Pharmaceutical Pricing in Asia: Pricing of high-cost medicines in several Asian countries

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1. Introduction

1.1 Background

Pharmaceutical expenditure is increasing worldwide. Between 1995 and 2006 per capita spending on pharmaceuticals increased by around 50%(Lu et al. 2011). The average annual growth rate of pharmaceutical expenditure significantly surpassed that of total health expenditure and of Gross Domestic Product (GDP) in a number of different countries worldwide(OECD, 2008). Particularly, high price medicines for diseases such as hepatitis C could have affected some government budgets heavily. This has resulted in increasing pressure on governments and individuals and endeavors to improve price accessibility to pharmaceutical products have been very important to achieve universal health coverage.

Pharmaceutical pricing policy is very important factor to determine accessibility to medicine(Kwon, Kim, Jeon, & Jung, 2014). Given that patent protection under IPR laws supported by TRIPS has strengthened patent holders' monopoly interests, negotiating pharmaceutical prices with them has become much tougher issues. Therefore, it is highly necessary to study and figure out how governments, including Asian ones, make pricing decisions and go through negotiation processes with pharmaceutical companies.

1.2 Purpose

This report aims to investigate the current status of pharmaceutical pricing policies for high price medicines in Asia-Pacific countries and explore the policy implications for other countries. Specifically, this report is to overview pricing policies for high price medicines and provide in-depth analysis of negotiation cases for high price medicines including Asian countries.

1.3 Structure

This report is composed of two parts :

Part A starts with discussion on the factors affecting drug prices in the context of this study and then conduct overview on pricing methods and measures to improve price accessibilities governments should consider in order to face up to the budget pressure from high price medicines.

Part B presents in-depth case analysis for selected countries : Brazil, Rwanda, Japan, India, Kenya, Malaysia. Cases have been selected so that various measures for price negotiation are analyzed and presented.

1.4 Methodology

Web-based data and literature review(review articles, case studies, reports from international organizations, etc.) were employed to generate evidence on theories and implementations of policy and negotiations. Expert consultation have been conducted to improve validity and reliability of the study based on prior web-based data and literature review. Separately, a survey has been developed to investigate the details of price negotiation cases from selected countries and analysis of the survey has been presented at the Meeting on Access to Medicines under Universal Health Coverage in the Asia Pacific Region in September 2018.

[Part A]

2. Determinants of Pharmaceutical Prices

Prices are basically determined jointly by supply and demand. In a perfectly competitive market, a consumer's demand curve for a particular good or service is perfectly elastic, with even small price increases making the consumer to shift to competing products. For producers to sell products in such a market, prices should be offered down to the point that P = MC, where P is the product's price and MC is the marginal cost for producing the product by the most efficient firm. However, most pharmaceutical products are competitively differentiated, so consumer demand is not perfectly elastic, but downward sloping. When a firm produces at the level of output where MC equals marginal revenue (MR), prices will be above the intersection of the MR and MC curves because normally demand curve the firm is facing is downward sloping above MR curves.

There are other factors to affect pharmaceutical prices. Basically, given the importance of pharmaceutical products in terms of population health and information asymmetry, political and regulatory context tend to play critical roles generating various risks to consider when producers decide to enter certain markets. Moreover, massive R&D costs led to only a few surviving big pharmaceutical companies opening negotiation process with governments. Particularly, prices of high-price drugs for (L)MIC countries are determined through more complex interactions between market and non-market factors such as risks and negotiation processes.

2.1 Pricing methods

Pharmaceutical pricing policy largely defines the market power of the payers or purchasers, which is determined by the number of potential customers represented (considered as a share of the total market for a product) and their willingness and ability to pay. Particularly, price regulation is a policy response to inadequate competition in a market that includes products considered to be necessities and that has been publicly subsidized to avert under-consumption.

A system characterized by a single purchaser or payer will have greater power to obtain price concessions from pharmaceutical sellers, as compared to a system in which the national market features multiple schemes operating (and purchasing) independently. However, competing insurers or funds may be able to be more active or discriminating in their purchasing in efforts to meet the demands of those covered, to the extent that those persons are free to choose a competitor – including one that is more or less active in purchasing – if they are dissatisfied(OECD, 2008).

Although the motives and rationale for regulating pharmaceutical prices and defining reimbursement prices are different, similar techniques are used in both cases. Those techniques can be reference pricing, cost-plus pricing, differential pricing, managed entry agreement, value based pricing, etc.

2.2 Innovativeness

Prices of new pharmaceuticals vary according to their degree of innovativeness(Lu and Comanor 1996). We see that innovative drugs, those

offering a major therapeutic advance, are able to command a substantially higher price differential than that of drugs offering only a modest therapeutic advance. Drugs embodying only modest improvement still allow firms to charge somewhat more than existing drugs. But drugs offering little or no therapeutic advance are unable to charge much more than existing drugs. Drugs offering substantial therapeutic improvement over existing drugs, in terms of efficacy, more favorable side-effect profile, reduced likelihood of side effects, or convenience, do not have to offer a price discount to gain market share. Purchaser willingness-to-pay for a drug's performance allows a higher price to begin with.

Most developed countries have established systems of intellectual property rights (IPR) that serve to foster innovation by providing innovators with rights that exclude unauthorized production and sale of an invention for a set period of time. Nevertheless, companies in developed economies have been complaining that patent infringement and duplication of products by firms in developing countries erode their profits. In response to these complaints, WTO approved TRIPS(Agreement on Trade-Related Aspects of Intellectual Property Rights) agreement in 1995. Under TRIPS, all countries must, as a condition for membership in the WTO, recognize and enforce patents in all fields of technology, including pharmaceuticals. Although many low- and middle-income countries initially made an exception for pharmaceuticals, they agreed to introduce or amend their patent legislation to include pharmaceutical product patents by 2005.

The impact of IPR protection, patents in particular, on product prices is straightforward. Patents, by providing monopoly power to the patent-holder, enable the latter to raise the price of the patented good above the level that would have prevailed in a competitive market. This is the immediate effect of patents. On the other hand, a longer-term, more dynamic perspective suggests

that the promise of these monopoly profits is precisely what is needed to spur the research and innovation that will lead to the introduction of newer and better products, which will over time displace the older patented products and raise consumer welfare. Nevertheless, patents enhanced under TRIPS system exercise undeniable effects on prices, sometimes even raising ethical issues.

2.3 Negotiation

Negotiation is a form of decision making in which two or more parties talk with one another in an effort to find resolutions given their opposing interests(Lewicki, Saunders, Minton, Roy, & Lewicki, 2011). To negotiate is to seek mutual agreement through dialogue(Luecke, 2003). Negotiation is the process of joint decision making. It is communication, direct or tacit, between individuals who are trying to forge an agreement for mutual benefit(Young, 1991). Negotiation can be thought of as fourth approach for decision making along with decision analysis, behavioral decision theory, and game theory(Raiffa, Richardson, & Metcalfe, 2002). Negotiations occur for several reasons: (1) to agree on how to share or divide a limited resource, such as land, or money, or time; (2) to create something new that neither party could do on his or her own; or (3) to resolve a problem or dispute between the parties. Sometimes people fail to negotiate because they do not recognize that they are in a negotiation situation(Lewicki et al., 2011).

Negotiations are commonly used approach to settle conflicts or opposing interests in pharmaceutical markets given its market characteristics. A great deal of heterogeneity exists in the valuations patients place on drugs. Patients vary in their medical and functional responsiveness to a medication. Patients

also vary in the values they attach to different characteristics of a drug; for example, some may care in particular about side effects, dosing convenience, the ability to keep functioning at work or to carry out activities of daily living when retired, or about a particular drug interaction. On the demand side, therefore, one should expect enormous heterogeneity in the marginal valuations of medications.

This demand heterogeneity, together with low marginal production costs, creates incentives for targeted marketing efforts, as well as for nonuniform pricing. Given a typical cost structure in which marginal short-run manufacturing costs are relatively minor, some marketing costs are variable but modest, and a demand side characterized by very substantial heterogeneity in marginal valuations, the “law of one price” does not hold and that nonuniform pricing occurs, both within and between countries(Berndt, 2002).

Several basic elements comprise negotiations such as interests, best alternatives to a negotiated agreement(BATNA), reservation price, zone of possible agreement(ZOPA), "creating" and "claiming" value, "change the game" itself, etc. These basic elements can be found and analyzed in the simplest bilateral negotiation between monolithic parties as well as in the most complex coalitional interactions(Luecke, 2003; Sebenius, 1992; Wheeler, 2002). Particularly, determining BATNAs and walkaways is a cornerstone of negotiation analysis(Wheeler, 2002). The reason you negotiate is to produce something better than the results you can obtain without negotiating. What are those results? What is that alternative? What is your BATNA—your Best Alternative To a Negotiated Agreement? That is the standard against which any proposed agreement should be measured. That is the only standard that can protect you both from accepting terms that are too unfavorable and from rejecting terms it would be in your interest to accept. Your BATNA not only is a better measure but also has the advantage of being flexible enough to permit the exploration of

imaginative solutions. Instead of ruling out any solution that does not meet your bottom line, you can compare a proposal with your BATNA to see whether it better satisfies your interests(Fischer, Ury, & Patton, 1981).

For example, Medicare in U.S. shows how BATNA could work. Currently, as mandated by Congress, only private insurers can negotiate with pharmaceutical companies over the price of drugs used by Medicare patients. These negotiations lead to savings of up to 30% off the list price of drugs, the government reports. But by negotiating as a monolith, shouldn't the United States be able to get better deals? Not exactly. Rules passed by the U.S. Congress leave the government with not just a very bad BATNA in potential negotiations over Medicare drug prices, but in essence no BATNA at all. Because Medicare beneficiaries want access to whatever drug they might need, Medicare is required to cover most drugs. Consequently, government negotiators would not be empowered to walk away from negotiations from drug companies. In such negotiations, the government would have no BATNA—no choice but to do a deal. On the other hand, other nations, such as Great Britain, as well as the U.S. Department of Veterans Affairs, negotiate steep discounts on drug prices, but patients have access to fewer drugs because the negotiators have a strong BATNA—the power to walk away from the table.

2.4 Market sizes

Basically, the number of potential buyers determines the size of the market. If the size of the market decreases, the demand curve shifts to the left, showing lower prices and more quantities. If the size of the market increases, the demand curve shifts to the right, showing higher prices and less quantities.

Unless demand curve shifts to the right enough, it doesn't make equilibrium prices with supply curve particularly when fixed cost is high and so shifting up the average production cost curve.

Thus, suppliers need a rather large and secure market for the new product in order to recover R&D and production costs, allow a risk premium and, in case of compulsory licensing, undercut the patent holder's price and possibly also prices of generic competitors. However, most developing country markets are probably not big enough to supply the sufficient incentives and developed countries constitute the lion's share of the pharmaceutical market. Smaller developing country markets might be interesting markets if many people need one particular medicine and the government can get funding from donors.

For compulsory licensing, the licensee can only sell the products to the requesting country/countries, not to the world market in general. The recipient(s) will constitute the entire market, at least at the time of the application for the CL. Other buyers may also become interested to use the Decision to buy the same product, but this is not necessarily known at the time of the production or when the price per unit is agreed. As well, it cannot be certain that the company will be granted a CL for other buyers as well.

2.5 Competition

Figures from the WHO show that when a patent expires in the US the average wholesale price falls to 60 % of the branded medicine's price when there is just one generic competitor. When there are ten competitors, prices fall all the way to 29 %. Another study of the American market found that generic medicine

prices fall with the number of competitors in the market. Prices only approach long-run marginal cost when there are as many as eight (or more) generic competitors. The result only applies to markets of sufficient size. For medicines less in demand, prices will remain above marginal cost and not induce generic firms to entry.

A study by the Agence Nationale de Recherches sur le SIDA drew similar conclusions for some developing country markets. Exploring determinants of ARV prices in Brazil and 13 African countries, they found that introduction of generic competition remained an essential factor for lowering prices even when controlling for other factors that influence price. Furthermore, they concluded that pooled negotiations will only translate to lower prices when there are multiple possible suppliers.

Some studies show that if there is only one generic product in the market, alongside the original product, the generic price will typically “shadow” the price of the original, placing itself just below the original. A Decision CL will introduce one more supplier into the market. The empirical studies seem to indicate that this increased competition can reduce prices, but probably not to marginal cost. But, there are only a few high-quality generic producers in the world, able to reverse-engineer new medicines and active pharmaceutical ingredients while at the same time adhering to good manufacturing practices, especially if they are also supposed to have low costs. The Decision will not substantially affect this fact, which means that even if a competitive bidding process should work, there would not be many possible bidders.

2.6 Cost

Manufacturing costs are low in pharmaceutical industry with high fixed costs and low marginal costs. Both research and marketing costs in the pharmaceutical industry are high but usually incurred before the final products are manufactured, and so they do not change with the volume of production. Hence they are termed fixed, or "sunk," costs. This is an important distinction because marginal costs determine price in a competitive market, but fixed costs do not.

Nonetheless, the industry's position has consistently been that these costs must be covered by the price of the final products. If these fixed costs are not covered, firms will lose incentive to develop and promote more innovative drugs. Whether sunk costs determine price is quite central finding factors affecting drug prices. As argued by the pharmaceutical industry and its critics, R&D investment is predetermined and the costs of this investment determine total costs, which, together with profit goals, determine prices. Prices are set according to cost. In summary, investment is predetermined and that costs determine prices.

Even for generics, the start-up costs may be substantial. The supplier needs to develop and implement a method for the production and does not necessarily get access to important know-how or the most efficient production method. The supplier must either expand manufacturing capacity or reduce manufacturing of other products. Start-up costs may be higher if the effective length of the license is very short and the supplier must proceed quickly to produce the full order. The effective length of the CL depends on the length of the authorization, and/or the remaining length of the patent itself. It also matters how complex it is to start production and sales. The study on patent expiry in the US showed that it

normally took two to three years for the generic producers from the time it started preparing to manufacture a medicine until it could begin to sell it. According to two sources cited by Abbott, the CL process from request to delivery, including reverse-engineering of the product, gaining regulatory approval and manufacturing the right quantity under good manufacturing practice, may take 1-3 years. The secretary-general of the Indian Pharmaceutical Alliance estimated 3-4 years, and the director of the Brazilian manufacturer Far Manguinhos thought that one year might be possible.

3. Pricing methods

Pharmaceuticals play a vital role in the health system. After inpatient and outpatient care, pharmaceuticals represent the third largest expenditure item of health care spending. Similar to other health care functions, the cost of pharmaceuticals is predominantly covered by government financing or compulsory insurance schemes (OECD, 2017)

In recent years a number of countries have seen the return of higher pharmaceutical spending growth again, partly due to steep increases in spending for certain high cost drugs such as Hepatitis C drugs or oncology drugs (OECD, 2017). Regardless of income levels, pharmaceutical financing, pricing and strategic purchasing have high priority in all countries. In terms of importance and feasibility, national/government level authority for pharmaceutical pricing, regulation, management, price negotiation policy, and post management of pharmaceutical price are recommended (S. Kim, Son, & Lee, 2017)

Pharmaceutical pricing matters especially in countries with weak pharmaceutical systems. In those countries, price affects affordability and access to medicines directly as the majority of pharmaceutical spending is through OOP pay, and the availability of medicines in public facilities is very low (Kwon et al., 2014).

Fundamentally, Pharmaceutical price regulation is important because of inadequate competition in the pharmaceutical market. Competition in the pharmaceutical market is limited due to information asymmetry and separated responsibility for the purchasing decision makers (physicians and prescribers)

and those who bear the cost (patients and third-party payers). Without price regulation, pharmaceutical manufacturers can benefit from relatively inelastic demand by pricing at high levels using their monopolistic power (OECD, 2008).

Countries should use a combination of different pharmaceutical pricing policies that should be selected based on the objective, context and health system. Pricing policies should have an appropriate legislative framework and governance and administrative structures, supported by technical capacity, and should be regularly reviewed, monitored and evaluated and amended as necessary. In promoting the use of affordable medicines, countries should employ a combination of pharmaceutical policies that address both supply and demand issues (WHO, 2015b).

3.1 Cost-plus pricing

Cost-plus pricing is a method for setting retail prices of medicines by taking into accounts production cost of a medicine together with allowances for promotional expenses, manufacturer's profit margins, and charges and profit margins in the supply chain (WHO, 2015b).

Cost-plus pricing is currently used for locally produced medicines in few European countries such as Cyprus, Greece and Slovakia. Some Asian countries also use cost plus pricing, including China, Japan and Vietnam. India once used this pricing mechanism but their 2012 national pharmaceuticals pricing policy has given up this approach for a market-based pricing(Nguyen, Knight, Roughead, Brooks, & Mant, 2014).

Cost-plus pricing might stabilize medicine prices in unregulated settings and the method might reduce out-of-pocket payments in an unregulated market(WHO, 2015b). Although its advantage in unregulated settings and intuitively simplistic in its application, cost-plus pricing has a number of limitations, which are often compounded by the lack of expertise and capacity in the poor resource settings of LMICs(Nguyen et al., 2014).

The main problem lies in the setting of the initial cost parameters. It is difficult to verify company supplied information on basic costs and profit margins. It is also difficult to assign overhead and research costs to individual medicines(Nguyen et al., 2014). Also, formulae used by countries to calculate cost-plus prices can be manipulated to the advantage of manufacturers and disadvantage of patients(WHO, 2015b). Cost-plus pricing arrangements may fail to provide incentives for companies to improve efficiency and reduce costs. A medicine with limited efficacy may be expensive to produce that can result in a high cost, low value product when a cost-plus approach is used(Nguyen et al., 2014).

According to WHO guideline (2015b), countries generally should not use cost-plus as an overall pharmaceutical pricing policy. Countries using a cost-plus method as an overall policy should consider replacing or complementing the cost-plus approach with other policies. In our Japan case, initial price of OPVIDO was expensive due to cost-plus pricing method for new drug. Without other drug price policy to complement it such as price-volume adjustment and external reference pricing, the financial burden would have been steadily high since Japan could not adjust initial OPDIVO price.

3.2 External Reference Pricing

External reference pricing refers to the practice of using the price of a pharmaceutical product in one or several countries to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. Reference may be made to single-source or multisource supply products(WHO, 2015b).

External benchmarking of pharmaceutical prices is the most widely used measure to limit prices or reimbursement prices in OECD countries. It is perceived by public authorities as a means to assure the fairness or appropriateness of the proposed or actual price in relation to what is paid in other countries(OECD, 2008) External benchmarking in Japan is used to adjust the price of a new drug if it differs significantly from the average of the drug's price in France, Germany, the United Kingdom and the United States(Kwon et al., 2014).

The precise methodology adopted varies according to the perspective of regulators, purchasers and payers but the process is usually undertaken in three key stages. The selection of reference countries, the determination of the level at which prices are compared and the price date in the reference country, and the method used to calculate the benchmark price(Nguyen et al., 2014).

External price benchmarking is simple and straight forward in terms of information and capacity requirements, although information on real prices in other countries is very difficult to get. However, it has weak theoretical foundation because it simply assumes that price in other countries is optimal(Kwon et al., 2014).

LMICs wanting to develop an external reference pricing system need to consider the resources and expertise required to collect and analyze data. There are technical difficulties in undertaking price comparisons for the same medicine across countries. Selecting reference countries at similar stages of development increases the difficulty in collecting reference price data since LMICs often lack a reliable historic and systemic data source on medicine prices. Current mechanisms that are publicly available and commonly used include the Management Sciences for Health (MSH) International Drug Price Indicator Guide or WHO's Global Price Reporting. These provide an indication of pharmaceutical prices on the international market and may be used as an alternative to price data from reference countries(Nguyen et al., 2014).

Countries should consider using external reference pricing as a method for negotiating or benchmarking the price of a medicine. In developing an external reference pricing system, countries should define transparent methods and processes to be used. Countries/payers should select comparator countries to use for reference pricing based on economic status, pharmaceutical pricing systems in place, the publication of actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease(WHO, 2015b).

3.3 Value-based Pricing

It is the price decisions based on benefits or effectiveness of new drugs over those currently available(Kwon et al., 2014). New and innovative drugs expand treatment options and increase treatment costs. Dozens of new medicines or new indications for existing medicines are approved each year. These may

increase treatment options for previously unmet needs or for new population targets or increase competition in existing market segments. While many of these drugs offer considerable therapeutic value to patients and represent significant improvements over alternative treatment options, they usually have a much higher price than traditional drugs(OECD, 2016).

Health Technology Assessment (HTA), which is one of value-based pricing, is defined as 'the systematic evaluation of properties, effects, and/or impacts of health care technology'. HTA can potentially be used to assess value for money when making decisions on pharmaceutical prices, but requires a high level of technical capacity (WHO, 2015b).

Since the introduction of the systematic use of HTA in the reimbursement process in Australia in 1993, most OECD countries use HTA in their pricing and reimbursement decisions(Kwon et al., 2014). Cost-effectiveness is a necessary condition of listing the new drug in Australia and Korea. In Korea, new drug should verify the comparative effectiveness and cost-effectiveness to be coved by National Health Insurance. SOVALDI and HARVONI, the drug of hepatitis C was listed in May 2016 based on HTA. As a result, the financial burden for patients who needed these drugs were reduced.

When therapeutic alternatives are available, incremental cost-effectiveness is usually used to make decisions as to whether the new product can be considered worth the additional cost. On the other hand, when no therapeutic alternative is available, an implicit or explicit definition of a cost-effectiveness threshold is required(Kwon et al., 2014).

Few LMICs formally use this method in pharmaceutical pricing and reimbursement decision making, and those that do have universal health coverage, such as Thailand and Taiwan. Choosing an appropriate cost-effective

threshold for decision rules that takes account of affordability is problematic in LMICs. Limited capacity to conduct pharmaco-economic evaluation due to shortage of qualified researchers and reliable local healthcare data coupled with poor infrastructures is another major barrier to more widespread use of pharmaco-economic assessment in LMICs(Nguyen et al., 2014).

Pharmaco-economic data are available from leading countries in the field such as Australia. However, caution should be exercised in its application to LMICs. Published evidence suggests that not only is it difficult to apply pharmaco-economic results from high-income countries, but extrapolation of the results from one LMIC to another can be problematic(Nguyen et al., 2014). Countries should consider reviews from other countries and reports submitted by pharmaceutical companies and should conduct assessments based on local information and local data(WHO, 2015b).

Countries could take a stepwise approach to develop legislative and technical capacity to take full advantage of the potential utility of HTA in pharmaceutical price setting. If possible, countries should use HTA as a tool to support reimbursement decision-making as well as price setting/negotiation or should combine HTA with other policies and strategies, particularly within-country reference pricing(WHO, 2015b).

3.4 Managed Entry Agreement(MEA)

A few countries have decided to give a greater role to health technology assessment in their reimbursement and/or pricing process. In parallel, many OECD countries have introduced or expanded the use of managed entry

agreements (MEAs), which are arrangements between the manufacturer and the payer that allow coverage of drugs subject to defined conditions. Managed-entry agreements cover a wide range of contractual arrangements, which can be just financial or performance-based (OECD, 2016).

