacturer agrees to cap the price of the medication and may also agree to limit the volume of sales or the total expenditure on the drug over a specified period. This helps payers budget for the medication's cost and avoid excessive financial burden. Another example is risk sharing agreement. Risk-sharing agreements involve sharing the financial risk of the medication between the manufacturer and the payer. If the drug's outcomes or effectiveness differ from the expected results, the financial responsibility is shared accordingly. The aim of these agreements is mainly to control the budget expenditure and to address the various uncertainties regarding the effectiveness of the treatment (Klemp et al., 2011).

In 1978, the Italian health care system was redesigned to take the form of a National Health Service (SSN), which is primarily funded by taxes collected at the national and regional levels (Folino-Gallo et al., 2008). Italy is divided up into twenty different regions, with eight of those regions accounting for approximately 80% of the country's total population. Since the very beginning of the SSN's constitution, regions have played an important role; however, their role was strengthened initially by a reform in 1992/1993 and then again by a more comprehensive reform of Constitutional Law in 2001 (Ferre et al., 2014). The primary goal of the SSN is to provide primary and secondary care to the entire population in a uniform and efficient manner, as well as to promote preventative health measures such as public health education, health worker

training, food and drink hygiene, workplace safety, and pollution mitigation (France et al., 2005). Similar to Malaysia, the healthcare system in Italy may also be divided into public and private sector.

The Italian central government will be responsible for regulating important aspects of the provision of healthcare, such as the total budget for each region, treatment package that must be covered by each region, the contracts for SSN employees, and the contracts between pharmacies and doctors. In the meantime, the regions will have complete control over the delivery of services, the mechanism for funding those services, and the responsibility of ensuring that citizens receive the essential and adequate levels of care they require (Neri, 2019). Budgets for health care provided by the central government are also entirely the responsibility of the regions. In the event that the allocated funds are exhausted, the deficit can be covered by the regions through a combination of cost-sharing, taxes, and cost-cutting measures (Terlizzi, 2019).

Italy has been one of the leading countries and a pioneer in the effort to incorporate MEA in the process of negotiating the prices of pharmaceuticals (Monique Dabbous et al., 2020b). The Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) is the national authority in charge of pharmaceutical regulatory, pricing, and reimbursement (PR) functions, as well as pharmaceutical spending governance (AIFA, 2003b). Two advisory committees support it: the Technical-Scientific Commission (Commissione TecnicoScientifico, CTS) and the Pricing and Reimbursement Committee (Comitato Prezzo e Rimborso, CPR).

In Malaysia, in order to understand and explore the stakeholders' perspectives towards PAS, Thanimalai et al conducted a study using online survey and semi structured interview involved spanning from the government staff, pharmaceutical

manufacturers and patient advocacy group. Three major themes were identified from the study, namely the high upfront cost, the need to identify treatment requirement and the readiness of the health system to implement PAS (Thanimalai et al., 2022). Hence, it is important to compare the implementation of PAS in both countries and identify possible ways for Malaysia to improve its implementation of PAS.

2.4 Pharmaceutical financial analysis in progressive interstitial lung disease

PFILD includes connective tissue disease-associated ILD (CTD-ILD), fibrotic hypersensitivity pneumonitis (HP), unclassifiable ILD, idiopathic non-specific interstitial pneumonia (NSIP), and rarely sarcoidosis, organizing pneumonia, and ILD associated with occupational exposures (George et al., 2020; Kolb and Vašáková, 2019). The presence of risk factors such as advanced age, being male, having a lower baseline pulmonary function, and radiographic honeycombing or the usual interstitial pneumonia (UIP) pattern of injury increases the likelihood of progression (A. W. Wong et al., 2020). Current treatment for PFILD includes antifibrotic therapy (nintedanib, perfinidone, tocilizumab), immunosuppressive therapies, antacid therapy, oxygen therapy and lung transplantation.

Interleukin-6 (IL-6) is a multipurpose cytokine which is involved in various biological activities that regulate immune responses, haematopoiesis and inflammation (Nishimoto and Kishimoto, 2006). IL-6 is involved in immune-inflammatory diseases such as rheumatoid arthritis and Castleman disease (Nishimoto, 2005). Tocilizumab is an anti-human IL-6R antibody, created by grafting a mouse anti-human IL-6 antibody into human IgG1K to create an antibody with IL-6R binding site (Sato et al., 1993). By competitively inhibiting IL-6 signalling, tocilizumab is effective in the treatment of RA, Castleman disease and Crohn disease (Nishimoto, 2005). In Malaysia, tocilizumab is

indicated in the drug formulary for treating moderate RA patients who do not respond to disease-modifying anti-rheumatic drugs (DMARDs) (Ministry of Health, 2021).

A study conducted in Thailand to assess the budget impact of tocilizumab in the treatment of refractory systemic juvenile idiopathic arthritis found that the total estimated cost for 5 years is USD 4.8 million. The usage of tocilizumab is also not cost-effective as the incremental cost-effectiveness ration (ICER) is USD 35799 per quality-adjusted life-year (QALY), far exceed the threshold at US 5128 per QALY gained (Kittiratchakool et al., 2020). Another study conducted in Russia to assess the budget impact of tocilizumab in rheumatoid arthritis found that tocilizumab have lower cost compared to other TNF-a inhibitors; adalimumab (Humira), certilizumab pegol and golimumab. Similar result was also shown in the treatment of systemic juvenile arthritis when tocilizumab was compared with kanakinumab, adalimumab (Humira) and adalimumab (Dalibra) (Kolbin et al., 2020). In Turkey, the usage of tocilizumab in the systemic idiopathic juvenile arthritis was compared with anakinra. The ICER for tocilizumab was found to be TRY179.053 less than anakinra which make it more cost-effective and preferable option (Erdogan-Ciftci et al., 2019).

The treatment of ILD can be costly. A study conducted in Germany to assess the economic burden of ILD found that, the cost associated with ILD increased with disease progression, up to 5695.49 euro per patient. Patient with connective tissue disease, extrinsic allergic alveolitis, sarcoidosis and smoking history are the factors associated with the higher treatment cost (Maqhuzu et al., 2019). Another study done in Australia using the healthcare database for the period of 2008-2015 found that, patient with systemic sclerosis related interstitial lung disease used more healthcare resources in terms of hospitalization, emergency department presentation and ambulatory care services, than those without ILD. The total cost for patient with