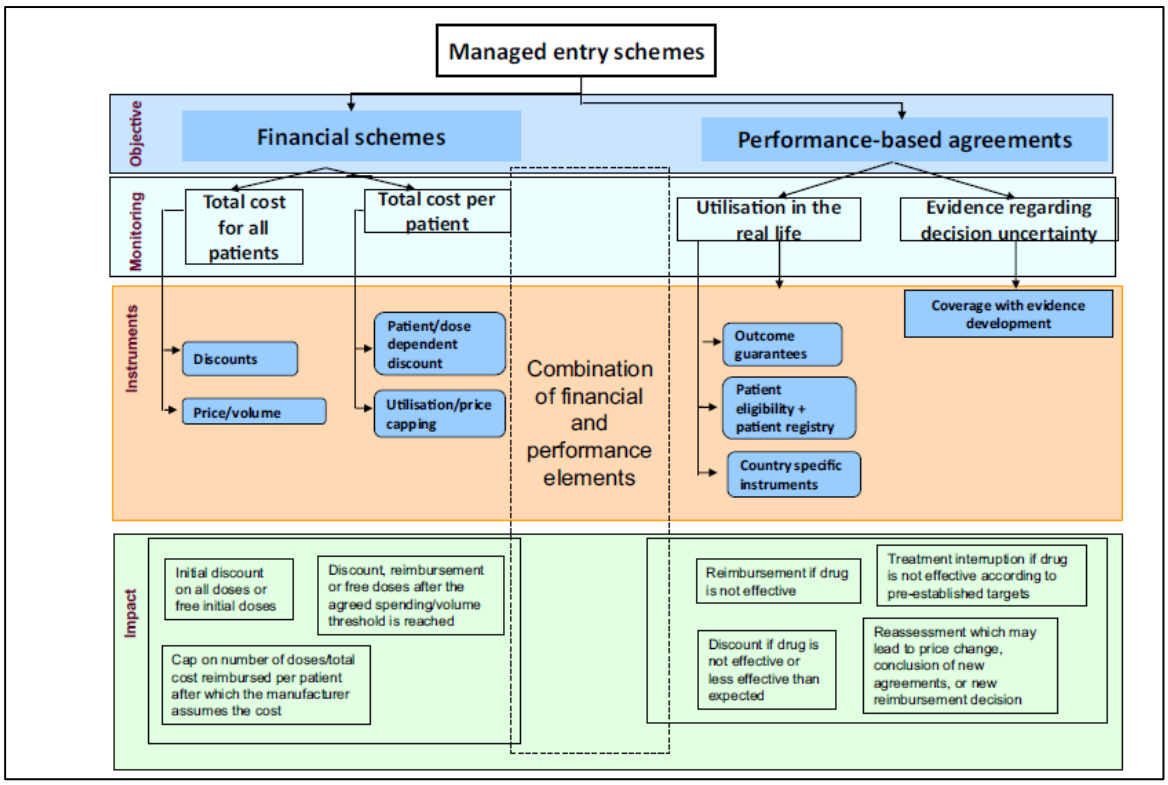


Figure 1 A framework to classify and analyse the impact of managed entry schemes

These agreements can take different forms, including price-volume agreements (PVAs), outcome guarantees, coverage with evidence development (CED), and disease management programs, risk-sharing agreements (RSAs), performance-based agreements (PBAs), patient access schemes (PAS), or managed entry agreements (MEAs)(Kanavos, Ferrario, Tafuri, & Siviero, 2017).

These agreements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of

technologies in order to maximize their effective use or limit their budget impact(WHO, 2015a).

For the example of financial based agreements, governments or insurers may also manage pharmaceutical budgets based on the total value of sales, rather than on a per-unit price basis, which is a form of risk sharing. Given the low marginal cost of production, pharmaceutical firms also may be willing to negotiate based on the total value of sales, rather than on a per-unit price basis(OECD, 2008). In this situation, a set budget for reimbursement based on a sales forecast is negotiated as a condition of entry(Nguyen et al., 2014).

Performance-based agreements may be patient based. Some programs involve an agreement between governments or coverage decision makers and the pharmaceutical company on the expected outcomes from a medicine. If the medicine fails to fulfill the expectation when used appropriately, the company is required to refund, in full or partly, the cost to the health service (Nguyen et al., 2014).

Price-volume agreements (PVA) are policies to adjust prices as volume increases after listing. In Korea, prices are adjusted if the actual volume outweighs the expected sales volume or the growth rate from the previous year by more than 60%. Another case is Japan. In their own policy, drug prices are discounted after the agreed spending/volume threshold is reached. For this agreement, Japan reduced the price of OPDIVO by 50% in February 2017.

Although there was not identified any MEAs in LMICs(Nguyen et al., 2014), this prospectively offers LMICs a way to provide some access to medicines without potentially compromising the value of manufacturers' sales elsewhere (Kwon et al., 2014).

In high-income countries, MEAs are the way to improve access to high-cost drugs and to cope with global pricing policies of multinational companies. However, confidential discounts through MEAs are becoming more widespread. Also, it could contribute to lowering price transparency and make external reference pricing difficult. In other words, long-term impact of MEAs has not yet been evaluated(OECD, 2016).

3.5 Differential pricing

Differential pricing (also called tiered pricing) is the adaptation of product prices to the purchasing power of consumers in different geographical or socio-economic segments. Differential pricing could potentially be a very effective strategy to improve access to essential medicines in low and middle-income countries where most patients pay for medicines out-of-pocket and therefore cannot afford prices comparable to high income markets(Yadav, 2010)

Differential pricing could also improve quality of medicines and achieve higher profits for pharmaceutical manufacturers. However, differential pricing can be sustainable only if it aligns the incentives of the different stakeholders: pharmaceutical manufacturers, national governments, end patients and civil society organizations(Yadav, 2010).

Despite some evidence that differential pricing of pharmaceuticals can benefit manufacturers and poor countries without adversely affecting higher income countries, the widespread and systematic use of such pricing has been limited to vaccines, contraceptives, and antiretrovirals (ARVs) mostly in low income countries(Yadav, 2010).

With imperfect market segmentation, the results of differential pricing could be questionable. In 2006, Honduras bought the Lopinavir/Ritonavir combination antiretroviral therapy for the treatment of HIV at a price six times higher than that paid by Brazil. The incidence of AIDS is similar in both countries (0.5%), but the per capita gross domestic product(GDP) of Honduras is one-quarter that of Brazil. Brazil's skillful handling of negotiations, the attractiveness of its market and the possibility that the country might adopt unilateral measures to buy or produce generic drugs probably had more impact on the final price they paid than the poverty of the Honduran people did on the price their government paid(ISGLOBAL, 2016).

For differential pricing, participation of pharmaceutical industry and market segmentation are crucial. To achieve appropriate and sustainable price differences will require either that higher-income countries forego trying to import low drug prices from low-income countries, through parallel trade and external referencing, or that such practices become less feasible(Danzon & Towse, 2003).

The option of compulsory licensing of patented products to generic manufacturers may be important if they truly have lower production costs or originators charge prices above marginal cost, despite market separation. With assured market separation, originators may offer prices comparable to the prices that a local generic firm would charge, which eliminates the need for compulsory licensing(Danzon & Towse, 2003).

The national governments of LMICs have a key role to play in providing the political will and objectively determined reimbursement policies to enable differential pricing. It is important to note that differential pricing is not a panacea to ensuring access. For patients with affordability levels lower than the

marginal cost of manufacturing, donor subsidies and government support will continue to be required(Yadav, 2010).

4. Measures to improve price accessibility to Pharmaceutical Products

Academics, activists and industry representatives have all proposed differing prescriptions for solving the problems surrounding innovation and access to medicines. In practice, most of the strategies that have emerged fall into one of four categories: the TRIPS flexibilities, unilateral decisions made by companies that own patents, unilateral actions taken by governments, or funding from public and private donors (ISGLOBAL 2016).

TRIPS Agreement presented a dilemma for policy makers. On the one hand, governments embraced the agreement for the economic benefits of increased trade. On the other, this obligation had a clear potential to strain national budgets and to place health technologies out of the reach of those in need.

To address these tensions, negotiators included 'flexibilities' in the TRIPS Agreement that could be used to promote the right to health. Such 'flexibilities' are expected to enable signatories to tailor and employ national intellectual property law, competition law, medical regulations and procurement laws to fulfil their human rights and public health obligations(United Nations 2016). Among the most discussed TRIPS flexibilities, compulsory licenses, wherein a government imposes the terms under which a patented product can be used or produced in generic versions without the consent of the patent holder have been widely used more than others such as Parallel Importation, research exception, etc.(Table 1). Notably, Least-developed countries pharmaceutical transition measure has not been utilized since 2011(FM't Hoen, Veraldi, Toebes, & Hogerzeil, 2018).

Table 1 Measures used by governments to gain access to lower-priced generic medicines, 2001-2016

Type of measure	Instances of use, no. (%)
TRIPS flexibility	
Compulsory licence	48 (27.3)
Public noncommercial use (government use) licence	52 (29.5)
Least-developed countries pharmaceutical transition measure	40 (22.7)
Parallel importation	1 (0.6)
Research exception	3 (1.7)
Non-patent-related measure	
Declaration of no patent in territory	26 (14.8)
Import authorization without reference to patent status	6 (3.4)
Total	**176 (100.0)**

(Source : FM't Hoen et al. (2018))

According to Son and Lee(2017), there were 108 attempts to undertake compulsory licensing in 27 countries between 1995 and 2014. Compulsory licensing was attempted more frequently in Asian, Latin American and Caribbean, and African countries than in North American and European countries: There were 43 attempts in 8 Asian countries, 28 attempts in 6 Latin American and Caribbean countries, and 26 attempts in 10 African countries as compared to 8 attempts in 2 North American countries; and 3 attempts in 1 European country(Table 2). Four nations made more than 10 attempts: Brazil, Indonesia, South Africa, and Thailand. India, Ecuador, Canada, and Malaysia each made more than four attempts. It should also be noted that there were just five attempts (4.6%) at compulsory licensing to export pharmaceuticals. Canada and India made three and two attempts, respectively, to export pharmaceuticals to the following countries: Chile, the United States, Rwanda, and Nepal.

Table 2 Attempts to issue compulsory licensing by region

Africa	Attempts	Asia	Attempts	Latin America	Attempts	Others	Attempts
South Africa	11	Indonesia	13	Brazil	16	Canada	5
Cameroon	3	Thailand	10	Ecuador	7	for export	(3)
Mozambique	3	India	8	Peru	2	United States	3
Zambia	3	for export	(2)	Argentina	1	Italy	3
Egypt	1	Malaysia	4	Chile	1		
Eritrea	1	China	3	Dominican Republic	1		
Ghana	1	South Korea	3				
Guinea	1	Taiwan	1				
Swaziland	1	Vietnam	1				
Zimbabwe	1						
10 countries	26	8 countries	43	6 countries	28	3 countries	11

4.1 Voluntary Licensing

Patent holders can grant licenses to third parties to manufacture and sell generic versions of the product in a specific country in exchange for a royalty, which is known as voluntary licensing. It allows the patent holder to retain control over the sale price of the generic product, but usually reduces the cost to the patient and increases the availability of the drug in the market. In the past, this type of license has been granted by patent holders to generic producers in countries like South Africa and India to reduce the cost of antiretroviral treatment for HIV/AIDS. The criticism that has been made of voluntary licensing—and differential pricing—is that it is not effective in reducing prices. The industry has been accused of a number of doubtful practices: waiting until the last moment to grant the voluntary license like Malaysian case which we will look at, overloading the operations with restrictive terms, and using this mechanism to limit the use of TRIPS flexibilities, such as compulsory licensing. To make matters worse, voluntary licensing operations often exclude middle income countries, which are home to a large proportion of the world's poor(ISGLOBAL 2016).

4.2 Patent Opposition

TRIPS establishes three criteria for granting a patent: novelty, inventive activity and industrial application. However, the agreement does not offer a precise definition of these criteria, leaving a margin of interpretation for the national legislatures in WTO member countries. Another strategy to overcome IP barriers that has proven successful is to challenge patents in order to ensure that patent offices subject applications to the full rigor of a country's intellectual property law(Gaudino, Gay, Grillon, Perfect, & Prabow, 2017). India, for example, has used the TRIPS flexibilities to strengthen the patentability criteria, thereby facilitating local production of generic drugs and increasing the population's access to essential medicines while at the same time complying with WTO regulations. Other countries, including Thailand, the Philippines and Brazil, are following India's example and challenging patents in the courts. Brazil and Argentina are in the process of amending their patent guidelines to redefine a number of concepts more narrowly, including novelty and inventive activity(ISGLOBAL 2016). This type of patentability criteria, which depends on legislative decisions made in each country, could bring the practice of 'hyper-patenting' to an end and facilitate access to medicines while protecting real innovation. Ensuring appropriate use of the patent system is an approach that complements compulsory licensing. Unfortunately, the intellectual protection terms imposed by the new generation of trade agreements further complicate the use of the TRIP flexibilities.

4.3 Compulsory Licensing

A compulsory license, also referred to as a non-voluntary license, is a license granted by an administrative or judicial body to a third party to exploit a patented invention, without the consent of the patent holder. Compulsory licensing is used in public health to address a variety of situations including: high prices of medicines; anti-competitive practices by pharmaceutical companies; failure by pharmaceutical patent holders to sufficiently supply the market with needed medicines; and in emergency public health situations. In practical terms compulsory licensing can be used to bring down the prices of medicines and to ensure a sufficient supply of medicines in the market in cases where the patent holder cannot, or will not, provide sufficient supplies at the right price. It is also a critical tool in emergency situations where the patent holder cannot respond to an urgent situation(UNAIDS, 2011). The patent continues to belong to the original owner, but the financial remuneration paid is fixed by the national authority that issues the license.

The possibility that a country might issue a compulsory license has become a strong bargaining tool in negotiations, as demonstrated by the case of Brazil in 2001, when the country successfully reduced the price it paid for drugs to treat AIDS. In South Africa, GlaxoSmithKline and Boehringer Ingelheim agreed to grant voluntary licenses for their antiretroviral therapy to generic companies in exchange for a royalty of 5% to avoid a situation governed by a compulsory license(ISGLOBAL 2016). Often, the decision to issue a compulsory license is preceded and followed by political and commercial pressure brought to bear by the government of the patent holder's country, particularly when this is the USA(Urias, 2015).

4.4 Government Use

The TRIPS Agreement, although not specifically mentioning government use, recognizes such use by its references to the concept of public, non-commercial use and of patents "used by or for the government". Where the state or a state agency uses patents without the consent of the patent holder, it is, like compulsory licensing, covered under Article 31. The distinction between government-use provision and compulsory licensing primarily relates to the nature or purpose of the use of the patent. In the case of government use, it is limited to "public, non-commercial purposes", whereas compulsory licenses can also cover private and commercial use(UNAIDS, 2011). A notable difference is the waiver of the requirement for the government or its authorized party to first seek a voluntary license. This waiver provides a considerable degree of flexibility and allows for speedier action. In other words, it allows for the use of patents to be 'fast-tracked', which is of importance when lifesaving medicines are required(Musungu, Oh, & WHO, 2006). As with compulsory licenses, government-use orders can be used to bring down the prices of medicines, to ensure a sufficient supply, and address emergency situations(UNAIDS, 2011). The right of the state or government to use patents without the consent of the patent holder is a standard feature of patent laws in many countries. Such use of patents by the government is viewed in common-law countries as an eminent domain taking of a license under the patent and thus, not an infringement of the patent. Government use does not override a patent. Rather, the right reserved by the government to make use of an invention is embedded in the initial grant of every patent. The patent owner can still sell the medicine, and retains the exclusive right to sell to private providers and hospitals(Musungu, Oh, & WHO, 2006).

4.5 Paragraph 6 System

The original TRIPS rules from 1995 only allowed compulsory licenses for the domestic market. Countries without domestic production capacity of medicines could therefore not use them. Nor was it allowed for countries with production capacity to grant compulsory licenses for export to countries without such capacity. The Doha Declaration on TRIPS and Public Health of 2001 acknowledged this problem, and two years of high profile negotiations to define the solution followed. The new rules were adopted in 2003. They allow WTO members to grant compulsory licenses for medicines to be exported to developing countries with grave public health problems and insufficient domestic production capacity. Both developing and high income countries may be exporters. A number of steps must be taken by both importer and exporter. There are several safeguards intended to prevent re-exportation of the medicines, as this would undermine prices on other markets. Importers shall only use the new rules when the medicine is patented in the exporting country (the location of the new producer)(National Board of Trade, 2008).

4.6 Parallel Importation

Parallel Imports, also called grey-market imports, are goods produced genuinely under protection of a trademark, patent, or copyright, placed into circulation in one market, and then imported into a second market without the authorization of the local owner of the intellectual property right(Maskus, 2001). Parallel trade does not refer to unofficial, illegal, or informal-sector activities that may take place inside a country or among countries. Moreover, parallel

trade is not trade in pirated or counterfeit products. The latter are unauthorized versions of products that infringe an IP right. Parallel Imports (also called gray-market imports) are genuine, often branded, products that do not violate an IP right. Importing the products from one country to another, however, may not be authorized by the right holder(MATTHEWS, 2007).

4.7 Pooled procurement mechanisms

Pooled purchasing strengthens the negotiating position of the members of the group, enabling them to obtain a lower final price. A number of successful joint purchasing mechanisms exist, including the Vaccines Alliance (GAVI) and the Pan American Health Organization's Revolving Fund For Vaccine Procurement. The latter makes group purchases of childhood vaccines to supply dozens of countries, obtaining more advantageous prices than those that could be secured through bilateral negotiation. Unfortunately, joint purchasing is a mechanism not used as often as it should be. In response to the influenza A pandemic in 2011, the members of the European Union expressed an interest in setting up a joint purchasing mechanism to acquire the appropriate vaccines, but the initiative was not successful. The practice is, however very common in other sectors, such as defense and construction(ISGLOBAL 2016).

Table 3 TRIPS Flexibility measures

Flexibility	TRIPS Article	Description
Parallel Imports	6	Goods legitimately placed on another market may be imported from another market without

		permission of the right holder because of the exhaustion of the patent holder's exclusive marketing rights.
Patentability criteria	27	WTO Members may develop their own definitions of 'novelty,' 'inventive step' and 'industrial application.' They can also refuse to grant patents for certain subject matter, e.g. plants and animals.
General exceptions	30	WTO Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner.
Compulsory licensing	31	A non-voluntary license may be granted by a duly authorized administrative, quasi-judicial or judicial body to a third party to use a patented invention without the consent of the patent holder, subject to the payment of adequate remuneration in the circumstances of each case.
Government use	31	A government authority may decide to use a patent without the consent of the patent holder for public, non-commercial purposes, subject to the payment of adequate remuneration in the circumstances of each case.
Paragraph 6 System	31	Compulsory licenses are allowed to be granted for medicines to be exported to developing countries with grave public health problems and insufficient domestic production capacity.

Competition-related provisions	8, 31(k), 40	Members may adopt appropriate measures to prevent or remedy anti-competitive practices relating to intellectual property. These include compulsory licenses issued on the basis of anti-competitive conduct and control of anti-competitive licensing.
Transition periods	65,66	LDCs are not required to provide patent or data protection in general until 1 July 2021 and on pharmaceutical products are not required to grant or enforce patents or data protection until 1 January 2033, or a subsequent date as agreed by WTO Members.

(Source : Musungu, Oh, and WHO (2006); United Nations (2016))

[Part B]

5. Brazil : Compulsory Licensing as a Threat

5.1 Introduction

Brazil was the first developing country to guarantee universal access to Antiretroviral Therapy(ART) through its National HIV and AIDS Program (NAP) by incorporating HIV testing and treatment delivery into its universal healthcare infrastructure. Law 9.313 guaranteed universal ART coverage to all eligible patients with no copayments. In 2007, Brazil issued its first compulsory license for import and manufacture of efavirenz (EFV), a first line HIV medication which was patented by Merck, Sharpe, and Dohme(Cherian, 2016; Nunn, 2009).

Brazil has been taken as the country to be examined as it is widely acknowledged as a leading user of Compulsory Licensing threats in negotiation with pharmaceutical companies to reduce the price of HIV/AIDS treatments. Brazil forms an interesting case study to gain insight on how the threats of issuing a compulsory license can be used to negotiate price reductions with pharmaceutical companies(Urias, 2015).

5.2 Background

Brazil's first AIDS case was reported in 1982 and, then years later, there were approximately 76,000 living with HIV in the country(Levi & Vitória, 2002). In a report published in 1993, the World Bank expressed its concern about the spread of the HIV/AIDS epidemic in Brazil. Due to its large population, the significant number of poor people and the precarious state of the healthcare system, experts estimated that there would be nearly 1.2 million people infected by HIV/AIDS by 2000. The World Bank stated that an appropriate intervention in the country could help to avoid new infections. Accordingly, a focus on prevention was recommended instead of treatment.

In 1996, Brazil became a pioneer among developing countries, when it started an official and well-structured policy of universal and free access to antiretrovirals through the public health system, named Sistema Único de Saúde (SUS, or Unified Health System). Indeed, the public commitment to tackle the HIV/AIDS epidemics had begun more than a decade earlier. In 1986, the Department of STD(Sexually Transmitted Diseases), AIDS and Viral Hepatitis was created with the support of the Ministry of Health of Brazil (MoH). In 1991, ARV drugs had already been included in the public health system with the distribution of zidovudine capsules (Teixeira, Vitória, & Barcarolo, 2004; Urias, 2015).

Through this program, Brazil challenged conventional wisdom, because most of the international development agencies were against developing countries implementing treatment programme, favoring 'cost-effective' prevention over a treatment that often exceeded US$10,000 per patient per year (PPPY) at the time(Nunn, 2009). Brazil has demonstrated that the combination of prevention and care is critical for stopping the AIDS epidemic. However, over time the

increasing number of patients and the inclusion of newer patented ARVs imposed some additional challenges for the Brazilian Government. Due to the rising costs of the program, the MoH clearly had to contain the health expenditures necessary to ensure the sustainability of the anti-AIDS program. To do so the MoH started seeking price reductions for high-cost drugs(Urias, 2015).

One important factor that triggered the Brazilian strategy of price negotiation was the sharp rise in costs due to the high depreciation of the local currency (Brazilian Real BRL) in 1999. This factor alone was the main cause of the 64 per cent rise in the cost of antiretroviral drugs in Brazil between 1998 and 1999. 1999 is the only year in the period 1997-2000, when the costs PPPY measured in BRL increases, even though it decreases in dollar. It is also possible to see a sharp increase in the total expenses with ARV drugs in 2009. This had to do with an expansion of the programm with a remarkable increase in the number of patients and with the inclusion of new drugs such as Darunavir and Raltegravir. In spite of the increase in the total expenses, the costs PPPY have decreased steadily until 2013.

5.3 Compulsory Licensing

Compulsory licensing is an important policy tool for government authorities to promote access to health technologies. With a compulsory license, a government imposes the terms under which a license on a patented product may be used in that country by a third party without the consent of the patent holder. While the state denies the patent-holder a monopoly, it does not deny them remuneration and the beneficiary of the license pays a royalty. The right

holder retains its exclusive rights, except with regard to the compulsory licensee. The Doha Declaration dispelled the myth that compulsory licenses should be limited to emergency situations by confirming that WTO Members were free to determine the grounds under which compulsory licenses could be issued(United Nations, 2016).

Under the TRIPS Agreement, WTO Members are only limited with regard to the procedure and conditions to be followed in the granting of compulsory licenses. Article 31 sets out the conditions to be met in the granting of such licenses. Although the Agreement refers to some of the possible grounds for compulsory licenses; such as in the case of a national emergency or situation of extreme urgency; as a measure to remedy anti-competitive practices; to enable the use of a dependent patent; and public, non-commercial use of patents, it does not limit the use of other grounds. Since the permissible grounds are not explicitly defined in the Agreement, it leaves developing countries wide discretion when determining public health sensitive compulsory licensing policies and law(Musungu, Oh, & Organization, 2006).

This flexibility to determine the grounds was re-affirmed in Paragraph 5(b) of the Doha Declaration on the TRIPS Agreement and Public Health, which states that “each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted”.

In order to fully use the flexibilities allowed, developing countries should incorporate within their patent laws provisions for compulsory licensing and specify as many of the possible grounds in order to avoid ambiguity or uncertainty. In many cases, the most significant barrier to the use of compulsory licensing is the absence of simple, straightforward legislative and administrative procedures to put the system into effect. This is often as crucial as having suitable legal provisions enacted. For a start, it will be useful to establish clear

decision-making processes, including the determination or designation of the authorities or bodies charged with the responsibility for the various stages of decision-making. In most countries, there will be a situation of overlapping roles and responsibilities in the case of ensuring access to medicines. Multi-agency involvement will also facilitate informed decision making(Musungu, Oh, & Organization, 2006).

5.4 Brazilian Law

In 1996, Brazil adopted TRIPS under the threat of trade sanctions from the US(Chaves, Hasenclever, Osorio-de-Castro, & Oliveira, 2015). Lack of government vigilance while implementing TRIPS, resulted in drug prices rising by 54 % from 1989 to 1990 due to a combination of hyperinflation, shutting of over 1700 local generic manufacturers and shift of multinational pharmaceutical production to overseas(F. M. Abbott & Reichman, 2007). Simultaneous implementation of new IP legislation and a universal access policy for ART had damaging effects on the healthcare budget and on ART access, due to closures of local API manufacturers.

In May 1996, Brazil enacted Law 9,279/9614, which amended its patent laws, bringing them into compliance with TRIPS standards. This law had a significant impact on the local pharmaceutical industry as it introduced the patentability of chemical products and processes, previously non-patentable. The Law 9,279/96 took effect in May 1997; thus, Brazil waived the ten years adaptation period to comply with TRIPS. The premature enforcement of the Brazilian Patent Law created constraints in the local production of ARV drugs because only those molecules that were in the market before 1996 could be copied(Orsi,

Hasenclever, Fialho, Tigre, & Coriat, 2003). This was aggravated by two other important decisions: the inclusion of a provision for 'pipeline patents' of pharmaceutical inventions and the exclusion of Parallel Imports, which will be analyzed for the case of Kenya(Urias, 2015).

Although it was not required by TRIPS, Brazil introduced a provision for 'pipeline patents' in its IPR law, due to pressure from major pharmaceutical multinationals. This mechanism allowed patent claims for pharmaceutical products to be accepted and approved with twenty years' patent protection based on the date of first foreign filing as long as such products were not marketed in Brazil. When such patent applications were filed in Brazil, the respective information on the invention had already been available in other countries (e.g. patents, scientific journals). Therefore, they no longer fulfilled the novelty requirement, since the information was already in the public domain. In addition to relaxing the definition of 'novelty,' pipeline patents were not examined but simply revalidated by the local authorities such as Brazilian patent office, the National Institute of Industrial Property (INPI)(Shadlen, 2009).

Accordingly, Efavirenz could benefit from Pipeline protection until 2012, on basis of Merck's patent validity in the US, which impeded access to available cheap generics(Reis, Terto Jr, & Pimenta, 2009). Efavirenz was taken as part of a first line ART regimen and was attributed to 21% of the total ARV expenditure for the NAP, with efavirenz and nevirapine having the greatest impact on the ARV budget directly due to retrograde patent protection(Grangeiro, Teixeira, Bastos, & Teixeira, 2006). Three of six drugs threatened with Compulsory Licensing were protected by revalidation patents and were attributed to high costs of treatment(Chaves, Hasenclever, Osorio-de-Castro, & Oliveira, 2015). Brazil spent between USD 420 -519 million on 5 ARVs protected by revalidation patents. In 2007 a petition for unconstitutionality was filed to invalidate the mechanism, with the MOH stating ''the pipeline brings prejudice to the

development of the country and has a series of impacts on the Brazilian public health''(da Fonseca & Bastos, 2014).

On the other hand, the Brazilian Intellectual Property Law includes some flexibilities allowed under TRIPS to cope with the potential negative impact of patents on access to medicines. The main flexibilities implemented in Brazil were Compulsory Licensing and experimental use of patented inventions. Article 68 refers to Compulsory Licenses in case of abuse of economic power, including the case of 'non-exploitation of the object of the patent within the Brazilian territory for failure to manufacture or incomplete manufacture of the product.' Article 71 allows Compulsory License in case of 'national emergency or of public interest' and 'provided that the patent holder or its licensee does not fulfil such need.'(Urias, 2015).

Brazil included provisions allowing for experimental use of patented technologies. Article 43, item 2, exempts 'acts carried out by unauthorized third parties for experimental purposes, in connection with scientific or technological studies or researches.' In addition, Law 10,196/2001 has amended Article 43 to include a 'Bolar exemption'. This amendment provided that the patent holder cannot impede 'acts performed by non-authorized third parties, regarding patented inventions, which aim exclusively the production of information, data and test results directed to procure commerce registration, in Brazil or any other country, to allow the exploitation and commercialisation of the patented product.' This provides exemption from claims of patent infringement for those acts of making, using, or selling a patented invention which are reasonably related to seeking regulatory approval to market a drug, provided that no commercial use of a patented invention occurs before the patent expires(Urias, 2015).

5.5 Local Production

Between the end of the nineteenth century and the first decades of the twentieth century, Brazil faced a serious public health crisis caused by endemic diseases, such as yellow fever, smallpox and typhoid fever. In response to this, the government deployed a series of state-owned institutes to undertake R&D to produce drugs and vaccines to tackle these diseases (Frenkel et al., 1978; Bermudéz, 1992; Ribeiro, 2001).

As an unintended result of this public health policy, by 1940s, the Brazilian industry comprised science based organisations, especially from the public sector, which were very active in the research, development and production of high quality vaccines, serum and other biological products. The construction of a new facility for the Serviço de Medicamentos Oficiais do Brasil, in 1956, eventually became the Instituto de Tecnologia em Fármacos (Farmanguinhos) at FioCruz and this was an important milestone in the public production of drugs in Brazil. Farmanguinhos was designed to research, develop and manufacture chemical based solutions for diarrhoea, anaemia, and conditions caused by parasitic worms as well as painkillers, tranquilizers, sedatives and antidepressants. Since then, Farmanguinhos has played a central role as supplier of affordable drugs to the Brazilian public health system. By 2009, Brazil had 20 state-owned laboratories that manufactured 80 per cent of the vaccines and 30 per cent of the medicines acquired by the Brazilian public health system. However, these laboratories specialized in the formulation of medicines and relied on imports of active pharmaceutical ingredients (API), notably from India and China(Urias, 2015).

By the 1970s, some Brazilian companies had adapted to these conditions and reoriented their core competences towards drug formulation, marketing and

distribution. Such reorientation was facilitated by the IPR law of 1969, which did not allow patent protection either for pharmaceutical products or for their respective manufacturing processes. Indeed local companies deployed a business strategy based on the commercialization of branded-copies of existing products. The APIs required for these copies were imported from countries that also did not grant patents to pharmaceutical products at that time (such as Italy, Japan, Spain, Hungary, Bulgaria and Romania). Thus, local private companies became relatively strong in drug formulation and distribution but very weak in terms of in-house innovative capacity for drug development and imitative capacity for API production. At the beginning of the 1990s, the Brazilian pharmaceutical industry was still limited to activities related to drug formulation and marketing, and increasingly dependent on imports of APIs and intermediates(Urias, 2015).

The local production of ARV in Brazil started in the first half of the 1990s. In 1993, a small private laboratory named Microbiólogica was the very first local firm able to synthesize zidovudine (AZT), and, in 1994, LAFEPE became the first public laboratory to supply ARV to the Ministry of Health(Cassier & Correa, 2003; Reis et al., 2009). However, it was in 1997 that the cornerstone of local production started taking shape. At that time, Farmanguinhos was mobilized by the MoH to produce off-patented ARVs. Between 1997 and 2002 the volume of production at Farmanguinhos increased sevenfold, notably due to ARV production(Cassier & Correa, 2003). Of the twelve drugs supplied through the universal access programme at that time, eight were produced locally.

Nevertheless, neither Farmanguinhos nor other state-owned suppliers of ARVs have mastered the entire drug manufacturing process. They have specialized in the final production phase, i.e. formulation and packaging of drugs. These laboratories do not have manufacturing capabilities to produce their own raw materials and, therefore, depend on suppliers of APIs. Due to the lack of

competitiveness of local suppliers, more than 90 per cent of the public demand of the APIs needed to produce ARVs are supplied by Indian and Chinese firms(Orsi et al., 2003). However, Farmanguinhos and a handful of private laboratories developed imitative capabilities for reverse engineering the synthesis processes of the different ARVs, including patented second-generation ARVs (such as Efavirenz, Nelfinavir and Lopinavir)(Cassier & Correa, 2008). These capabilities became a central component in MoH's strategy of price negotiation with pharmaceutical MNEs.

5.6 Negotiations

Negotiations with Merck were held over 2 years and 16 meetings, during which the MoH demanded a similar price for EFV offered to Thailand of 288 PPPY, compared to the Brazilian price of USD 580 PPPY. Also quoted were lower prices of Indian generics to strengthen argument(Reis et al., 2009). Studies highlight Merck's inequitable pricing strategy encouraging over-reporting of incidence rates to avail discounts(Bate & Boateng, 2007). In 2005, the treatment combination consisting of zidovudine, lamivudine and efavirenz was the most widely used (47%) imported first line ARV(Ruiz et al., 2011).

Urias(2015) listed 14 episodes of Brazil's price negotiation for ARV medicines and illustrated a framework through an analysis of the price negotiations between MoH and Merck & Co. for the ARV Efavirenz with selected epidodes(i.e. Episodes 1A, 2A, 3B and 5)(Table 4).

Table 4 Brazil's negotiation episodes

Table 5-2. Price negotiations and their respective outcomes

	Drug	MNE	Year	Outcome	Δ Price
1A	Efavirenz	Merck & Co. (USA)	2001	Discount	-59%
1B	Nelfinavir	Roche (Switzerland)	2001	Discount	-41%
2A	Efavirenz	Merck & Co. (USA)	2003	Discount	-24%
2B	Lopinavir + Ritonavir	Abbot Labs (USA)	2003	Discount	-13%
2C	Nelfinavir	Roche (Switzerland)	2003	Discount	-10%
3A	Lopinavir + Ritonavir	Abbot Labs (USA)	2005	Discount	-46%
3B	Efavirenz	Merck & Co. (USA)	2005	Status Quo	0%
3C	Tenofovir	Gilead (USA)	2005	Discount	-51%
4	Atazanavir	BMS (USA)	2006	Discount	-7%
5	Efavirenz	Merck & Co. (USA)	2006	CL	-62%
6	Tenofovir	Gilead (USA)	2008	Discount	-14%
7	Tenofovir	Gilead (USA)	2008	Discount	-22%
8A	Atazanavir	Merck & Co. (USA)	2010	VL / Discount	-8%
8B	Raltegravir	BMS (USA)	2010	VL / Discount	-28%

Key: CL = Compulsory License; VL = Voluntary License

(Source : Urias (2015))

In the first two episodes (Episodes 1A and 2A), MoH's bargaining power was strengthened by support from the state-owned laboratories, which had developed expertise in Efavirenz production, a critical factor to improve BATNA as it would enable local production in case of Compulsory Licensing. Merck and MoH agreed on price reductions of 59% and 25% for Efavirenz in episodes 1A and 2A, respectively.

The situations changed in 2005 (episode 3B). Merck persuaded the Ministry of Development, Industry, and Trade (MoDIT) by presenting investment plans to be carried out only if a compulsory license was avoided. Merck started conversations directly with MoH. Besides that, the US Government was much more involved in this episode, especially because two other US-based Multinational Enterprises(MNEs) were also facing compulsory license threat for their ARV drugs. In fact, at some point, MoDIT took over the negotiation with

the pharmaceutical MNEs. Merck was able to confront MoH and stall the negotiation until a point that MoH had to succumb. The parties did not reach an agreement for a price reduction and no Compulsory License was issued.

There was another reversal in 2007(episode 5). Merck adopted the same strategy as in episode. This time, Merck's bargaining power was much weaker, especially because the support from US Government was not strong and the company' s efforts towards MoDIT did not affect MoH's decision to call for price reduction. On the other side of table, MoH was very well positioned thanks to Indian companies able to supply the needed drug for just a fraction of the MNE's price. At the same time, local companies were organised to assist state owned labs in the local production of Efavirenz. The Brazilian government issued a compulsory license after rejecting Merck's counter offer.

The negotiation episodes between MoH and Merck & Co. reveal many facets of negotiation. BATNAs enhanced by local state-owned laboratories played critical roles in the negotiation process alongside Indian generic companies. BATNAs widened the zone of possible agreement(ZOPA) by lowering Brazil's reservation price and made it difficult to reach agreements. When Merck successfully mobilized US government into the negotiation, it obviously turned negotiation process in favor of itself by potentially aggravating Brazil's reservation prices or enhancing bargaining power through perception(Wheeler, 2002). However, when Merck failed to present price cut in a timely manner, it suddenly lost its bargaining power and marekt for its product. What is important is that bargaining power not only depends on the intrinsic nature of the product and its potential impact.

5.7 Compulsory Licensing as a threat

Pushing negotiations armed with alternatives like local manufacturing and possible generic imports gives credibility to Compulsory Licensing threats which has been termed “the Brazilian Model”(Cherian, 2016). On the other hand, Compulsory Licensing increases the possibility of local production or generic imports by overcoming patent obligations. It.makes BATNA improved and real. Having established a reliable state funded generic manufacturing capacity for ARVs, the government promoted local production of ARVs, and generic procurement with a generic preference law in 1999. By 2001, 63% of ARVs were locally manufactured generics and 37% were patented drugs imported. Brazil was able to attain discounts varying from 40-70% using negotiations, with savings of 1.2 billion in ARVs using CL threats(Nunn, 2009) .

In 2005, after minimal discounts from negotiations, tenofovir and efavirenz were targeted for Compulsory Licensing. Tenofovir escaped Compulsory Licensing after earlier discounts offered by Gilead, but repeated threats without action failed to attain significant discounts from Merck and led to the Compulsory Licensing for efavirenz in the end. Together with market size brought about by sustainable NAP, industrial capacity buildup has strengthened the bargaining power of Brazil and lent credibility to Compulsory Licensing Threats(Shadlen & Fonseca, 2013).

After Merck declined to reduce the price by more than 2%, a Public interest declaration (Ministerial Ordinance 886) preceding the issue of a public non-commercial use license was announced on 27 April 2007, followed by Presidential decree 6.108 announcing the grant of the Compulsory License as prescribed by the Ministry of Health on 7 th May 2007(Cherian, 2016). Farmanguinos, the largest state-owned pharmaceutical manufacturer was

licensed to import and manufacture generic EFV. The license was non-exclusive, renewable and valid for 5 years. The established royalty rate was 1.5% of the purchase price of drug, to be paid by the Brazilian MOH. MOH received technical assistance from WHO with prequalification of 2 generic manufacturers and UNICEF providing transactional support. The 1 st batch of (3.3 Million 600MG Tablets) generic EFV was delivered in July 2007. Over the next 7 shipments, a total of 27 Million 600mg tablets were imported to supply local needs until local production began in 2009. Smaller amounts of 200Mg tablets were also imported to meet local needs(Viegas Neves da Silva, Hallal, & Guimarães, 2012).

5.8 Retaliations

The Brazilian provisions for compulsory licensing resulted in external pressure, especially from the United States Government and from PhRMA. In December 1998, PhRMA requested the United States Trade Representative (USTR) to list Brazil as a Watch List country on its annual 'Special 301' Report17. One year later, PhRMA submitted a complaint to the National Trade Estimate Report on Foreign Trade Barriers (NTE), concerning Brazil's limited intellectual property protection. In February 2000, PhRMA requested the USTR to list Brazil on its 2000 'Special 301' Priority Watch List. Finally, in May 1, 2000, the USTR ranked Brazil among the Watch List countries of its 'Special 301' Report. Finally, in early 2001, the USTR filed a complaint in the WTO Dispute Settlement Body and requested the establishment of a WTO Dispute Settlement panel, concerning article 68 of Brazil's patent law. However, after intense protests by the global AIDS movement and the subsequent negative repercussion, the United States withdrew its complaint(Love, 2007; Nunn, 2009; Urias, 2015).

5.9 Outcome

It was reported by the Brazilian MOH that they saved 58% or USD 104 Million from 2007 to 2012 from generic efavirenz imports alone. Generics were initially imported from Indian manufacturers (Ranbaxy labs, Aurobindo pharma), and later manufactured locally by 5 national firms : FarManguinhos-Rio, LaFepe-Pernambuco, Globequimica, Cristalia, and Nortec(Lago & Costa, 2009). Nationally produced generics were more expensive than imported generics due to R&D costs, and depended on imports of APIs from other countries which is vulnerable to currency valuation rate increases(Meiners, Sagaon-Teyssier, Hasenclever, & Moatti, 2011).

In 2008, MOH reported that a 98.4% of eligible patients (190,000 Patients) were accessing ART under the National AIDS program with access to comprehensive medical care, and blood testing. An estimated 75% of patients were on 1st line regimens using EFV. From 2007 to 2012, the number of patients using efavirenz increased from 72,816 to 96,944. In 2015, ANVISA set a maximum retail price for Stocrin (USD 8.03/Pill) and the Fiocruz Efavirenz (USD 1.48/Pill) for public distribution with price ceiling excluding local taxes. The Compuslory Licensing was renewed in 2012 and will expire in 2017(Cherian, 2016).

6. Malaysia : Government Use

6.1 Introduction

Malaysia exercised its first Government Use for HIV/AIDS in 2003. After 14 years, this country used the same measure for Hepatitis C in 2017. We can learn from this case how to use Government Use on what conditions. As one of TRIPS flexibilities, Government Use enables prompt policy response to urgent public heath issues. Particularly, given the high cure rate, high prevalence in middle-income countries and expensive prices of new Direct-acting antivirals(DAAs) medications against HCV, governments, originator companies, generic producers and civil organizations have actively participated in improving accessibility and Malaysian case can provide valuable model for further movements.

6.2 Background

In 2016, the total population of Malaysia was estimated at 31.7 million persons and Malaysia did not have a unified system of universal access to healthcare for its citizens. The healthcare system in Malaysia was a two-tiered system consisting of government funded public sector(65% of its population) and private sector. Malaysia's public health system was financed mainly through

general revenue and taxation the federal government, while the private sector was funded primarily through OOP payments and some private health insurance. Spending on health reached 4.6% of GDP, reaching 56% of total health expenditure (THE) in 2009. The main sources of THE in 2008 were the Ministry of Health (42%), followed by household out-of-pocket expenditure at nearly 34% (WHO, 2012).

Malaysia has a substantial pharmaceutical industry and the government offers tax incentives for research and development (R&D) and for the production of pharmaceuticals, related products and biotechnology. The Malaysian government claims that the country is well-placed to participate in global drug development given its good clinical infrastructure and qualified investigators(WHO, 2012).

In 2007, there were about 500,000 patients in Malaysia infected with Hepatitis C and 2,000 new cases were reported every year. To make matters worse, the cost of treatment for Hepatitis C was extremely expensive and making it less accessible to the patients. Hepatitis C is an infectious disease caused by the Hepatitis C virus (HCV) that spreads through blood contacts such as blood transfusion, needle sharing, and so on.

Before DAAs became available, hepatitis C treatment consisted of multiple injections over a period of up to one year and frequently caused severe side effects. Treatment was only successful 40-80% of the time. DAAs have transformed treatment options for patients and clinicians, but multiple barriers to access for patients exist, in particular, price. Since the approval of the drug in 2013, sofosbuvir's pricing and patents, and Gilead's tactics to monopolize markets have been at the centre of several controversies worldwide. As with the introduction and scale-up of antiretroviral therapy for HIV/AIDS over the past

15 years, new and innovative public health approaches to HCV treatment will require affordable access to DAAs(DNDi, 2016).

6.3 Government Use

The right of the state or government to use patents without the consent of the patent holder is a standard feature of patent laws in many countries. Such use of patents by the government is viewed in common-law countries as an eminent domain taking of a license under the patent and thus, not an infringement of the patent. Many patent regimes provide for government use of patents without the need to grant a compulsory license. In such cases, a determination by a government agency or Minister is generally required to attest that the government use is justified and is within the terms of the national law. These government rights are usually framed in broad terms and are often subject to less procedural requirements than are compulsory licenses(Musungu, Oh, & WHO, 2006).

The TRIPS Agreement, although not specifically mentioning Government Use, recognizes such use by its references to the concept of public, non-commercial use and of patents “used by or for the government”. Where the state or a state agency uses patents without the consent of the patent holder, it is, like compulsory licensing, covered under Article 31. The distinction between government-use provision and compulsory licensing primarily relates to the nature or purpose of the use of the patent. Government Use is limited to “public, non-commercial purposes”, whereas compulsory licences can also cover private and commercial use. Another difference is the waiver of the requirement for the government or its authorized party to first seek a voluntary license. This waiver

provides a considerable degree of flexibility and allows for speedier action. As with compulsory licences, government-use orders can be used to cut down the prices of medicines, to secure a sufficient supply, and manage emergency situations(UNAIDS, 2011).

In addition, there may be further flexibility inherent in the term given that there is nothing in the TRIPS Agreement to prevent different ways of defining the term. In this case, the word "public" could be interpreted as referring to the purpose of the use, so that even a private entity charged with exploiting a patented invention for the benefit of the public would also come within the scope of "public, non-commercial use". Referring to both government use and compulsory licensing, the World Bank in its technical guide on procurement of ARVs, describes them as "principal means enabling procurement authorities to overcome patent barriers to obtaining lower priced generic medicines and related supplies" (Musungu, Oh, & WHO, 2006).

6.4 Malaysian Patents Act

Under the TRIPS Agreement, governments can utilize patents to facilitate access to affordable medicines. In compliance with the TRIPS Agreement, Section 84(1) of the Malaysian Patents Act provides for the "Rights of Government":

"Nothwithstanding anything contained in [this] Act –

(a) where there is national emergency or where the public interest, in particular, national security, nutrition, health or the development of other vital sectors of the national economy as determined by the Government, so requires; or

(b) where a judicial or relevant authority has determined that the manner of exploitation by the owner of the patent or his licensee is anti-competitive,

The Minister may decide that, even without the agreement of the owner of the patent, a Government agency or third person designated by the Minister may exploit a patented invention."

The patent owner shall be notified of the Minister's decision "as soon as is reasonably practicable". Section 84(3) provides for "the payment to the owner of the patent of an adequate remuneration".

The Ministry of Domestic Trade and Consumer Affairs is responsible for intellectual property in Malaysia, and the administration of the Patents Act 1983. The examination and granting of applications for patents and other intellectual property claims lies with the Intellectual Property Corporation of Malaysia.

Sections 48 to 54 provides for compulsory licenses (there is a prescribed form under the Act for applications for a compulsory license). Sections 37(2) and 58A provide for parallel import, based on the international exhaustion of rights principle. Section 84 provides for the "Rights of Government", the term for "Government Use" in the Patents Act.

6.5 The first Government Use in Malaysia

In 2003, Malaysia became the first country in Asia following the adoption of the Doha Declaration to issue a Government Use license. There were 59,000 people in Malaysia infected with HIV, only 6,000 have gone for follow-up

treatment in government hospitals, and up to a few years ago only 1,500 of the estimated 4,000 HIV-positive people on the verge of developing full-blown AIDS were receiving treatment. The challenge to treat HIV/AIDS victims was big (Sunday Star, 4 July 2004).

The health authorities initiated the measure after considering various options(i.e., between compulsory licensing and government-use). The Government-Use authorization was initiated by the Ministry of Health (MOH) and the license was issued by the DTCA. In November 2002, the MOH presented a paper to the Malaysian Cabinet with a recommendation to import generic ARV drugs, under a section in the Patents Act that allowed the Minister to exploit a patented invention where it is required by the public interest. The Cabinet approved the import on the basis of this provision.

The Government Use authorization was for the import of generic versions of patented antiretrovirals or ARVs (to treat AIDS) from the Indian company Cipla for use in government hospitals and clinics. The authorization, which was for a period of two years beginning 1 November 2003, was obtained from the Ministry of Domestic Trade and Consumer Affairs (DTCA) for the import of AZT, ddI and Combivir.

According to Khor (2010), the average cost of MOH treatment per patient per month dropped significantly from 2001 (before the government-use measure) to 2004, as can be seen from Table [6].

Table 5 Malaysia: Comparison of cost of treatment per patient per month before and after import of generic ARVs under a government-use order

Treatment	2001 price for patented ARV (US$)	2004 price for patented ARV (US$)	2004 price for generic ARV (US$)	Percentage of cost reduction
Stavudine + didanosine + nevirapine	261.44	197.10	45.32	83%
Combination of zidovudine and lamivudine + efavirenz	362.63	136.34	115.14	68%

(Source : Ministry of Health, Malaysia)

For one combination of drugs (stavudine, didanosine and nevirapine), the cost of treatment per patient per month fell from US$261 (for the patented ARV) to US$45 (for the generic ARV), an 83% decline. For another combination of drugs (zidovudine and lamivudine and efavirenz), the cost fell from US$363 to US$115, or a decline of 68%.

Also as a result of the exercise of the right of Government Use, the patent holders dropped their own prices, leading to considerable reduction in the cost of treatment, which encouraged the MOH to consider free treatment for more people who needed treatment. Previously, free treatment had only been provided to a few selected categories of patients. In addition, the number of patients that could be treated in government hospitals and clinics increased from 1,500 to 4,000, according to the MOH.

In June 2004, the MOH began prescribing the imported generic medicines, which were distributed through government hospitals. Then Health Minister Dr Chua Soi Lek announced on 6 June 2004 that the monthly cost of treating a patient would be reduced from RM1,200 to RM200-220, after the drugs were imported from India. “With the cheaper cost, we can treat at least 4,000 HIV patients compared to the present 1,500,” he said(The Star, 7 June 2004).

6.6 Developing BATNA

6.6.1 Voluntary Licensing

Gilead excluded Malaysia from its voluntary licenses on sofosbuvir in 2014 and entered protracted price negotiations with the government and reportedly refused to agree to any amount below USD 12,000 for a 12 week course of treatment(generic prices are close to USD 300)(Hepcoalition, 6 Oct 2017). Malaysia and Thailand were among the many middle-income countries that were excluded from the voluntary licensing agreements that Gilead and Bristol-Myers Squibb, the intellectual property holders of the hepatitis C drugs sofosbuvir and daclatasvir, respectively, concluded with generic companies. Of the up to 150 million people infected with chronic hepatitis C globally, approximately 75% lived in middle-income countries. The negotiated price remained out of reach for the majority of Malaysians and beyond the capacity of the health budget of the country. Given no voluntary licensing and unsuccessful price negotiations, Malaysia had to look for other alternatives(DNDi, 2016).

6.6.2 Generic manufacturers

Governments and generic companies in countries like Egypt — where millions live with the virus and suffer from symptoms such as cirrhosis, liver failure and cancer — developed a strong political will to make and market low-cost DAAs. They changed the way people think about quality generics. The Egyptian patent office found — after a technical examination of the sofosbuvir compound — that it is not novel chemically, and, therefore, does not fulfil the criteria of novelty

and inventiveness, both of which are necessary for a pharmaceutical compound to be patented(Businessline, 16 May 2016).

Several NGOs filed patent oppositions on some patents for sofosbuvir and other DAAs, arguing that these do not fulfil the necessary conditions of inventiveness and novelty. Patent opposition cases were filed in several countries: Argentina, Brazil, China, India, Russia, Ukraine, and the European Union. While most oppositions have targeted the primary patents for sofosbuvir, patents covering daclatasvir and velpatasvir have also been opposed. These interventions have led to the rejection of some key patent applications for sofosbuvir in Brazil, China, Egypt and Ukraine(WHO, 2018).

TRIPS establishes three criteria for granting a patent: novelty, inventive activity and industrial application. However, the agreement does not offer a precise definition of these criteria, leaving a margin of interpretation for the national legislatures in WTO member countries. India, for example, has used the TRIPS flexibilities to strengthen the patentability criteria, thereby facilitating local production of generic drugs and increasing the population's access to essential medicines while at the same time complying with WTO regulations(ISGLOBAL, 2016).

Egyptian and Bangladeshi manufacturers launched the generic versions of sofosbuvir ahead of Indian companies in early 2015. Indian manufacturers — which have a reputation for their reverse engineering skills and were the first to market low-cost versions of life-saving cancer (imatinib) and HIV drugs (zidovudine) within two-three years of their US launch at the turn of the century — now face competition from Egyptian and Bangladeshi manufacturers. Clearly, their governments were backing them using flexibilities available under WTO rules(Hepcoalition, 6 Oct 2017).

With relevant patents rejected in Egypt, Egyptian generic companies could manufacture medications, which they can export. Countries where patents are not approved or compulsory licensing are issued can import from those companies. Otherwise, countries issuing compulsory licenses should look for exporters which should issue compulsory licenses under Paragraph 6.

6.6.3 Developing new medication

According to DNDi's press release, in April 2016, the Drugs for Neglected Diseases initiative (DNDi) and the Egyptian drug manufacturer Pharco Pharmaceuticals signed agreements covering the clinical testing and scale-up of a hepatitis C treatment regimen, which can treat all strains, or 'genotypes' of Hepatitis C at a price of just under $300.

DNDi launched clinical trials to test a combination treatment of the drug candidate ravidasvir and the registered hepatitis C drug sofosbuvir in pan-genotypic patient populations in Malaysia and Thailand. Ravidasvir is one of a new generation of direct-acting antivirals (DAAs) that are revolutionizing the treatment of hepatitis C. In a Phase III clinical trial in Egypt, conducted by Pharco, ravidasvir showed cure rates of up to 100% in patients with genotype 4 when used in combination with sofosbuvir, which also is a DAA.

DNDi licensed rights for ravidasvir in low- and middle-income countries from Presidio Pharmaceuticals. Pharco agreed to supply DNDi with the combination sofosbuvir plus ravidasvir for its clinical studies for $300 per course of treatment. For the scale-up of this regimen, once approved, Pharco has agreed to set the commercial price at $294 or less per treatment course.

DNDi's Phase II/III studies in Malaysia and Thailand would be conducted with the full cooperation of both governments and compare sofosbuvir plus

ravidasvir with a current standard of care, sofosbuvir plus daclatasvir. These studies planned to enroll approximately 1,000 participants and will evaluate the efficacy, safety, and pharmacokinetics of the sofosbuvir plus ravidasvir combination in patients with various levels of liver fibrosis, various genotypes, and with/without HIV co-infection.

Once these trials had been successfully completed and the safety and efficacy data of this combination assessed, governments could be encouraged to design their national health strategies to use all options at their disposal to gain access to life-saving DAAs, including price negotiation, voluntary licensing, or the use of TRIPS flexibilities such as patent oppositions and compulsory licensing. They can improve their BATNA with this potential new drug and Government Use or compulsory licensing would make it possible.

6.7 The second Government Use

As of 20 September 2017, Malaysia's Ministry of Health officially announced Government Use on the key hepatitis C drug, sofosbuvir. This was expected to neutralize Gilead Science's monopoly in the country, opening the door to robust generic competition to bring prices down. Government could afford to procure optimal treatment for people living with hepatitis C in Malaysia.

YB Datuk Seri Dr. S. Subramaniam, the Minister of Health, Malaysia said from press statement.

"As Hepatitis C has become a major public health concern in Malaysia, it is crucial to increase access to its treatment for the benefit of the nation. Therefore, the Cabinet has approved the use of Rights of Government under

Patent Act 1983 (Act 291) by exploiting the patented invention of Sofosbuvir tablet 400mg. The last time Malaysia instigated the Rights of Government was in 2003 for anti-retroviral drugs (treatment for HIV infection). This sets Malaysia to be the first country to initiate such move in the world."

"The decision to initiate the Rights of Government was made after the MOH efforts to be included in the Medicine Patent Pool (MPP) and price negotiations with patent holder were unsuccessful. Through the implementation of The Rights of Government, the cost of treatment will be lower and more patients can be treated. At the same time, access to treatment can be improved to achieve the Sustainable Development Goals (SDG) target set by the United Nation (UN) and targets of the World Health Organization's Global Health Sector Strategy on Viral Hepatitis 2016-2021 to eliminate viral hepatitis as a major public health threat by 2030."

In August 2017, US company Gilead, which holds the patent to Sofosbuvir, announced that Malaysia would now be included in the company's own licensing scheme allowing some generic versions to be sold locally. Under the scheme, Gilead signed agreements with some Indian drug companies to make and sell Sofosbuvir in about 100 countries, but Malaysia was excluded with some other countries including Egypt at that time.

The decision to issue a Government Use license seems to be the main reason why the firm was then including Malaysia. It might hope that the Government would now find it unnecessary to have a Government Use license and reverse its decision or use such a late inclusion into voluntary licensing as a rationale for retaliatory and preventive movement against similar moves by other countries. This seems to be the same mistake Merck made in Brazil case. By losing bargaining power due to failing to propose voluntary licensing(VL) in a

timely fasion, Gilead lost sizeable markets, which could impact other potential markets excluded from the VL list like Malaysia.

Giving up on the Government Use would be compromising Malaysia's bargaining power. There are limits to what Malaysia can import or produce under the voluntary license provided by Gilead, which restricts the list of generic firms it can work with. Malaysia would have to reach agreements only with the Indian companies under Gilead's voluntary licensing. This would endanger the project by which DNDi and the Egyptian company can supply Malaysia with a suitable combination drug at affordable prices. Malaysia would see no reason to jeopardize a chance to critically improve their BATNA. Given VL proposed by Gilead, Malaysia can have both the government-use license and utilization of the company scheme, as one does not preclude the other. So they can have the best of both(The Star, 11 Sep 2017).

The government should still take the follow-up measures needed by issuing the government-use license, completing the clinical trials, negotiating with the Egyptian generic producer for the lowest possible prices, and rolling out the new Hepatitis C medicines.

6.8 Retaliation

Since the announcement of Government Use, big pharmaceutical companies had been pressuring Malaysia to retract its position, arguing that it discourages innovation. They claimed Malaysia risked being put on the US Watch List on IP-related trade barriers. This behavior seems to protect their bargaining power

preparing for future negotiations with Malaysia or any other countries by raising their potential cost when not being compliant with patent holders' agenda.

The Pharmaceutical Research and Manufacturers of America (PhRMA) urged the US Trade Representative (USTR) to take action.

"The Malaysian government has approved what it is characterizing as a government use license for a breakthrough innovative medicine. This action could cause serious harm to a U.S. manufacturer that was engaged in ongoing negotiations with the Government of Malaysia on a voluntary license at the time this compulsory license was unilaterally issued. Additionally, if not met with a forceful U.S. Government response, this action carries significant risks of contagion to other markets, which would significantly undermine the current R&D model for innovative medicines on which the U.S. pharmaceutical industry and patients around the world rely.

... For these reasons, PhRMA requests that Malaysia be designated a Priority Foreign Country in the 2018 Special 301 Report, and that the U.S. Government continue to seek assurances that the problems described herein are quickly and effectively resolved."(PHRMA, 2018)

US-based NGO Public Citizen defended the countries using compulsory licensing, saying that issuing the license does not override a patent right and the right reserved by the Government to make use of an invention is embedded in the initial grant of every patent. They also pointed out that the patent owner could still sell the medicine, and retain the exclusive right to sell to private providers and hospitals.

6.9 Outcome

As of 13th November 2017, Malaysian pharmaceutical company Pharmaniaga Logistics Sdn Bhd(Pharmaniaga), Egyptian pharmaceutical company Pharco Pharmaceuticals(Pharco) and non-profit research and development organization Drugs for Neglected Diseases initiative(DNDi) signed a collaboration agreement to supply a new hepatitis C treatment regimen to be sold for US$300 in the public sector in Malaysia.

In partnership with the Malaysian Ministry of Health, DNDi was currently running clinical trials testing a potentially pan-genotypic treatment, combining the drug candidate ravidasvir, produced by Egyptian drug manufacturer Pharco Pharmaceuticals, with the existing hepatitis C medicine sofosbuvir. The clinical trial was ongoing in six hospitals and co-sponsored by the Malaysian Ministry of Health, with initial results expected in early 2018.

The agreement covered the supply of ravidasvir, once approved in Malaysia, and supply of sofosbuvir. A Government Use license issued by the Malaysian Ministry of Domestic Trade, Co-operatives and Consumerism in September 2017 enabled the importation of generic sofosbuvir in order to make this drug available in the public health system throughout the country at affordable prices.

In March 2018, the combination of sofosbuvir and daclatasvir was made available in stages at all 18 government hospitals nationwide. While sofosbuvir requires a compulsory licensing, daclatasvir does not, because the manufacturer did not apply for patent rights in Malaysia and the Government did not grant data exclusivity to it on public health grounds. Without the patent barrier, the Government is able to buy generic daclatasvir.

Using a new medication and generic sofosbuvir, researchers reached 97% sustained virologic response in patients with hepatitis C both with and without cirrhosis; Drugs for Neglected Diseases Initiative (DNDi) addresses the impact of this research in April 2018.

In the late-breaking poster presented at ILC 2018, DNDi showed data from 300 patients with a variety genotypes, cirrhosis status, HIV coinfection and prior exposure to HCV treatments. These patients received sofosbuvir and ravidasvir, both medicines produced by Egyptian drug manufacturer Pharco Pharmaceuticals, for 12 weeks if without cirrhosis and 24 weeks if with compensated cirrhosis.

Overall, SVR12 was reached in 97% (95% CI: 94.4-98.6). Cure was achieved in 96% of those with cirrhosis, 97% of those with HIV, 97% of those with genotype 3 and 96% of those exposed to prior treatment.

7. Rwanda-Canada : Paragraph 6 System

7.1 Introduction

Doha Declaration brought about tremendous changes to the ways of overcoming patent related barriers experienced by underdeveloped and developing countries. Many cases utilizing TRIPS flexibility followed. Particularly, Paragraph 6 addressed a critical barrier as it opened ways for countries without proper local manufacturing capacities to utilize compulsory licensing as proven in Rwanda/Canada case. Although there has been no additional case under Paragraph 6 system, changing environments related to patents will increasingly require this measure for successful access strategies. Particularly, this Canada-Rwanda deal provides valuable lessons regarding the strengths and weaknesses of the Paragraph 6 System

7.2 Background

Rwanda is one of the few African nations that have successfully implemented a Universal Healthcare Coverage system (UHS) that includes universal ART access, as part of legislative reform in 2000. With a relatively low GDP spending of 5% on health, the Rwandan healthcare system sets an example for successful healthcare system in resource limited settings. Following genocide in 1994,

rebuilding has allowed a basic universal healthcare system to be established, ensuring basic care to 90% of the population, primarily targeting 60% of the population living below the poverty line(Cherian, 2016).

The Mutuelles de santé insurance system uses a pooling strategy to ensure coverage, using tiered copayments across income groups. From 2007-2009, the Community Based Health Insurance (CBHI) coverage had increased from 75 to 86 % of the population (MOH, 2010). With an overall prevalence rate of 3% the HIV burden weighs heavy on the healthcare budget. Rwanda has successfully implemented universal coverage for HIV/AIDS patients by integrating the National AIDS Program into its UHS. Rwanda's AIDS program has replicated success similar to high income settings due to the holistic approach taken towards treatment of HIV, raising life expectancy by 81% (Nsanzimana et al., 2015). PEPFAR reported that 92 % of eligible patients received free ART by 2011 with very low rates of attrition(Cherian, 2016).

Out of Rwanda's population of approximately 9.3 million people, an estimated 200,000 were infected with HIV or AIDS. As of late 2007, only 44,395 of those infected were receiving anti-viral treatment. Without anti-viral drugs, HIV proAIDS gresses to much more rapidly. The onset of AIDS often prevents the infected from working, exacerbating Rwanda's cycle of poverty. In addition to the many Rwandans suffering from HIV and AIDS infection, there are estimated to be over 200,000 children who have been orphaned due to the AIDS epidemic. Therefore, war-torn Rwanda is in need of access to inexpensive anti-viral drugs in order to prolong and enhance the lives of the sick and of their families.

Rwanda's AIDS crisis is compounded due to the nation's inadequate medical resources. There is only one physician for every 60,000 people in Rwanda, and only thirty hospitals in the entire country. In contrast, the United States has one doctor for every 400 people. The lack of doctors and hospitals makes

distribution and patient follow-up very difficult. Therefore, Rwanda needs an advanced infrastructure in place in order for the Paragraph 6 Agreement with Canada to be effective(Cotter, 2008).

The HIV/AIDS generic treatments were not affordable even at their competitive price to the majority of Rwandan people. While the GDP per capita of Rwanda is approximately $1000 per year, the majority of Rwandans live below the poverty line, earning approximately 250 Rwandan francs per day, which amounts to approximately $157 per year or $ 0.43 per day. The cost of brand-name antiretroviral treatment ($10,000 per year) is even higher. By the end of 2008 the WHO estimated that about 58% of people who need treatment in sub-Saharan Africa are not receiving it. Income disparity tends to exaggerate the problem of prohibitively expensive treatment in many countries with the greatest need for antiretroviral medicine(Chung, 2010).

7.3 Paragraph 6 System

7.3.1 Why is Paragraph 6 needed?

Pharmaceutical production is concentrated in some high income and large developing countries. Many countries have no production capacity at all. The reason the TRIPS rules from 1995 had to be changed was that they only allowed compulsory licenses for the domestic market. Countries without domestic production capacity of medicines could not use them. Nor was it allowed for countries with production capacity to grant compulsory licenses for export to countries without such capacity. Countries without local production capacity and proper imports have no alternative to expensive branded medicines under

patent protection. Paragraph 6 System is basically a platform to newly create BATNA for such countries.

The Doha Declaration on TRIPS and Public Health of 2001 acknowledged this problem, and two years of high profile negotiations to define the solution followed. The new rules were adopted in 2003. They allow WTO members to grant compulsory licenses for medicines to be exported to developing countries with grave public health problems and insufficient domestic production capacity. Both developing and high income countries may be exporters. A number of steps must be taken by both importer and exporter. There are several safeguards intended to prevent re-exportation of the medicines, as this would undermine prices on other markets.

7.3.2 When is Paragraph 6 system used?

Importers shall only use the new rules when the medicine is patented in the exporting country (the location of the new producer) – see the [Table 7] below. When the medicine is patented in the importing country, but not in the exporting country, the importer may instead use a “regular” compulsory licensing. Thailand and Brazil used this option in 2006 and 2007. The exporting country in their cases was India, where there were no patents on the products in question.

Table 6 When to use Paragraph 6 System(Decision)

		Importing country	
		Product patented	Product not patented
Exporting country	Product patented	The new rules are used Both countries grant compulsory licences.	The new rules are used Only exporting country grants a compulsory licence.
	Product not patented	The new rules are *not* used The importing country grants a "regular" compulsory licence for import. (The option used by Thailand and Brazil)	The new rules are *not* used Regular import from any manufacturer

(Source : National Board of Trade (2008))

It is not clear if Rwanda had patent in place for the drug, but Canada had patents in place. So, regardless of Rwanda issuing compulsory licensing, Paragraph 6 System should have been used to allow Canadian company to export generic to Rwanda unless Rwanda had other legitimate exporters.

7.3.3 How to use Paragraph 6 System

The Paragraph 6 specifies a process for using the system. It involves maximum five parties: the importing country, the agent/company in the importing country, the relevant authority in the exporting country, the exporting company and the WTO. National Board of Trade (2008) presented the following schematic view of all the steps that must be taken before the pharmaceuticals can reach the importer.

Table 7 How to use Paragraph 6 System

Importing Member/company	Exporting Member/company
Recognition of a public health problem requiring pharmaceutical product(s) that	

• cannot be produced domestically and • is patented in producing countries	
If product is patented domestically: • negotiate for a voluntary license from the patent holder – can be waived in cases of government use, national emergency, extreme urgency, anticompetitive practices if national rules allow • If negotiations fail – seek and obtain a CL, as regulated by article 31	
Country notifies the WTO of intention to use system as an importer 42 Not required for LDCs	
Country/agent notifies the WTO of • product's name and expected quantities • grant or intention to grant a CL, if there is a domestic patent in force • confirmation of no or insufficient manufacturing capacity – Not required for LDCs	
	Since the product is patented, the exporting company must • negotiate for a voluntary license from the patent holder – can be waived in cases of government use, national emergency, extreme urgency, anticompetitive practices if national rules allow • If negotiations fail – seek and obtain a CL, as regulated by article 31
	Relevant authority grants a CL for the product(s) and quantity needed, for the country(ies) that notified

	Exporting company identifies product as produced under the system through labelling or marking
	Exporting company discloses quantities, destination(s) and distinguishing features on a website
The remuneration obligation is waived for importing country	Exporting company pays adequate remuneration to patent holder
	Relevant authority notifies the WTO of the CL and its conditions and the information posted by company
Country takes reasonable measures to prevent reexportation of product	

7.4 The Canadian Access to Medicines Regime (CAMR)

Shortly after the implementation of the Decision of the General Council of 30 August 2003(“Decision”), the Canadian government responded to pressures by Canadian civil organizations and the UN Special Envoy on HIV/AIDS in Africa by committing, in September 2003, to enact Canadian legislation, enabling compulsory licensing for export to developing countries and LDCs.

In May 2004, Canada amended its patent laws to reflect the WTO decision, becoming one of the first member nations to do so. These amendments were codified in Canada's Access to Medicines Regime ("CAMR") which allows the production and export of generic drugs to developing countries without the permission of the patent holder in connection with the TRIPS Agreement. CAMR provisions are contained in Section 21 of the Consolidated Statutes of Canada as part of the Patent Act. The CAMR legislation sets forth the process for obtaining a compulsory license for export and compliance with CAMR is

governed by the therapeutic products directorate of Health Canada, the agency to which a manufacturer applies for export authorization under CAMR(Tsai, 2008).

CAMR has its own application process that is more demanding than the WTO process outlined in Article 31 of the TRIPS Agreement. This has led to much criticism from developing countries and generic manufacturers alike(Cotter, 2008). Due to CAMR's complicated nature, it took nearly four years for Rwanda to implement the regime. Unlike the process under TRIPS alone, CAMR requires the generic producer to attempt to get a voluntary license from the patent holder before Canada can issue a compulsory license.

The three pharmaceutical companies that held patents for the anti-viral drug that Apotex wished to produce-GlaxoSmithKline, Shire, and Boehringer Ingelheim-were unwilling to give Apotex a voluntary license. To comply with CAMR, Apotex attempted to negotiate with these pharmaceutical companies for over a year without success. Only when Rwanda notified the WTO of its intention to declare a national emergency in July 2007 did Canada finally grant a compulsory license to Apotex despite the resistance of the patent owners. Additionally, before the life-extending drugs could be shipped, CAMR required Apotex to create a website providing information about the generic drug specifically surrounding its packaging in order to prevent illegal diversion to other markets besides Rwanda. This website was completed in early 2008, and therefore Apotex has fulfilled its duties under CAMR(Cotter, 2008).

7.5 Law on Patents 1963

Rwanda is party to a number of international agreements dealing with IP. Most notably, the country is a member of the WTO and thus a signatory to the TRIPS Agreement. Rwanda, however, was not obliged to comply with the standards set by the treaty until 2013. Furthermore, the East African State need not provide patent protection for pharmaceutical products until 2016. In 2011, the East African state acceded to the Patent Cooperation Treaty (PCT) and became a member of the African Regional Intellectual Property Organization (ARIPO). When Rwanda imported medicines under the Canadian Access to Medicines Regime (CAMR), patent law in the country was regulated by the Law on Patents 1963 and a ministerial decree putting the said legislation into effect. The 1963 Act obviously did not implement the TRIPS Agreement(Nkomo, 2013).

7.6 Negotiations

The Paragraph 6 System has been used only once, by the trade of Apo-TriAvir from Canada to Rwanda. The Canada-Rwanda deal would not have been possible without the initiative taken by the Canadian government to change its legislation. Additionally, Apotex, a Canadian generic drug producer, took an active role in the transaction by agreeing to supply Apo-TriAvir to Rwanda(Chung, 2010). Nevertheless, this Canada-Rwanda deal revealed the strengths and weaknesses of the Paragraph 6 System as specified under the Decision of 30 August 2003 while showing various negotiation elements to consider.

There were prior initiatives to use Paragraph 6 System before Rwanda case. All of them employed the Canadian application of the system. The first was an abortive attempt by the NGO Médecins Sans Frontières/Doctors without borders (MSF), acting on behalf of a country, not known which. The second came on the initiative of Ghana. The third began in July 2007 when Rwanda notified its intention to use the system to the WTO. Neither MSF nor Ghana came so far in the process as to send in notifications(National Board of Trade, 2008).

When MSF committed itself to test the new law. In December 2004, the Canadian company Apotex agreed to produce a fixed-dose combination of the three HIV/AIDS drugs zidovudine, lamivudine, nevirapine later to be known as TriAvir. Nine Canadian patents were related to the drugs. Four of these were owned by the Glaxo Group, two by the Wellcome Foundation, two by Shire Biochem and one by Boehringer Ingelheim and Dr. Karl Thomae GmbH. A similar combination drug did not exist in Canada(Hestermeyer, 2007).

As the Canadian Patent Act originally did not include fixed-dose combinations of zidovudine, lamivudine, and nevirapine, it had to be amended in September 2005. Health Canada finally approved Apo TriAvir almost a year later in August 2006, when the process was still not finished and no pills had been exported. Apotex failed to fulfill the requirements for a compulsory license because there was no importing country. No developing country government MSF worked with was willing to be named, possibly because of the criticism that Brazil and Thailand encountered after their compulsory licenses(Hestermeyer, 2007). The MSF argued that the experience showed that the Decision is not the “expeditious solution” mandated in the Doha Declaration. While the process went on, two Indian companies received WHO prequalification and approval by the US government respectively for copies of the same combination medicine. MSF started buying these copies instead and abandoned the effort in Canada(National Board of Trade, 2008).

For the second application of the mechanism, in collaboration with two Canadian NGOs, Ghana expressed an interest to use the Canadian law to import generics, both for itself and as a regional importer to the benefit of the ECOWAS countries. Ghana had issued a regular compulsory licensing in 2005, and thus had experience with the instrument. The Ghanaian law was revised, but there was never a notification to use the system(National Board of Trade, 2008).

On the other side, as a procedural requirement of the CAMR, Apotex approached the patentees to negotiate voluntary licenses. Shire Pharma, Glaxo Welcome, and Boehringer Ingelheim agreed to issue voluntary licenses under conditions deemed unfeasible by Apotex, including providing tracking information to prevent diversion to non-eligible countries. Apotex claimed that the patent holders were intentionally stalling the negotiations, although the patent holders denied. In its press release of September 20, 2007, Apotex claimed: "In the end, GSK and Shire did not oppose the application, but chose not to grant a voluntary license, requiring Apotex to navigate the complexities of the CAMR. Boehringer Ingelheim was also not prepared to freely grant a license."(Cherian, 2016)

After negotiations were unsuccessful, the Apotex approached the Canadian patent office for compulsory licensing for export (Rimmer, 2008). It was granted a compulsory license on September 20, 2007. The refusal to voluntary license under reasonable conditions was replaced by non-assert clauses which required further formalities by the CAMR. In October 2007, Canada notified the WTO of the grant of the compulsory license and of its intention to export Apo TriAvir to Rwanda. Apotex did not actually receive Rwanda's final tender approval-winning the bid to supply Rwanda with the generic drug-until May 2008, and the first and only package of Apo TriAvir to reach Rwanda to date was shipped on September 23, 2008, more than five years after the WTO's implementing

decision(Tsai, 2008). The multiple patent holders contributed to overall delays in the procurement process(Cherian, 2016).

Rwanda could have imported a similar combination drug from India, which was available at $0.14 per tablet and not yet affected by India's new patent legislation. It would only have had to impose a compulsory license in its own territory, and possibly not even need this step, as it is not clear whether any of the nine inventions have been patented in Rwanda(Hestermeyer, 2007). Noteworthy is the fact that Rwanda could have wholly avoided using the 30 August mechanism because the same combination that it sought to import from Canada was also available at comparable cost from India where the three drug components are not under patent protection(Ndlovu, 2009). The Rwandan government might have been rethinking their use of the Canadian system on this ground. According to a Rwandan newspaper, the responsible minister said that there was no finalised deal with Apotex, and that they would buy from the cheapest source, as long as the medicines were of the same quality(National Board of Trade, 2008).

It took more than a year for a shipment to be delivered after Rwanda first notified the WTO of its intention to import Apo TriAvir. Apotex's uphill battle shows only part of the difficulties that CAMR poses for similar prospective generic manufacturers seeking to manufacture for export. Unless these procedural complexities are eliminated, CAMR, in its present form, would not be able to deliver on the humanitarian objectives of the TRIPS Agreement(Tsai, 2008). Despite Apotex's allegedly philanthropic intentions, it faced many legal challenges from the patent holders, which further inhibited the process(Cotter, 2008). From Rwandan perspective, they had chances to improve BATNA from multiple choices such as indian generic drugs and Canadian producer, but cumbersome process of the current implementation of Paragraph 6 System compromised such bargaining power.

7.7 Compulsory Licensing

On July 19, 2007, Rwanda became the first country to notify the WTO of their intention to use the Decision. Also in this case the exporter was the Canadian company Apotex and the product was the same combination product to treat HIV/AIDS that Apotex had developed for the MSF. Rwanda reserved the right to modify the amount, as it was impossible to predict needs with certainty(National Board of Trade, 2008).

Rwanda informed the TRIPS Council that based on its evaluation of its public health needs, it would import during the next two years 260,000 packs of the fixed-dose combination TriAvir, manufactured by Apotex. A unique feature of the notification is that it specifies that since it was not possible to give a certain prediction on the extent of Rwanda's public health needs, the country reserved the right to modify their estimate specified in the notice as necessary or appropriate. It is difficult to imagine how Rwanda proposed to "modify their estimate specified in the notice as necessary" because if such a modification exceeded what was specified in Apotex's compulsory license, then it would mean a new compulsory license which would have to go through the same cumbersome process. It must be noted that a renewal of the license can only be granted where the drug specified has not been manufactured or exported in its entirety(Ndlovu, 2009).

The notice also specified that, pursuant to paragraph 7 of the Doha Declaration, Rwanda would not enforce rights provided for in Part II Section 5 of the TRIPS Agreement that may be granted within Rwanda's territory with respect to the drug(s) intended to be imported. This particular point is important because if a patent exists for the drug intended for importation, the importing country is supposed to also issue a compulsory license. However since

LDCs are excluded from the obligation to grant patent protection as stipulated by the 2002 Decision extending their transition period then the requirement of also issuing a compulsory license also falls away, provided of course the LDC has not granted a patent for that product(Ndlovu, 2009).

After Rwanda notified compulsory licensing, on 19 September 2007, Apotex filed for and obtained a two-year-compulsory license on the nine Canadian patents for manufacturing 15.6 million tablets and exporting them to Rwanda. The Canadian Intellectual Property Office granted the license and subsequently notified it to the WTO. Canada notified the Council for TRIPS of the license on October 4, 2007. The license allowed manufacture and delivery of 15.6 million pills of the requested product to Rwandan health authorities. According to one source it will be enough to treat 21,000 patients for one year(Hestermeyer, 2007).

7.8 Outcome

In 2008-2009, 2 shipments of Apo-Triavir totaling 240,239 bottles (60 Tabs) were delivered to Rwanda. The drugs were then delivered in 2 shipments using PEPFAR's Supply Chain Management System. The WHO global price reporting mechanism (GPRM) showed that this was approximately 20,000 patient treatment years of Tri-avir. The payment to Apotex was made by the Global Fund. Compared to originator prices of AZT/3TC and Nevirapine, discounts were approximately 75% on the Apotriavir FDC.

The Rwandan MOH mandated the national pharmaceutical procurement agency (Centrale d'Achats des Médicaments Essentiels Consommables et

Equipements Medicaux du Rwanda - CAMERWA) to procure all ARVs for national use, in order to leverage bargaining power through pooled procurement. CAMERWA received logistical support from a PEPFAR subsidiary (SCMS) to procure drugs from WHO Prequalified suppliers and then supplies pharmacies nationally. This strategy successfully protected the program from stock outs of ARVs and ensured quality control. The lack of a Rwandan national drug regulatory authority necessitated this measure to ensure drug quality (El-Sadr et al., 2012).

Supporting the procurement of drugs from Apotex, AZT/3TC/NVP was the WHO recommended first-line therapy which was used by approximately 44 % of Rwandan patients on ART (PEPFAR). Total expenditure on HIV and AIDS in Rwanda increased from USD 74.6 million in 2007 to USD 110.8 million in 2008 (an increase of about 33%).The number of people on the regimen was reported to be 56,731 in 2008 and 75,041 in 2009. Corresponding to the scale-up of ART and increase in testing and treatment centers, a parallel expansion of the National AIDS program in 2007 and 2012 to increase coverage was done by revising guidelines to increase coverage of ART. In 2009, the MOH revised guidelines for first-line therapy from AZT/3TC/NVP to TDF/3TC/NVP, which reflects in procurement data while further increasing the eligibility criteria to a CD4 cell count of 500/mm(UNGASS, 2010).

In 2005, PEPFAR reported that 60% of the population was within a 3.5 Km distance from a health center, and 95% within a 10 Km range. The scale-up of treatment in conjunction with expansion of testing centers in both rural areas and urban areas. The number of treatment centers increased from 133 in 2006 to 195 in 2008. The NAP has reported high rates of adherence due to proximity of treatment and testing centers. Biribonwaha reported adherence to ART regimens was significantly high at 95% in their study population of both rural

and urban areas with very low attrition rates (Nuwagaba-Biribonwoha et al., 2014).

7.9 Other developments

In 2009 Rwanda enacted the Law on the Protection of Intellectual Property No. 31/2009 of 26/10/2009 (LPIP). The LPIP establishes a TRIPS compliant framework for the protection of IPRs, including patents. It provides for an ex officio compulsory license which allows a state department or third party to use a patented invention without the agreement of the patent holder for reasons of inter alia public health. The importation of generic medicines for the treatment of HIV/AIDS and other life-threatening diseases under the 30 August Decision would certainly fall into this category. Where the ex officio cornpulsory license is granted to address 'a state of siege or other extremely urgent circumstances or a non commercial public interest'," there is no need for the compulsory license applicant to demonstrate that it attempted to acquire a voluntary license from the patentee(Nkomo, 2013).

The LPIJP, however, requires that the patent holder be paid adequate compensation. The provision does not specify who must pay the compensation. Therefore, where importation occurs under the 30 August Decision, this requirement can be interpreted as an obligation owed by the exporting country." Use of an invention under an ex officio compulsory license is limited to the purposes for which the compulsory license was granted. This implies that if the license was issued for the purpose of importing medicines, the drugs could not thereafter be re-exported to a neighbouring country. This represents a missed opportunity as far as the implementation of paragraph 6 of the 30 August

Decision is concerned. Such an interpretation is supported by a provision which says that use of a patented invention by a state department or the third party appointed by the Government shall aim mainly at supplying the Rwandan market . This mirrors article 31 (f) of the TRIPS Agreement. Therefore, it appears that the Rwandan legislation implements the compulsory license provisions of the TRIPS Agreement without taking into consideration the 30 August Decision(Nkomo, 2013).

8. Kenya : Parallel Imports

8.1 Introduction

Parallel Importation is the most commonly used TRIPS flexibilities together with compulsory licensing. Their effective and timely implementation requires political will and well-defined administrative structures and procedures for coordination and decision making. This poses major challenges to countries interested in implementing these flexibilities(Osewe, Nkrumah, & Sackey, 2008).

Nevertheless, Parallel Importation can be an important vehicle enabling access to affordable medicines, because there still are substantial price differences for pharmaceutical products in different markets(Musungu, Oh, & WHO, 2006). Facilitating some form of Parallel Imports provides opportunities for eligible countries to shop around for better-priced pharmaceutical products. Developing countries should avail themselves of the widest scope in terms of Parallel Imports and incorporate explicit provisions to put into effect an international exhaustion regime in their national patent laws. It is important to remember that while this “flexibility” is allowed in the TRIPS Agreement and confirmed by the Doha Declaration, it does not automatically translate into the national regimes, and it will be necessary for specific legal provisions be enacted in national law.

In this sense, Kenya provides an priceless lesson for other developing countries on how to utilize Parallel Imports by incorporating into local IPR law

together with other TRIPS flexibilities and by negotiating with stakeholders against various challenges.

8.2 Background

Kenya is located in Eastern Africa, on the coast of the Indian Ocean. The country is bordered by Tanzania, Uganda, Ethiopia, South Sudan, and Somalia. It encompasses savannah, lake lands, the Great Rift Valley, and mountain highlands, with abundant wildlife and a human population of about 47.6 million. With a gross domestic product (GDP) of US$1143 per capita in 2016, Kenya is considered a lower-middle income country.

The National Health Accounts survey was undertaken in 2015 to figure out the flow of funds in the health sector for the year 2012/13. Total health expenditures in that year were US$2743 million, up from US$2155 million in 2009/10. Total health spending in 2012/13 accounted for 6.8% of GDP, up from 5.4% in 2009/10. The country's expenditures on health as a percentage of total expenditures increased from 4.6% in 2009/10 to 6.1% in 2012/13, with per capita expenditure increasing from US$56 in 2009/10 to US$67 in 2012/13. The private sector continues to be the major source of health care financing, contributing 40% of total health expenditures in 2012/13, up from 37% in 2009/10. The government's contribution to total health expenditure was 34% in 2012/13, an increase of 17 percentage points over the 2009/10 estimates. Donor contributions (from foreign countries and international nongovernmental organizations) accounted for 26% of total health expenditure in 2012/13, down from 35% in 2009/10(Ministry of Health, 2015).

The Kenya Essential Medicines List provides a guide as to which medications should be stocked, especially in public facilities; some hospitals have also developed their own medicine formularies to suit their specific needs. The Ministry of Health procures and distributes medicines that are used for malaria, tuberculosis, sexually transmitted diseases, HIV/AIDS, and family planning programs, because these medications are funded through international partners (at the national level). The county governments are responsible for procuring medicines for the facilities under their jurisdiction (other than those procured by the Ministry of Health). Medicines for other conditions, such as antibiotics, are sourced from private wholesale suppliers, nongovernmental organizations (such as MEDS), and KEMSA. KEMSA and MEDS have a wide range of products available and lower prices than private wholesalers. In the private sector and faith-based health facilities, the availability of medicines and their prices are higher than in the public sector(Aywak et al., 2017).

In public health facilities, only 40% of essential medicines are available at any one time, and supply problems are common because of inadequate funding and inappropriate selection and irrational use of the available medicines. These problems occur despite guidance on the appropriate use of medication in public hospitals provided in standard treatment guidelines. Hospitals are also mandated to have Medicines and Therapeutics Committees that are charged with the responsibility of ensuring rational use of medicines in their institutions. In public primary care facilities, health care, including medicines, is provided free of charge, with patients paying only minimal registration fees. Children under 5 years of age are entitled to free health care including medicines in public and faith-based health care facilities, and a waiver system is in place for patients older than 5 years of age who cannot afford treatment. Publicly procured medicines for priority health programs, such as those for contraception, malaria, HIV/AIDS, and tuberculosis, are provided free of charge through public and

faith-based health care facilities. Cost-sharing applies for treatment of other conditions in adults and children over 5 years of age, at higher-level public facilities. The private sector provides health services, including medicines, on a full cost recovery basis. There is currently no policy in Kenya to guide the pricing of medicines in any sector(Aywak et al., 2017).

8.3 Mechanism of Parallel Import

8.3.1 What is Parallel Imports

Parallel trade does not refer to unofficial, illegal, or informal-sector activities that may take place inside a country or among countries. Moreover, parallel trade is not trade in pirated or counterfeit products. The latter are unauthorized versions of products that infringe an IP right. Parallel are genuine, often branded, products that do not violate an IP right (MATTHEWS, 2007). Parallel Imports, also called grey-market imports, are goods produced genuinely under protection of a trademark, patent, or copyright, placed into circulation in one market, and then imported into a second market without the authorization of the local owner of the intellectual property right(Maskus, 2000).

Parallel Importation arises as a consequence of a doctrine known variously as the ‘first sale’ doctrine or the ‘exhaustion of rights’ doctrine. The doctrine holds that upon the first authorized sale of the physical item, the intellectual property owner is adequately remunerated and consequently, some or all of the intellectual property owner’s exclusionary rights are ‘exhausted’ as applied to that physical item. This exhaustion of rights in turn leads to the phenomenon of Parallel Imports, or grey marketing, which occurs when an item validly marketed

under the intellectual property regime in country A is imported into country B against the wishes of B's corresponding intellectual property holder(Nyaga, 2009).

8.3.2 Why Parallel Imports happens

The incentive for Parallel Importation is the price differences between identical products in different markets. Parallel Importation usually occurs when the price differences are high, because then the potential gains including price savings, product availability and profit for most stakeholders should be large enough to compensate for the transaction costs, including shipping costs and complying with customs regulations. The price differences can happen due to a variety of factors. In the case of the pharmaceutical market, where important price differentials exist between countries, price differences can result from government-enforced price controls, pricing manipulated by the owner of an IP right holder, fluctuations in currency values, a combination of these conditions, and other factors(MATTHEWS, 2007).

The difference of the prices between markets is the economic driver for parallel import activity. There are two main explanations for this disparity. Firstly from the practice of IP rights holders to establish separated international market. It is therefore argued that Parallel Importation interrupts a right-holders ability to establish separated market thereby eroding their potential profits from international sales. Secondly, national price regulations established to achieve particular social objectives also accounts for the disparity. In this regard, it could be argued that Parallel Importation defeats the purpose of price regulation as distributors in more regulated (lower price) markets ship medicines to less regulated (higher price) markets. Parallel Importation will

therefore arise where international price differences exceed the cost of transporting and selling goods across boarders(Nyaga, 2009).

According to Weigand(1991), three factors, sometimes working alone but often in consort, virtually assure that parallel marketing channels will arise if they cannot be prevented by trade mark owners who try to protect their authorized channel members. They are (1) foreign exchange rate differences, (2) the power of the discriminating monopolist, and (3) opportunistic behavior by members of administered marketing channels.

If the cause is floating exchange rates, then products flowing into parallel market channels can only move from the lower valued currency country to the higher valued currency country, the immediate cause is external to the firm, the opportunity will only endure until underlying conditions such as the exchange rate or an artificially low purchase price are corrected, and can only occur internationally. Exchange rate fluctuations are more likely to explain parallel transactions, if the rate change is swift. If a rate change is protracted it allows the manufacturer to make appropriate price adjustments that offset middlemen's windfall profits.

The discriminating monopolist must face the possibility of Parallel Imports moving from the lower priced to the higher priced country because of price policies established by the manufacturer; the importation will continue as long as the policy holds and will take place internationally. Parallel Importation can also occur when the strategist tries to price discriminate between markets, charging a lower price in those markets with lower purchasing power and more in higher income markets. The concept of price discrimination is nearly perfect, if price strategists can find a way to prevent lower priced goods destined for a low income market (or, more accurately, a market composed of buyers who are less willing to pay a higher price) from flowing into the higher priced market.

And finally, Parallel Imports originating from opportunistic channel behavior can happen unpredictably because distributor opportunism has no particular time schedule and can occur either internationally or domestically. Even in the authorized channels where the strategists have carefully selected their distributors, this behavior can happen. Opportunistic behavior is more likely to happen when the middleman's gross margin is sufficiently large enough for the marketing activity. Moreover, it is especially attractive if the transaction occurs outside the distributor's allotted territory. If the sale is geographically remote, the opportunistic distributor may assume that the sale is not made at the cost of their own full markup sales.

8.3.3 Methods of Parallel Imports

There are a number of ways of doing importation in parallel but the following methods, however, represent the bulk of market imports and are focus of much of the economic and legal attention(Weigand, 1991).

Weigand (1991) presented three method. First, and most often are those products made overseas by, for example Japanese firms(See Figure 2). These foreign units may be subsidiaries, joint venture companies, or some other entity which have common interests with the American company. This foreign affiliate may sell to nearby authorized distributors, for example, a Korean firm. Somewhere in the authorized channel, however, distribution control is lost and the product gets into an unauthorized channel and some of it is exported back to the Japan. Here it competes with identical and domestically produced products.

A second method of Parallel Importation is when a foreign manufacturer licenses a company to be the exclusive importer of a product carrying a foreign

name or trademark. That company registers the foreigner's name and becomes the legal trademark owner in their own market and agrees to pay royalties. Now, suppose that a third party trader purchases this same product which was intended for a third market. They then ship the product to the licensee's market as Parallel Imports.

A third method of Parallel Importation[Figure3] happens when a manufacturer exports from its producing plant, only later to have the exports diverted back to the home market. This Parallel Importation strategy is known as re-importing. Re-importing is particularly attractive when the manufacturer's strategy is to enter the foreign market at a sizably lower price due either to the market being poorer or there being dramatic exchange rate differences, and when the foreign market is geographically close to the home market, thus minimizing return transport costs.

This way of importing in parallel may also be developed on premises that an active parallel import cannot exist without price differentials between international markets. [Figure 3] shows a two-country representation of product flows along a manufacturer-distributor-retailer-consumer channel. When Parallel Importation occurs, products are leaked from every possible level of the supply chain, and an unplanned distribution flow is formed. Sales revenue and profits may therefore be re-allocated across supply chains in different countries, creating tension between the manufacturer and different distributors, which affects the manufacturer's overall profitability(Skoko, 2014).

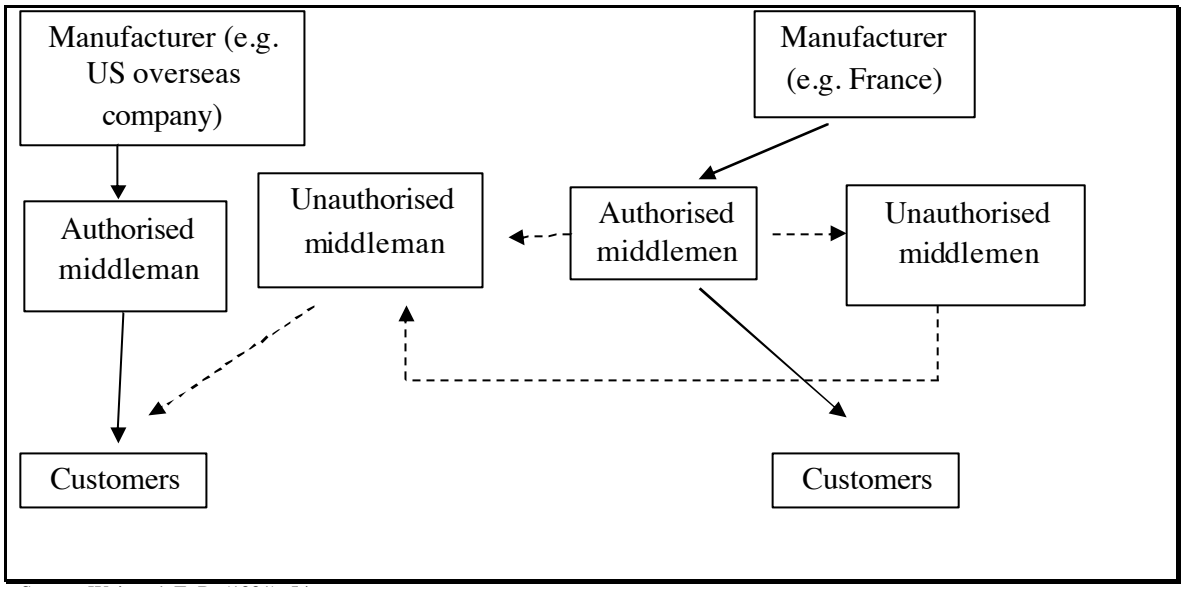


Figure 2 First case of the Parallel Imports process

The ability to exploit price differentials appears likely to result in the creation of Parallel Imports. Price differentials inevitably invite arbitrage behavior, if transportation costs, duties and tariffs between the countries are modest or negligible, as is the case in the software industry. Because of a favorable price differential, a parallel importer can enter the market and compete with authorized products. In contrast, if Parallel Imports are not allowed, buyers have no other choice than to purchase products priced well above the marginal cost in non-segmented markets(Skoko, 2014).

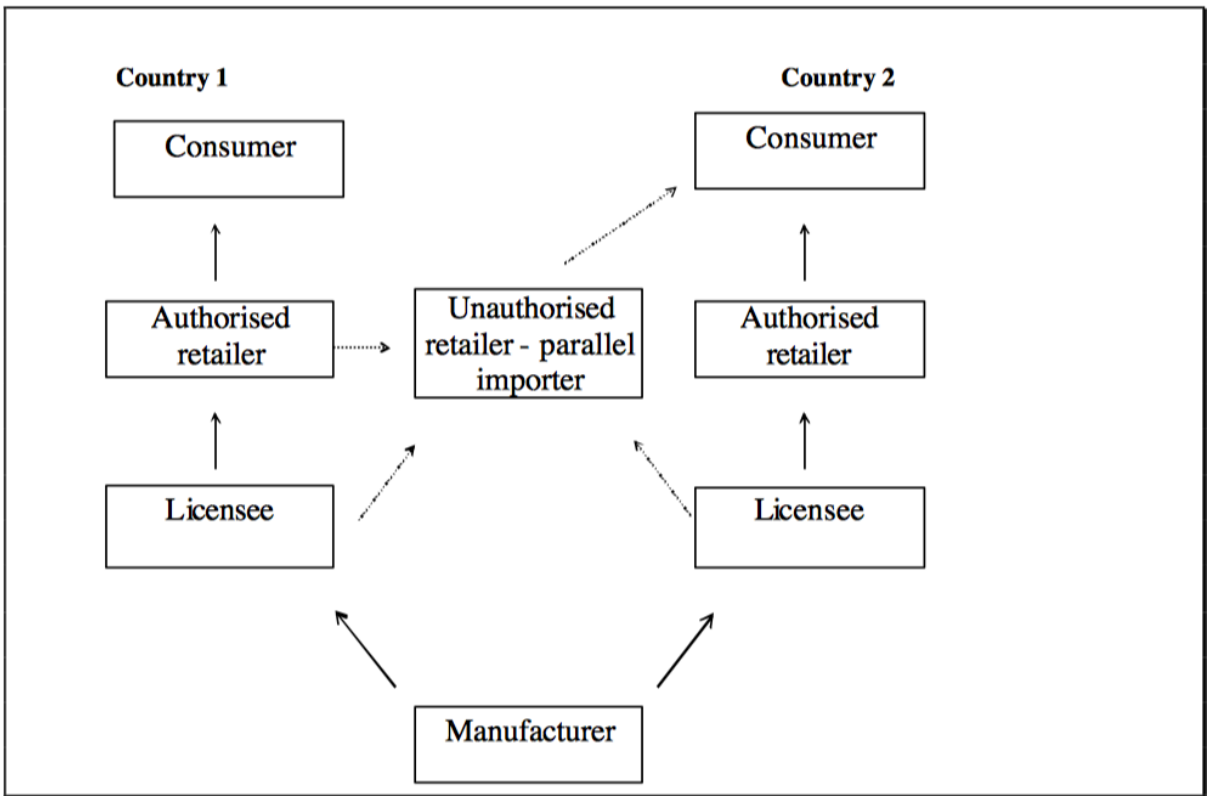


Figure 3 Third case of the Parallel Imports process

Skoko (2014) also presents a fourth way of Parallel Imports : mail orders. This type of unauthorized channel is emerging with Internet development and is a very important source of parallel trade. Retailers and consumers can currently purchase products either from catalogues from large, local retailers or going directly to mail order houses in different market. Anyone with a credit card and access to an Internet-linked computer can order CDs, software, books and whatever from overseas suppliers.

8.4 Parallel Import in TRIPS

The provisions relating to Parallel Importation are specifically contained under article 6 of the TRIPS Agreement. Article 6 of the TRIPS Agreement provides for the exhaustion of intellectual property rights (IPRs) as follows:

> For the purpose of dispute settlement under this Agreement…nothing in this Agreement shall be used to address the issue of exhaustion of intellectual property rights.

The TRIPS Agreement is essentially silent on Parallel Importation. It is as such on the respective WTO members to adopt the most favorable exhaustion principle that suits their own circumstances and needs. Exhaustion principle is important since it determines when an IPRs holder ceases to exercise control over use and disposition of goods therefore allowing free transfer of goods within and across borders as is the case with Parallel Importation. However, the exhaustion principle adopted by any country is subject to the other TRIPS Agreement provisions on national treatment and most-favored nation principles(Ogendi, 2013).

In this sense, Parallel Importation is allowed under the TRIPS Agreement. Article 6 of the TRIPS Agreement provides that matters relating to exhaustion of rights shall not be subject to dispute settlement. According to Musungu(2006), they have three main options:

1. Members may adopt the principle of international exhaustion of patent rights. Adoption of this principle in the national patent law would allow any party to import into the national territory a patented product from any other country in which the product was placed on the market by the patent holder or any authorized party.

2. Members may adopt regional exhaustion of rights, where adoption of this principle would allow the possibility of importing into the national territory a patented product originating from any other member state of a regional trade agreement.

3. The third option is that of national exhaustion of rights. This principle limits the circulation of products covered by patents in one country to only those put on the market by the patent owner or its authorized agents in that same country. In this case, there can be no Parallel Importation.

If a developing country adopts the international exhaustion regime, the first sale by the patent holder in any country will exhaust any parallel intellectual property rights in the importing country; hence the rights may not be used to prevent importation. Parallel import medicines are normally purchased from a party other than the patent holder; for example, a medicine wholesaler that initially purchased from the patent holder or its authorized representatives.

The Doha Declaration has re-affirmed that each Member is “free to establish its own regime for such exhaustion without challenge”. That this has been clarified in the Doha Declaration is an added reassurance for Members trying to adopt an international exhaustion principle that is legitimate and consistent with the TRIPS Agreement to do so. Therefore, Members may decide how the principle should be applied within their national territories.

Importantly, the TRIPS Agreement avoids mandating worldwide standards on the legality of Parallel Importation, making Parallel Importation entirely an issue for domestic legal concern(Nyaga, 2009).

8.5 Industrial Property Bill(2001)

Kenya like many other countries have taken advantage of article 6 to adopt the most favorable system of international exhaustion to effectively allow for the widest possible scope for utilizing Parallel Importation flexibility under the TRIPS Agreement. In effect, this means that Kenya can import any product including essential medicines as long as they have been released legally in any market(Ogendi, 2013).

Kenyan law and policy on Parallel Importation has been extraordinarily fluid and a touchstone of Kenyan attitudes to access to medicines since mid-1999. Musungu(2006) elaborated on the trajectory of the legalization process as below :

Pursuant to Section 36 of the then in-force Industrial Property Act (1989):

> The owner of the patent shall have the exclusive right to preclude any person from exploiting the protected invention by any of the following acts (a) when the patent has been granted in respect of a product i) making, importing, offering for sale, selling and using the product; or ii) stocking such product for the purposes of offering it for sale, selling or using the product;

The above prevented all forms of Parallel Importation, making Kenya a separated market and thereby allowing patent holders to control all aspects of the national market for patented products. Prices and availability were insulated from the world market and there was no form of alternative supply or other competition for on-patent products.

Parallel Importation became one of the key lobbying points for civil society organizations and international NGOs during the review of the Industrial Property Act due to its potential to provide immediate results in terms of lower pricing, improved stability of supply, and enhanced competition. The Industrial Property Bill (2001) proposed a change from Kenya's previously restrictive legislation in the form of a provision to what is reflecting an orthodox interpretation of the concept of international exhaustion:

> The rights under the patent shall not extend to acts in respect of articles which have been put on the market in Kenya or in any other country or imported into Kenya by the owner of the patent or with his express consent.

This corresponded with the minimal option proposed by civil society organizations to allow Parallel Importation of brand name products. However, discussions with stakeholders and politicians suggested that a more expansive interpretation of international exhaustion might be acceptable. As a result, the KCAEM proposed a more aggressive interpretation of the principle of international exhaustion that was nonetheless regarded as TRIPs compatible:

> The rights under the patent shall not be enforceable against any person who imports or in any way deals in the patented product, or a product obtained by the patented process, once the said product has been lawfully placed on the market in any country with the consent of the owner, a licensee or any other authorised person

This would have allowed for the Parallel Importation of brand name products, generics produced under voluntary or compulsory licenses and, arguably, generics produced in countries where the brand name was not the object of patent protection which was still controversial.

As it was the Industrial Property Bill text that went to Parliament for debate and adoption, attention focused on the closing language of sub-section 58.2, "…by the owner of the patent or with his express consent". During Parliamentary debate a proposal was made to amend this to, "…by the owner of the patent or with his express consent or by any other authorised person." This amendment would have effectively introduced the same concept as that proposed by the KCAEM. Debate on this proposal concluded with the deletion of all the language that was its subject and produced the following text in the IP Act (2001):

> The rights under the patent shall not extend to acts in respect of articles which have been put on the market in Kenya or in any other country or imported into Kenya.

This text entered into force on 1 st May 2002, pursuant to the commencement date published by the Minister for Trade and Industry. There was some concern that this text did not prevent the importation of pirated or otherwise illegal products by removing all references to who places a product on the market. However, the apparent understanding of Parliament, and the interpretation subsequently adopted by regulatory bodies and other stakeholders, was that Parliament would not sanction an illegal act, whether in its jurisdiction or otherwise. This understanding was confirmed by Clause 37 of the Industrial Property Regulations (2002), which provides that:

> The limitation on the rights under a patent in section 58(2) of the Act extends to acts in respect of articles that are imported from a country where the articles were legitimately put on the market.

Upon the entry into force of the 2001 Act, several non-profit organizations prepared to place orders for the import of generic drugs, particularly anti-retrovirals and treatments for opportunistic infections associated with HIV/AIDS.

However, on 4 th June 2002 an amendment to the 2001 Act that had been included in the Statute Law (Miscellaneous Amendments) Act, 2002, entered into force:

> 58.2 Delete the fullstop at the end thereof and add the words "by the owner of the patent or with his express consent".

The Statute Law (Miscellaneous Amendments) Act, 2002, contained numerous contentious issues and was passed late at night when most MPs were absent, and key activists on access to medicines issues were out of the country. This amendment blocked the planned Parallel Importation of generic drugs by NGOs. The amendment was contrary to the Parliamentary rule that no amendments should be permitted to any Act prior to six months after its entry into force and the Minister for Trade and Industry, KIPI and the Attorney General's Chambers all stated that they had not been its source. Once the amendment came to the attention of MPs, the Minister for Trade and Industry, the Vice President (as Chairman of the Parliamentary Business Committee) and the Parliamentary Health Committee vowed to reverse it forthwith and to instruct the relevant authorities not to enforce it pending reversal. In an unprecedented move, the amendment was reversed in August 2002.

8.6 Outcome

Kenya became the one of major beneficiaries of Parallel Importation. In fact, the bulk of medicines used in Kenya currently are generics imported from foreign countries under the Parallel Importation. The benefits have been astonishing. Kenya is presented as a best practice in this regard. In 2002, for

example, the successful use of Parallel Importation helped reduce medicines prices by up to 40%-65% because of generic competition. The market share commanded by pharmaceutical Parallel Imports was between 30% and 35% thus representing a significant market portion(Ogendi, 2013).

The first Parallel Importation of generic drugs under the 2001 Act occurred in early June 2002. This was a symbolic shipment of anti-retrovirals and drugs for the treatment of HIV/AIDS opportunistic infections imported by MSF and AAK from India for use in MSF's clinics providing free treatment. However, this importation was rapidly followed by a significant order from MEDS to be distributed at cost through mission hospitals. MEDS has since continuously relied on Parallel Importation of generics for some of its key drugs affected by intellectual property rights, in particular anti-retrovirals, and the public sector has recently also begun to take advantage of this mechanism(Musungu, Oh, & WHO, 2006).

There are institutions and individuals who engage in Parallel Importation of pharmaceutical products in Kenya : registered pharmaceutical distributors and retailers; Non Governmental Organizations; large private as well as public institutions which buy pharmaceutical products in bulk; local distributors appointed by MTCs to market the latter's products in Kenya; individual marketers employed by MTCs; and the so called "brief case importers" who are ordinary business men who have no professional training in pharmacy and therefore fall outside the regulatory ambit of the Pharmacy and Poisons Board. 166(Nyaga, 2009).

It is notable that local distributors as well as employees of MTCs were themselves engaging in Parallel Importation. This means Parallel Imports offer direct competition to the products placed in the market by local patent right

holders. Their employees and agents are therefore engaged in activity which definitely undermines the MTCs' interests.

Various sources have been used for Parallel Imports. These include: neighboring countries of Tanzania, Uganda, Burundi, and Rwanda; Egypt; United Arab Emirates, particularly Dubai; China; and India. Neighboring countries are a major source of the imported products. Compared to Kenya, pharmaceutical products were generally cheaper in the neighboring countries. Various reasons were given for this disparity in prices among similarly situated African countries. These include market segmentation by MTCs operating in the region and the consequent treatment of Kenya as a prime market; differences in currency value in the East African region; and absence of a regulatory framework for pharmaceuticals in Rwanda and Burundi which means that drugs are cheaper in these countries(Nyaga, 2009).

The imported products are determined by economic considerations of demand, supply and profit margin. Since the importers are seeking profits, they mostly import drugs for chronic diseases such as diabetes, cancer and high blood pressure where they rely on per unit cost to maximize their profits. They also import drugs for acute diseases such as antibiotics where they rely on volumes of sale to make their profit. Importantly, the imported products could be on or off- patent. Since Kenya is an important market for multinational pharmaceutical companies, they usually register their patents in Kenya. Products which are not in high demand are therefore unlikely to be parallel imported, which is a critical shortcoming. It is noteworthy that ART medicines are not parallel imported, because since the year 2005, ART has been availed by the Government in public hospitals for free(Nyaga, 2009).

8.7 Challenges

Kenya has several challenges related to Parallel Imports, which other countries can share and learn from. The first problem relates to the issue of quality and safety. Marketing of similar products under different brand names does not guarantee that the quality is the same(Ogendi, 2013). If Parallel Imports take place in the absence of an adequate regulatory and policy framework, safe issue can happen any time until consumers receive products. There is the real possibility of counterfeit products finding their way into the country disguised as Parallel Imports(Nyaga, 2009).

The second concern relates to the effect of Parallel Importation on differential pricing. Given that Parallel Importation occurs due to different pricings across countries, countries benefiting from these pricing strategies may be forced to buy medicines under a uniform pricing system at the same price as a consumer in developed nations. In this regard, a market-specific differential pricing based on per capita income should be encouraged as opposed to Parallel Importation(Ogendi, 2013).

Thirdly, there exists ambiguity in relation to the law relating to Parallel Importation in Kenya. This is because crucial laws such as the Trademarks Act and Pharmacy and Poisons Act do not provide for Parallel Importation despite the fact that they regulate the pharmaceutical products industry in Kenya. The Trademarks Act in particular has been used in the past to frustrate Parallel Importation. This was a subject matter of a recent court case from Lords Healthcare Limited v Salama Pharmaceuticals Limited. This case concerned the supplying of a parallel imported inhaler for asthma patients in Kenya under the trademark Budercort-200. Lord sued the defendant for patent infringement

while the defendant sought to rely on Parallel Importation provisions as his defense(Ogendi, 2013).

Lastly, In 2009, Kenya enacted the Anti-Counterfeit Act which combined generic medicines with counterfeits. In this regard, the legislation, if implemented, would have affected the importation of generic medicines by the exploitation of Parallel Importation provisions in the law. Fortunately, the legislation, as enacted, has been declared unconstitutional by the High Court on 20 April 2012 following a successful petition by three persons living positively with HIV and AIDS. However, it is yet to be seen whether the government will amend the law to exempt generic medicines from its application(Ogendi, 2013) .

9. India Case Review: IPR law and drug policy

9.1 Introduction

Although India is one of the largest pharmaceutical market in the world, the price accessibility of the Indian people is very low due to the absence of sophisticated price control systems, high OOP and low insurance rate, which covers only a very small proportion of the Indian population in India. For compensating this situation, India made IPR law in favor of facilitating generic drug production. The patent opposition based on this IPR law could be used to increase access to high-cost drug. International pressures were placed on the patent opposition, India modified its IPR law in accordance with the TRIPS agreement in 2005 and began to use compulsory licensing, on particularly oncology drug, since then.

On the other hand, large pharmaceutical companies offer various patient access program for patient accessibility, without lowering their drug prices in consideration of reference pricing with other countries.

Through this case study, we could learn about the solutions provided by the Indian government and pharmaceutical companies to increase the price accessibility of drugs, and consider these for clues to increase the accessibility of high-cost drugs.

9.2 Background

India exports medicines to more than 200 countries worldwide. Pharmaceutical market in India consists of more than 20,000 manufacturers and is termed as the 3rd largest market in the world, by volume. In spite of that, more than half of its population has no access to essential medications in public sector due to heavy dependence of a majority of patients on private sector(Ahmad, Khan, & Patel, 2015).

The availability of medicines in public sectors is more important, because these are the primary sources of free medicines for a majority of India's low-income population. Availability of medicines is better in private retail pharmacies but affordability remains a big challenge due to the significant proportion of out-of-pocket money. Under this situation, studies have reported that medications in India are overpriced and unaffordable, although It is a common notion that drug prices in India are relatively low(Ahmad et al., 2015; Kotwani, 2013).

9.2.1 Health Financing in India

According to the WHO (2017), current expenditure on health (CHE) as a share of gross domestic product(GDP) in India has been about 4%, and private expenditure as a share of CHE is three times more than public.

Out-of-pocket(OOP) expenditure was 65% of CHE in 2015. high OOP payments contributes to a serious lack of financial protection. In reality, 52.5 million of the population were pushed below the poverty line of PPP$ 1.90 per capita per day in 2011(WHO, 2017).

Total OOP payments and medicines OOP payments were catastrophic for 17.9% and 11.2% households, respectively, in 2011-2012 at the 10% of total consumption expenditure threshold, implying 29 million households incurred catastrophic OOP payments in the year 2011-2012. Further, medicines OOP payments pushed 3.09%, implying 38 million persons into poverty in the year 2011-2012. Purchase of medicines constitutes the single largest component of the total OOP payments by households. Among the leading cause of diseases that caused significant OOP payments are cancers, injuries, cardiovascular diseases, genitourinary conditions and mental disorders(Selvaraj, Farooqui, & Karan, 2018).

Roy, Gupta, and Agarwal (2012) conducted one study to assess the costs of prescribed medicines and treatment of community acquired pneumonia and their affordability in the 27 private pharmacies in Delhi, India. When comparing to the monthly per capita expenditure on food, minimum monthly and daily wages for different classes of workers, the costs of medicines are highly variable and not affordable for the economically poor in India.

9.2.2 Health Insurance

The vast majority of the Indian population is unable to access quality healthcare. Central and state government employees are insured through the Central Government Health Scheme (CGHS) and Employee State Insurance Scheme (ESIS). Also, army, railway and oil companies have relatively good coverage of medical and drug expenses, but these comprise only a very small proportion of the Indian population(Schoonveld, 2016).

About 5% of population is covered with health insurance in 2018. Taking private health care into account, hardly 10% of Indians are covered by health

insurance. In February 2018 India government announced that they would introduce new health insurance program for universal health coverage, the National Health Protection Scheme (NHPS, also known as Modicare). to ensure access to all population and high-quality health care regardless of financial status(Shastri, 2018). In new health insurance program, health service would be cashless with the funding generated through taxes. Especially, people would get free access to medicines, which is essential medicines and included in the benefit list(Wasington Post, 2018)

9.2.3 Disease burden

With almost one-fifth of the world's population living in India, the health status and the drivers of health loss are expected to vary between different parts of the country and between the states. The burden of most infectious and associated diseases reduced in India from 1990 to 2016, but five of the ten individual leading causes of disease burden in India in 2016 still belonged to this group: diarrhoeal diseases, lower respiratory infections, iron-deficiency anaemia, preterm birth complications, and tuberculosis. For India as whole, the disease burden or DALY rate for diarrhoeal diseases, iron-deficiency anaemia, and tuberculosis was 2.5 to 3.5 times higher than the average globally for other geographies at a similar level of development, indicating that this burden can be brought down substantially(L Dandona et al., 2017).

The contribution of most of the major non-communicable disease groups to the total disease burden has increased all over India since 1990, including cardiovascular diseases, diabetes, chronic respiratory diseases, mental health and neurological disorders, cancers, musculoskeletal disorders, and chronic kidney disease. Among the leading non-communicable diseases, the largest

disease burden or DALY rate increase from 1990 to 2016 was observed for diabetes, at 80%, and ischaemic heart disease, at 34%(L Dandona et al., 2017).

9.3 Drug Pricing Policy

9.3.1 The Drug Price Control Order (DPCO)

The drug prices in India are controlled using what is called the Drugs Prices Control Order (DPCO). The DPCO is an order issued by the government under Section 3 of the Essential Commodities Act, 1955 empowering it to fix and regulate the prices of essential bulk drugs and their formulations. National Pharmaceutical Pricing Authority (NPPA) has limited authority to fix, review and justify pharmaceutical prices under the DPCO, 1995. NPPA began working since August 1997. In order to fix and revise the prices of controlled drugs, the NPPA monitors the prices of decontrolled drugs in order to keep them at a reasonable level(Narula, 2015).

In 1979, 347 drugs were included in the price control list of DPCO and later the drug list has been revised and shortened to 76 in 1995. Recently, on May 15, 2013, the Ministry of Chemical and Fertilizers (Department of Pharmaceuticals) authorized NPPA to regulate the availability and pricing of all the drugs mentioned in National List of Essential Medicines (NLEM). As a result, the prices of the essential medicines originally included in 1979 were reduced dramatically, and they were made available to the public at low cost(Ahmad et al., 2015)

Almost a year later on May 29, 2014, another amendment was made in DPCO, which authorized the NPPA to control prices of other 108 life-saving drugs which were not originally included in the NLEM. This policy significantly reduced the prices of some important life-saving drugs for disease conditions such as cancer, HIV/AIDS, tuberculosis, cardiovascular diseases, diabetes, etc(Ahmad et al., 2015)

The DPCO uses market-based mechanisms to set price ceiling. The ceiling price is decided by taking the simple average of prices of brands with more than 1% market share. In the case of each drug which is under price control, a single maximum selling price is fixed that is applicable throughout the country and that is called as ceiling price(Kumar, Gupta, & Kumar, 2014)

Table 8 Comparison of DPCO 1995 & 2013

S. No.	DPCO 1995	DPCO 2013
1	It is governed by Essential commodities act 1955	It is governed by national pharmaceutical pricing authority, based on national list of essential medicines
2	Prices of only 74 drugs were regulated by this act	Prices of 652 drugs are regulated by this act
3	If once the prices are fixed, they can't be changed as per the act	Based on simple average price (SAP) the highest prices can be lowered depending on the margins
4	Ceiling and non-ceiling prices of drugs are not specified	Ceiling and non-ceiling prices of drugs are specified
5	This act facilitates Win –Win situation for the government, but not for the industries	The prices of the drugs are fixed by the mutual agreement of government and industries for the welfare of the public

(Source : Kumar et al. (2014)

There are several problems in design for policy implementation. Firms, producing the drug which is in price control list, could coordinate strongly with other firms in the market for setting the price. Also, it could create incentives to firms for producing other dosage or other forms of the drugs in price control list, which could not be controlled. Furthermore, neither the Department of Pharmaceuticals nor the NPPA have the institutional ability to monitor prices of medicines, and there is no punishment when there is violation of the price-cap ceiling in India. Without solving these limitations, price control for accessibility would not be worthy at all(Forbes India, 2018).

9.3.2 Policy Reform

The drug pricing mechanism in India has changed in 2018. Price regulation would cover 100% of drugs, not just essential drug which is 17% of drugs with the new price index for pharmaceutical products. Before the reform, the government loosely regulates prices of all medicines in public interest and prices of essential drugs are capped by the government. The drug price regulator, National Pharmaceutical Pricing Authority (NPPA) revises these prices annually based on the wholesale price index. For all other medicines, companies are allowed to raise prices by no more than 10% in a year(The times of India, 2018).

Under the proposed mechanism, NPPA plans to link prices of all medicines with the new pharmaceutical index. Drug makers would be allowed to revise prices annually only on the basis of movement in the index. Though it is expected that the rate of price increase would be lower than current mechanism, there are experts who believe that linking prices to an index may actually result in increase in prices rather than a decrease due to impact of large pharmaceutical companies(The times of India, 2018)

9.4 Intellectual Property Rights Law (IPR law)

9.4.1 IPR law in India

Indian IPR law, which was designed to help generic production, has played a key role to facilitate manufacturing of a wide range of essential medicine at relatively low cost.

In India, patents were allowed only on the manufacturing process, not on the material for medicines until the launch of the WTO. Specifically, since the patents on manufacturing process were recognized for seven years, the same material was reproduced and the process was not violated by the patent law(H. Kim, 2007).

Article 27 (1) of the TRIPS Agreement explicitly encompasses all material and process as patents, not allowing discrimination based on technology, patents on the manufacturing process was obligatory. So, there was dispute between India and WTO in 1997 and, in August 1998, India acknowledged the violation of the agreement (H. Kim, 2007)

After the dispute, India revised domestic patent IPR law, and WTO made Doha Declaration, the ground for compulsory license. The revised law of India in 2005 limited the granting of patents to new drugs developed based on existing drugs instead of recognizing patents on the material. It was for the prevention of the monopoly of pharmaceutical companies through the development of new drugs with very minor differences. In fact, most of US patented products have been upgraded to new versions based on existing medicines, so patents are not easy in India's IPR law(H. Kim, 2007)

On the other hand, there is argument that Indian drug policy with IPR law makes patient access low because big pharms tend to delay introducing new drug to India for protecting patent and preventing reduction of drug price through generic competition in India. So, in terms of time for introducing new drug, India is too long compared to US or EU(Berndt & Cockburn, 2014).

However, in perspective for the people in India, innovative drug which is too costly to afford is not worthy. Also, there is opinion that India's IPR law enable lowering the drug price for public health and US should be protected. In reality, IPR law does not violate WTO requirements under TRIPS agreement, and India accounts for only about 1 percent of the market of the United States pharmaceutical industry(The New York Times, 2014).

9.4.2 GLEEVEC (Imatinib)

The Indian pharmaceutical industry had already sold copies of Gleevec at a 1/10 price, but Novartis, pharmaceutical company of Gleevec, insisted that it would hinder the development of the drugs for their patent protection. However, domestic IPR laws in India have priority over international law and the Supreme Court of India ruled on April 1, 2013, that the Patent Office and subordinate courts refused the patent application, and enabled production of generics legally(Yang, 2017).

9.5 Patent opposition

9.5.1 Patent Opposition in India

Though TRIPS established three criteria for granting a patent, the agreement does not offer a precise definition of these criteria, leaving a margin of interpretation for the national legislatures in WTO member countries. Another strategy to overcome IP barriers that has proven successful is to challenge patents in order to ensure that patent offices subject applications to the full rigor of a country's intellectual property law(Gaudino et al., 2017)

India, has used the TRIPS flexibilities to strengthen the patentability criteria, thereby facilitating local production of generic drugs and increasing the population's access to essential medicines while at the same time complying with WTO regulations. Because the range of permitting patent law is narrow, there is room for legitimate patent opposition without granting patents to new drugs based on the IPR Act(ISGLOBAL, 2016)

The Indian IPR law also provides an opportunity to the public to take part in a patent proceeding to challenge the patent applications and the granted patents by raising objections by filing an opposition with the Indian patent office. The Indian patent law provides two kinds of patent oppositions proceedings. The opposition proceedings before the grant of a patent are usually called pre-grant and those after the grant are usually called post grant opposition.

9.5.2 SOVALDI (Sofosbuvir)

SOVALDI (Sofosbuvir), which has a list price of $1,000 a pill in the United States, was rejected a patent by the Indian patent authority in January 2015 on

the basis it represented only minor changes to a previous formulation(Iyengar et al., 2016).

In September, 2014, Gliead, the pharmaceutical company that manufacture high-cost hepatitis C drugs such as SOVALDI and HARVONI, voluntarily signed license agreements with 11 Indian generic manufacturers to locally produce SOVALDI, HARVONI and EPCLUSA for distribution in 101 low-income countries. As a result, the total cost of sofosbuvir treatment per patient is reduced to $324 in India(Balakrishnan, 2017; Iyengar et al., 2016).

But, India has reversed course and granted approval to Gilead Sciences Incorporation's patent for its hepatitis C drug SOVALDI. After an appeal by Gilead, the Indian Patent Office of New Delhi approved its application for the drug saying it found its compounds to be 'novel' and 'inventive', which means there is a major change, in April 2016(Reuters, 2016)

9.6 Compulsory licensing

9.6.1 Compulsory Licensing in India

A compulsory license, also referred to as a non-voluntary license, is a license granted by an administrative or judicial body to a third party to exploit a patented invention, without the consent of the patent holder. Compulsory licensing is used in public health to address a variety of situations including: high prices of medicines; anti-competitive practices by pharmaceutical companies; failure by pharmaceutical patent holders to sufficiently supply the market with needed medicines; and in emergency public health situations. In practical terms

compulsory licensing can be used to bring down the prices of medicines and to ensure a sufficient supply of medicines in the market in cases where the patent holder cannot, or will not, provide sufficient supplies at the right price (UNAIDS, 2011).

With the passsage of the IPR law in 2005, India was supposed to become in compliance with the (Kumar et al.) agreement. Despite Indian long history for generics, amended IPR law was expected to be a major change in Indian pharmaceutical policy which motivated many multi-national companies to introduce new innovative drugs(Schoonveld, 2016).

For the drug price reduction and prevention of other problems associated with patent, the Indian government has started issuing compulsory licensing to local generic companies for particularly oncology agents(Schoonveld, 2016). Nonetheless, NEXAVAR is the only successful compulsory licensing case of India so far among several compulsory licenses.

9.6.2 NEXAVAR (Sorafenib)

Compulsory licensing of NEXAVAR was granted by a country on health grounds, where patients are unable to access a life-saving medicine. In an order dated 9 March 2012, the Controller of the Indian Patents Office ruled against the patent owner German pharmaceutical giant Bayer Corporation, the manufacturer of NEXAVAR(Bonadio, 2012).

With the ruling, Indian generic drug manufacturer Natco has received a right to start manufacturing and selling NEXAVAR, the drug for the treatment of advanced stages of kidney and liver cancer. Natco has already developed a process to manufacture the drug and received a license to manufacture the drug in bulk and to market it in April 2011.

Bayer launched the drug in 2006 and received a license to import and market the drug in India on 1 August 2007. The Patent Office found that Bayer did not import the drug at all in 2008 and only started importing in small quantities in 2009 and 2010.

In fact, while its global sales of NEXAVAR was $934 million in 2010, sales in India was Rs 16 crore in 2009. Also, only 2 per cent of the 8,842 patients needing the drug got the medicine, it observed. It seemed that patients need for the drug far exceed the supply of that. It could be the evidence that Bayer was not making the drug accessible to more people, so Natco was applied for a compulsory license legally(Intellectual Property Watch,2012)

9.7 Patient Access Program

9.7.1 Patent Access Program in India

In India, more than 1.3 million people developed cancer each year. Cancer is the third highest cause of death amongst non-communicable diseases (NCDs). Although affordability is often cited as the cause of this poor cancer care access, there are many other barriers to treatment. These include late diagnosis, limited and hard to-reach infrastructure, low awareness of treatment options, inadequate biomarker testing, lack of reimbursement of medicines, and poor adherence to treatment. Only one out of four patients who are prescribed medicines actually starts the treatment and only a few of these barriers are being addressed.

India does not have universal access to healthcare or centralized payers, however it does have large central and regional healthcare funding programs. These programs typically offer coverages to government employees and their families and a few programs are also designed for the economically disadvantaged segment of the population. For their access to drugs, various NGOs and pharmaceutical companies provide patient assistance programs(Limb, 2013).

9.7.2 Roche 'The blue tree' program

In 2015, Roche India developed "The Blue Tree" program in order to properly tackle the full range of barriers to cancer care. This single platform supports patients and their families with disease awareness and testing, funding solutions, home delivery of medicines, free medicines, treatment adherence support and standardized reports.

According to the Roche(https://www.roche.com/), the blue tree project supported over 4,000 patients in 2017. Roche partnered with more than 750 doctors and this enabled access to treatment across 300 cancer centers in India. Patients on the program have shown a 40% increase in therapy adherence rates.

10. Japan Case Review: New drug pricing policy

10.1 Introduction

Japan has a unique pricing policy which acknowledges 'the cost' in pricing and values highly the innovative drug through the 'premium' for developing new drugs. Due to this policy, the price of new drug, OPDIVO (nivolumab), has been the most expensive in the world. The indication of OPDIVO has been broadened and, accordingly, the financial burden of Japan has increased. In line with the pricing policy reform, Japan reduced the price of OPDIVO 50% in February 2017 with Price-Volume Agreement(PVA), which is one of the Managed Entry Agreement. Also, introducing the Health Technology Assessment(HTA) with Foreign Price Adjustment(FPA), Japan reduced the price of OPDIVO to 23.8% again in April 2018. We could get a valuable lesson from the case of OPDIVO in Japan, in terms of the importance of both initial pricing and re-pricing.

10.2 Background

10.2.1 Overall Health system

Japan is a country that adopts the Social Health Insurance system. It introduced National Health Insurance in 1961, and all citizens are covered by

health insurance through the principle of mandatory enrollment. The insurance is a combination type in which the insurance is divided into several. Employees' Health Insurance is for more than 1,800 mid- and large-size company and Government-Managed Health Insurance is for smaller firms and it is a collective health insurance. Those who are not covered by the Employees' Health Insurance or Government-managed Health Insurance are required to participate in the region-based National Health Insurance, and there are more than 3000 municipalities who act as the independent insurers(Schoonveld, 2016).

The main sources of funds are the premiums paid by the insured to each insurer, subsidies by the general government, and the co-payments of the medical users. The co-payment is a decentralization system and ranging from 10 to 30 percent. The co-payment rate is different depending on the age and employment status. There is a 'capping system' provided for the insurer to pay the co-payment exceeding a certain level so that the excessive medical burden does not arise(Lee, Lee, & Byeon, 2017).

An important principle for Japan's benefit package is 'no mixed treatment'. Japan prohibits both covered benefit and uncovered benefit at the same time. Inpatient, outpatient, and pharmacy are all based on the system of outpatient treatment, and the insurer pays the medical care fee to the medical institution according to the medical treatment reward score corresponding to each medical treatment item. A network of largely private hospitals and clinics is reimbursed on a fee-for service basis, although a DRG-based system is gradually being implemented over time since 2003(Lee et al., 2017; Schoonveld, 2016).

10.2.2 Universal Health Coverage in Japan

Japanese health system is close to the ideal Universal Health Coverage, which ensures all people could obtain the health services they need without suffering any financial hardship. However, maintaining healthcare financing system, under which most medications and people are covered, is getting difficult due to the aging society and the existence of high-price drugs such as anti-cancer agents. Approval of OPDIVO, which is topic of our case study, has raised the national discussion in Japan because of the possibility that the high-price of OPDIVO might collapse overall Japanese healthcare system(Fukuda & Igarashi, 2016).

Many countries that have social health insurance system like Japan have introduced Health Technology Assessment (HTA) for pricing and reimbursement decision. HTA implementation in Japan has been criticized at first because it might prohibit patients' access to medical treatments. However, the HTA has been been promoted as the solution of rising national burden of medical costs and has been tried for repricing recently. Japanese government expects that HTA could make Japanese health financing system sustainable, and therefore, it could ensure patients' access to essential medicines ultimately(Fukuda & Igarashi, 2016).

For the perspective on covering of new drug, a total of 304 New Molecular Entity(NME)s were listed in the NHI price list during October 2004 and December 2014 and the Japanese NHI coverage rate was 97.4%. The average time between marketing authorization and the initiation of reimbursement was 66 days and there were 88 drugs that gained premiums for innovativeness/usefulness. In terms of NHI coverage scope and speed, the Japanese pricing policy could be evaluated that it could secure the accessibility to new drugs very well than in

other countries setting public prices for reimbursement(Takayama and Narukawa 2016).

10.2.3 Negative list system

In National Health Insurance system, insurance benefits refer to benefits such as medical services provided to insured person. There are two methods for determining the scope of insurance benefits: 'positive list system' for listing the items to be paid and 'negative list system' for listing the items for non-payment and payment for all other items system which is not on the list(K. H. Kim, Kim, Yi, & Park, 2011).

Japanese drug list system is ‘negative list system’ with the purpose for UHC. However, OPDIVO, the drug expensive enough to threaten the entire health financing system in Japan, has arisen a nationwide question about the financial sustainability of ‘negative list system’. It is also argued that the Japanese pharmaceutical policy, which has not yet introduced medical technology evaluation for benefit list, should determine the appropriateness of payment and the appropriate drug price based on HTA(Lee et al., 2017)

10.2.4 Cancer in Japan

Cancer trends between 1958–2013 in Japan shows that decrease in mortality rates and an increase in incidence rates. Stomach and liver cancers mainly contributed to the decrease in mortality rates, reflecting the reduced attribution of infection-related factors (i.e. H. pylori and hepatitis virus). Prostate and female breast cancers was the main reasons for increase of incidence rates. Another thing noted was that incidence and mortality of cervical cancer began to increase from 1990(Katanoda et al., 2015). Despite the

increase of cancer incidence, the decrease of mortality rates would have been thanks to development of the cancer treatment. Cancer remains the main cause of death even though the mortality rates has been decreased, so it is clear that how to treat cancer is still an important issue.

Recent cancer treatment includes surgical treatment, radiotherapy, chemotherapy and immunotherapy. Immunotherapy is treatment elected as the breakthrough of 2013 in 'Science' and expected as the fourth generations cancer therapy. For example, Ipilimumab, Nivolumab and Pembrolizumab are immune checkpoint inhibitors that have demonstrated more effective results than conventional drugs in clinical trials. Nivolumab and pembrolizumab demonstrated predominantly high survival rate and durable objective response to advanced melanoma, NSCLC and other solid tumors with minimal adverse events(Suzuki, Ishida, Yoshikawa, & Ueda, 2016).

Globally, the price of anti-cancer drug has steadily increased. Also, new anti-cancer or immunomodulating drugs tends to be expensive especially in case of the 'innovative' drugs. Without proper intervention, the price of cancer drug would directly affects to health financing continuously(OECD, 2015).

10.2.5 Financial burden due to Cancer drug

In Japan, there has been no request for the economic data of drugs, medical devices, and interventions. In fact, even if economic data are submitted, the data has little influence upon decisions of pricing of the products. Consequently, economic data for only eight new drugs were submitted to the Ministry of Health, Labor, and Welfare (MHLW) from FY (fiscal year) 2006 to FY 2011 although there were 256 ingredients for reimbursement during the same period(Shiroiwa, Fukuda, Ikeda, & Takura, 2017).

However, Japan is one of the fastest aging countries in the world, facing a rapid rise in healthcare expenditure. According to MHLW, National healthcare expenditure was estimated approximately JPY 40 trillion (USD 364 billion as of May 2017, Bank of Japan), which accounted for 8.3% of GDP. As the expenditure was JPY 32 trillion (USD291 billion) and 6.4% of GDP ten years ago, the expenditure had increased by 25% and the rate had increased by 1.3 times. According to OECD health data, current expenditure of health is 11.2% of GDP, which is the third largest after the United States and Switzerland. This situation is exacerbated by newly developed and high-priced healthcare technologies such as anti-cancer and anti-hepatitis drugs. This has led to the growing awareness of the importance of economic evaluation and has sparked a trial implementation of cost-effectiveness evaluation for drugs and medical devices from FY2016(Shiroiwa et al., 2017).

10.2.6 Managed Entry Agreements

For managing financial burden, Japan introduced 'Price-volume arrangement (PVA)', one form of the Managed Entry Agreements. PVA is policy to adjust prices as volume increases after listing. Governments or insurers could manage pharmaceutical budgets based on the total value of sales, rather than on a per-unit price basis(Nguyen et al., 2014)

According to Pricing Reform announced in 2016, Japan increased the rate of cuts for high-cost drugs by up to 50%. Based on this, Japan lowered the price of SOVALDI and HARVONI in April 2016 by 31%, and in February 2017, the price of the drug is 50% lower than planned(Lee et al., 2017).

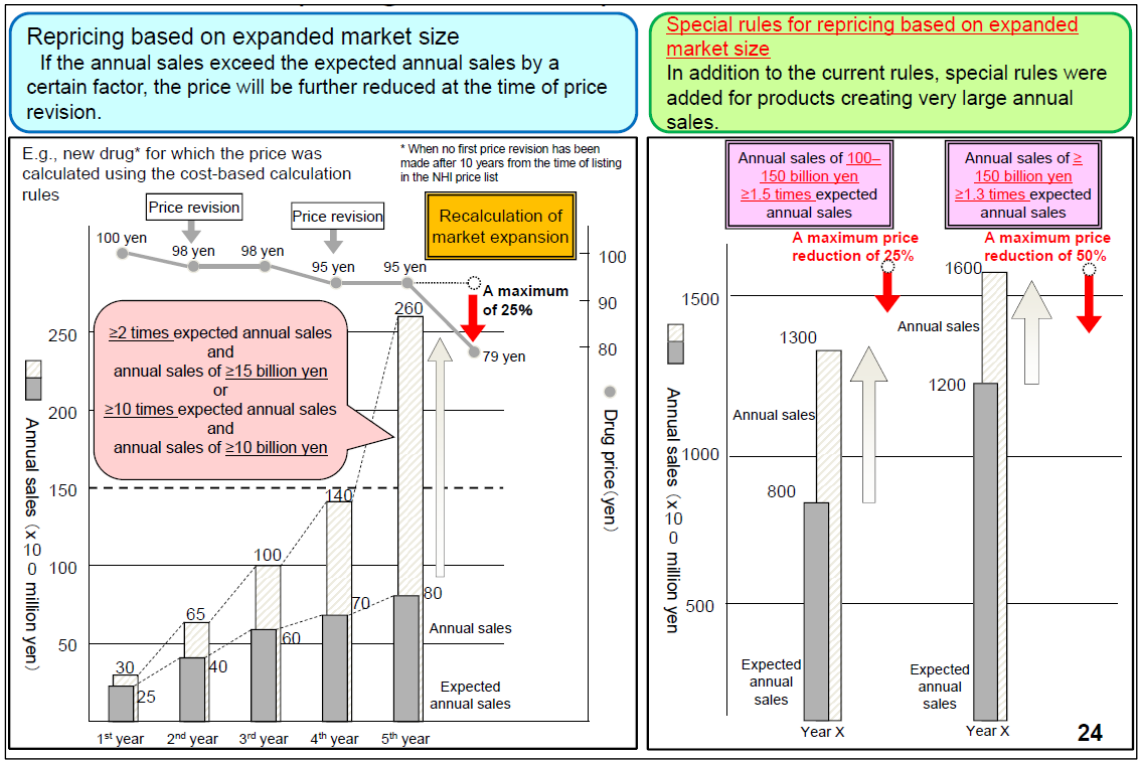


Figure 4 Repricing based on expanded market size

10.3 Drug Policy in Japan

10.3.1 New drug pricing policy

New drug applications are reviewed by the Pharmaceutical and Medical Devices Agency (PMDA), an agency within the Japanese Ministry of Health, Labor, and Welfare (MHLW). MHLW also determines coverage policy and pricing for healthcare products that are purchased by hospitals and pharmacies. National Health Insurance Prices are established by the Central Social Insurance Medical Council (CSIMC) a separate body within the MHLW. Every other year, the MHLW selects 20 members for the CSIMC from academia and various interest groups,

including the Japan Medical Association, the Japan Pharmaceutical Association, and the Japan Trade Union Confederation (Schoonveld, 2016).

The prices for new drugs are controlled by the MHLW in accordance with a structured system, consisting of comparative method or cost calculation method, and an adjustment based on international prices(MHLW, 2016).

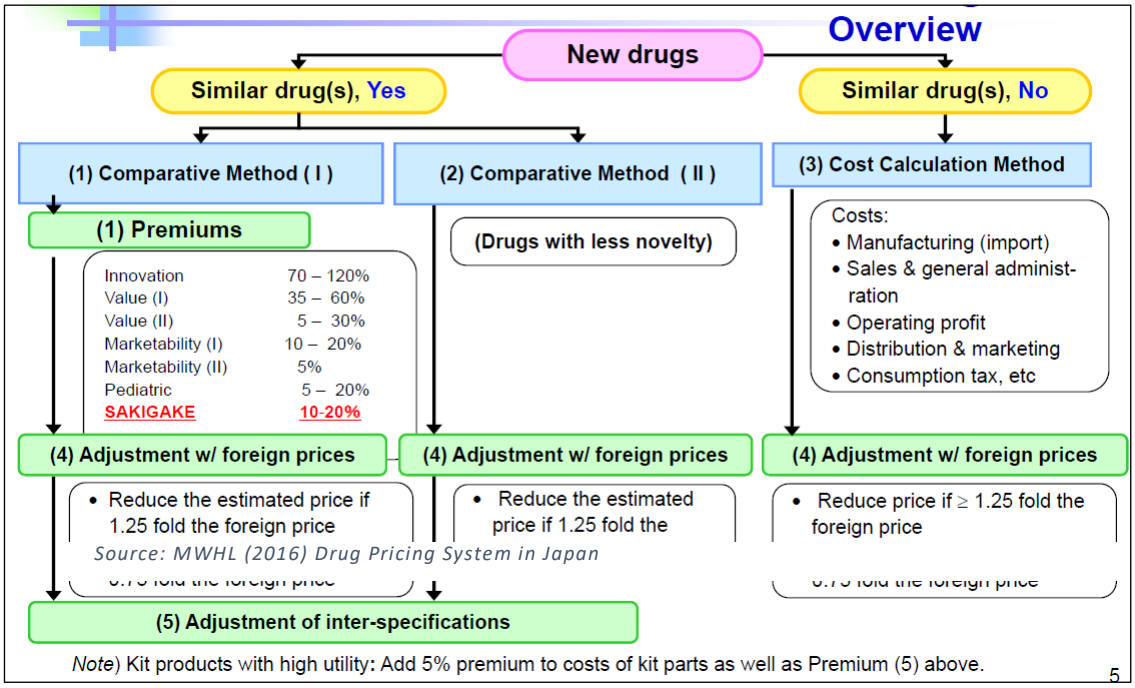


Figure 5 Price calculation method for new drugs

10.3.1.1 Comparative Method

Most drugs are approved on price under the comparative pricing method, which is similar to internal reference pricing. In this method, pricing is determined on the basis of a selected comparator and an improvement related

premium over the price of that comparator. Selection of the comparator is based on a sequential analysis of indication, mode of action and the chemical structure of the new agent in comparison with existing drugs. Choice of indication could have a dramatic effect on price, as it is the first factor that determines the choice of comparator(Schoonveld, 2016).

After selection of the drug comparator, the relative usefulness and innovativeness of the new agent are assessed to determine an appropriate price premium over the comparator drug. There are various categories with different price premiums and related requirements(Schoonveld, 2016).In case of a new but less novel drug, the price is set at the lowest among the prices of drugs in its class entered to the NHI Price List during the past several years(MHLW, 2016).

10.3.1.2 Cost calculation Method

With no an appropriate reference drug, the price of the new drug is set based on costs such as those of raw materials and manufacturing. These drugs are still subject to adjustment with average foreign price(MHLW, 2016)

10.3.1.3 Foreign Price Adjustment

Prices that are calculated on the basis of the comparator or cost-plus method are subject to a Foreign Price Adjustment(FPA), which is one of external reference pricing. Under FPA the price is compared to the average price of the United States, France, Germany and the UK and corrected up or down depending on the outcome of the comparison. Carefully planning prices and related sequencing for launch between the US, France, Germany and the UK could have a dramatic impact on the profitability of the Japanese opportunity for a new drug (MHLW, 2016; Schoonveld, 2016).

The FPA was originally introduced to reward for significant drug innovation. Even under the most favorable innovativeness premium of 120 percent, in perspective of manufacturer, it is hard to reach an acceptable price level for an innovative drug unless the comparator is an already high-priced drug(Schoonveld, 2016).

For example, the price of SOVALDI(Sofosbuvir), the drug for hepatitis C, was calculated based on the similar efficacy comparison method. The comparator was a combination therapy of Telaprevir, Ribavirin, and Peginterferon. Sofosbuvir is considered an innovative drug, and can attract a 100% premium. However, the calculated price of JPY 46,793.4 (USD 425.4), which represents the total price of the comparator and the premium, was less than 0.75 times the average foreign list price of JPY 92,402.9 (USD 840.0). Hence, the official price of Sofosbuvir was eventually raised to JPY 61,799.3 (USD 561.8) for a 400mg tablet(Shiroiwa et al., 2017).

10.3.2 SAKIGAKE: the extra premium of new drug

The SAKIGAKE designation system is applied to the world's first approval, of innovative drugs/medical devices/regenerative medicine products. It was created under the trial by the MHLW since June 2014, aiming at the development and provision of the leading-edge therapeutic drugs to patients in Japan ahead of the rest of the world(MHLW, 2016).

This SAKIGAKE provide not only 10-20% extra premium of drug price and but also priority of consultation and review, such as approval of drugs within 1-month consultation and 6 months review which is the half of the usual approval period.

There are four criteria of SAKIGAKE(MHLW, 2016):

1) innovativeness of the therapeutic drug

2) Seriousness of the target disease

3) Outstanding efficacy in the target disease

4) Drugs intended to be developed from the early development phase in Japan in order to obtain new drug approval for the first time in Japan.

In case of OPDIVO for the indication of biliary tract cancer, it met all four criteria, received the extra premium of SAKIGAKE and was get priority for early consultation and review(ONO & BMS, 2017).

10.3.3 Post management system: Re-pricing system

In Japan, post-management system for drug is based on investigative drug price adjustments. The MHLW conducts inspections every two years, and medical institutions and pharmacies are reimbursed at the prices listed in the drug price standards. The market price is usually lower than the list price of drugs due to the discount by medical institutions. The list price is reduced based upon the degree of divergence. If actual sales are much higher than the expected sales at the time of reimbursement, the official price is amended based on the MHLW's rule of expanded market size. Results of the cost-effectiveness evaluation also could be used for one of the re-pricing processes(Lee et al., 2017; Shiroiwa et al., 2017).

10.4 Policy Implementation - OPDIVO

OPDIVO is an immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. In Japan, ONO launched OPDIVO for the treatment of unresectable melanoma in September 2014. Thereafter, OPDIVO received an approval for additional indication of unresectable, advanced or recurrent non-small cell lung cancer in December 2015, unresectable or metastatic renal cell cancer in August 2016, relapsed or refractory classical Hodgkin lymphoma in December 2016 and recurrent or metastatic head and neck cancer on March 24, 2017. In addition, ONO has submitted supplemental application for additional indication of gastric cancer, and is conducting clinical development program including esophageal cancer, gastro-esophageal junction cancer, small cell lung cancer, hepatocellular carcinoma, glioblastoma, urothelial cancer, malignant pleural mesothelioma, ovarian cancer, biliary tract cancer, etc(ONO & BMS, 2017).

10.4.1 Pricing at market entry

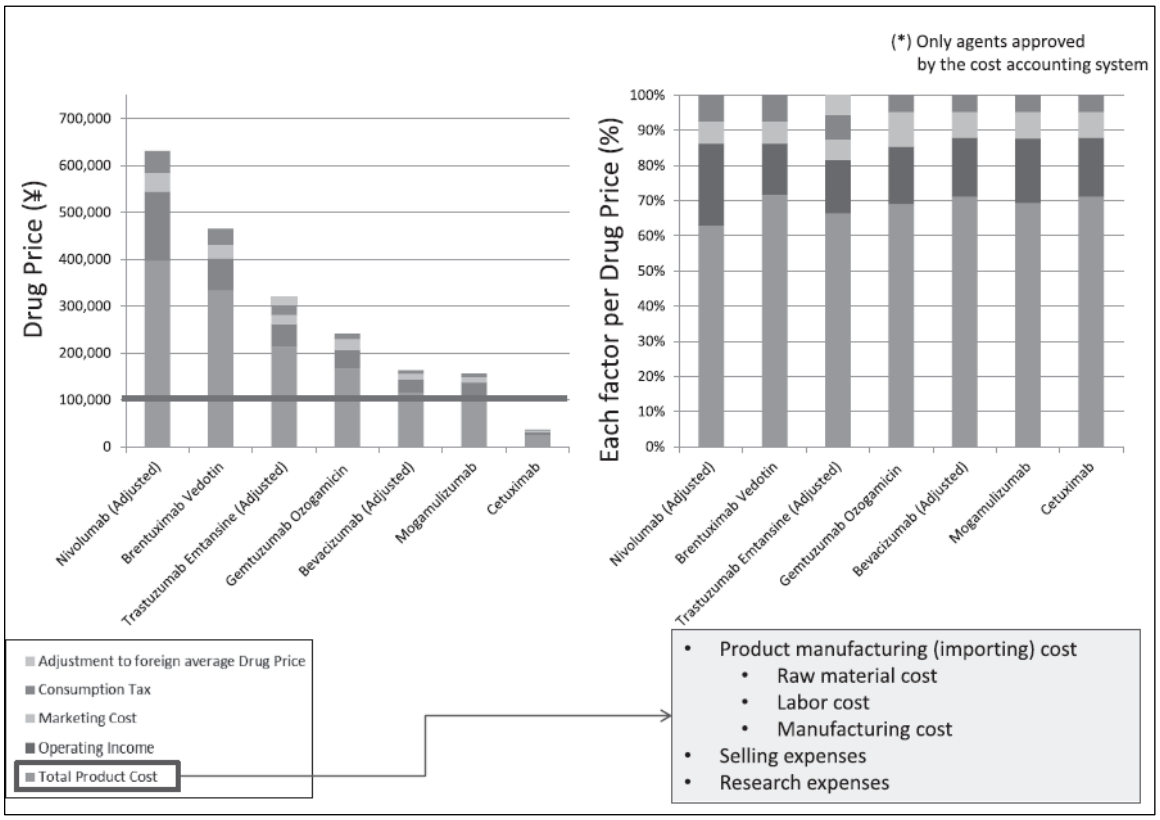


Figure 6 NHI Pricing at market entry

Source: Nakajaima et al. (2017). "Analysis of New Drug Pricing and Reimbursement for Antibody Agents for Cancer Treatment in Japan." Journal of the Institute of Rehabilitation Science 7(3): 173-184

Initially, OPDIVO was new innovative drug for melanoma which has no similar drugs to compare in 2014. So, cost-plus pricing was adapted in pricing OPDIVO based on data submitted by its pharmaceutical company. Seen as the chart above, OPDIVO price consisted of consumption tax, marketing cost, operating income and almost total product costs. Especially, more than 60% of the price was for the product costs. The product costs contained raw material cost, labor cost, manufacturing cost, selling expenses and research expenses. When compared with other drugs which used cost-plus based pricing, percentage of

the total product costs was not that different but the price of OPDIVO was too expensive than any other drugs(Nakajaima & Aruga, 2017).

According to the documents of Central Social Insurance Medical Council (CSIMC) in 2014, OPDIVO obtained approval in Japan ahead of the world. Also it had a new action mechanism, and the usefulness in the Japan Phase II trials was acknowledged. As a treatment option for malignant melanoma, it considered clinically significant than the traditional treatment. This evaluation of OPDIVO made the extra premium for pricing up to 60%.

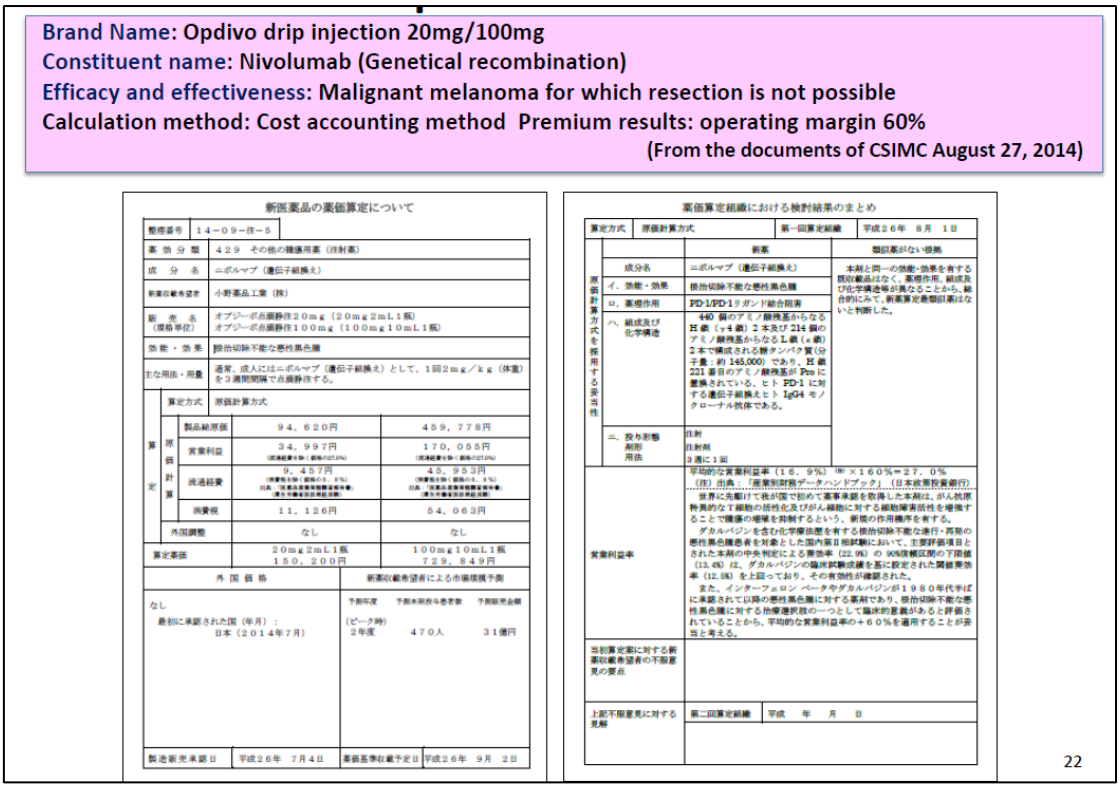


Figure 7 NHI Pricing Case(1)

Source: Japanese Pharmaceutical Manufacturers Association (2014) NHI pricing formula in Japan

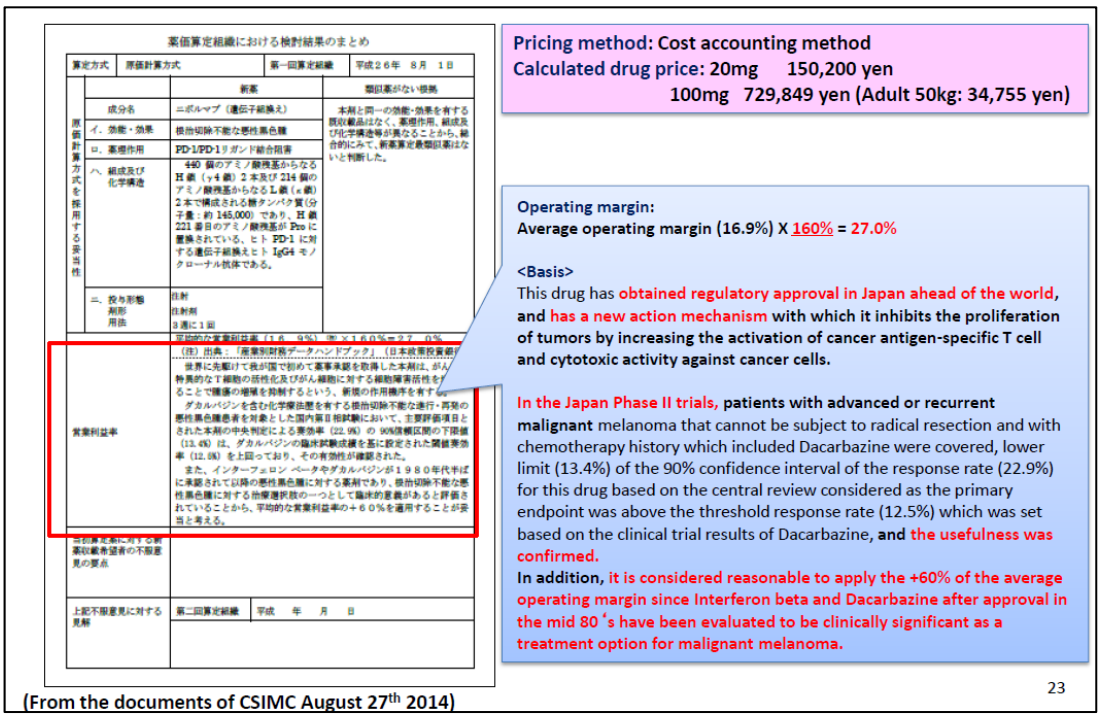


Figure 8 NHI Pricing Case(2)

Source: Japanese Pharmaceutical Manufacturers Association (2014) NHI pricing formula in Japan

Approved in Japan ahead of the world, Foreign Price Adjustment(FPA) could not be applied to the OPDIVO in 2014. So, the first price of OPDIVO was determined with this basis calculation at higher price, JPY 730,000 for 100mg without any adjustment.

10.4.2 The first price reduction with MEA

In line with Pricing Reform announced in 2016, Japan increased the rate of discounts for high-cost drugs by up to 50%. In the case that the sales volume is not high but total sales reach 150 billion yen, the MHLW(2016) announced that the drug price also would be cut to 50%. It means that drugs with large absolute sales are subject to a larger reduction rate even if the growth rate is not large.

Considering that 'high-cost drugs' with revenues of more than 150 billion have a large impact on health insurance finances, it could eliminate financial uncertainty through drug price adjustments(Lee et al., 2017). According to MHLW (2018), intermediate re-evaluation and ‘Emergency Cuts’ were also allowed even if a revaluation cycle of 2 years has not yet arrived.

OPDIVO, approved as a drug for melanoma was scheduled to cut the price through post drug evaluation system based on the results of the actual transaction in September 2015. However, the drug price was not large at the time of the investigation and drug price cuts were suspended. Since December 2015, the amounts of claims have increased 40 times as the indication of OPDIVO has gradually expanded and the usage has increased rapidly. Although the scheduled reduction of drug price was April 2018 based on the actual transaction in September 2017, OPDIVO was continuously imposing a heavy burden on finance since December 2015(Lee et al., 2017).

Japan reduced the price of OPDIVO to 50% in February 2017 with the ground of the ‘Price-volume arrangement’ and ‘Emergency Cuts’ announced in the drug pricing system reform in 2016. At that time, claims for OPDIVO exceeded JPY 150 billion, which was the criteria for price reduction up to 50%(Lee et al., 2017).

10.4.3 The second price reduction with HTA & RFA

MHLW announced the reduction of the price of OPDIVO used for treatment of lung cancer by 23.8% from about JPY 365,000 yen to 277,000 yen per 100mg in April 2018(The Japan Times, 2018).

When reassessing the price of drug in 2018, the revised rate related to the actual transaction price showed a decrease of 1.36% overall. Adding to this rate, two policy of the drug pricing reform in 2016, Health Technology Assessment

(HTA) and Foreign Price Adjustment (FPA) would have been influenced new price of OPDIVO(The Japan Times, 2018).

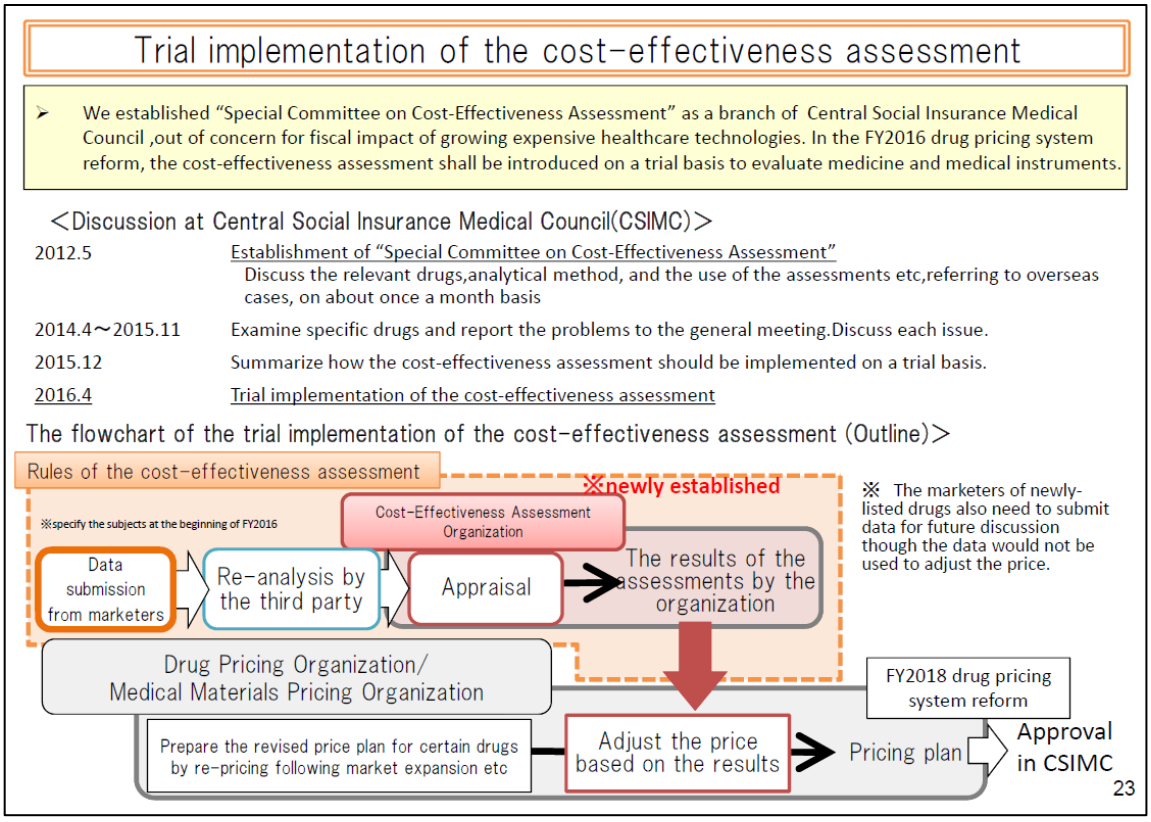


Figure 9 Trial implementation of the cost-effectiveness assessment

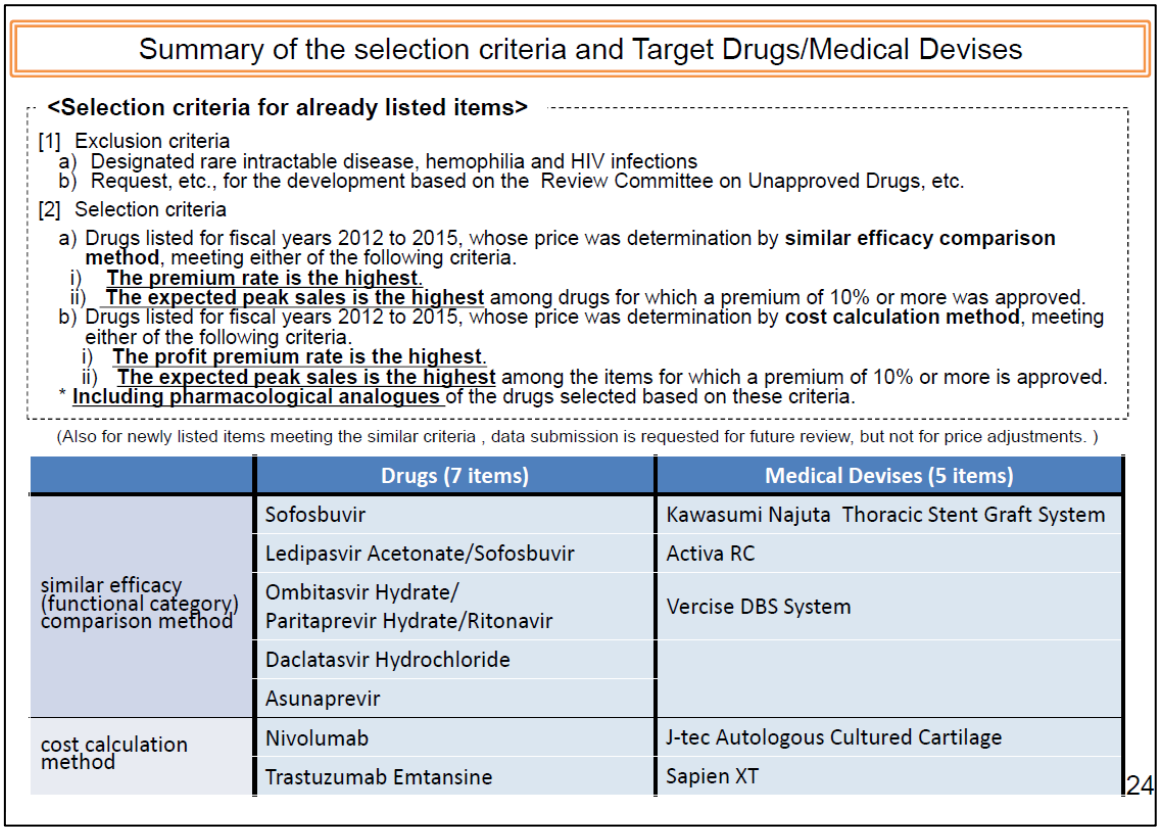
In drug pricing system reform in April 2016, Japan introduced the trial implementation of the cost-effectiveness assessment, one of HTA, to evaluate the medicine and medical instruments for reducing the fiscal impact of expensive healthcare technologies.

OPDIVO was selected to one of the trial medicines, with two criteria(MHLW, 2018):

Source: MHLW (2018) Update of Drug Pricing System in Japan

1) the profit premium rate is the highest

2) the expected peak sale is the highest among the items for which a premium of 10% or more is approved.



Summary of the selection criteria and Target Drugs/Medical Devises

<Selection criteria for already listed items>

[1] Exclusion criteria
a) Designated rare intractable disease, hemophilia and HIV infections
b) Request, etc., for the development based on the Review Committee on Unapproved Drugs, etc.

[2] Selection criteria
a) Drugs listed for fiscal years 2012 to 2015, whose price was determination by **similar efficacy comparison method**, meeting either of the following criteria.
i) **The premium rate is the highest**.
ii) **The expected peak sales is the highest** among drugs for which a premium of 10% or more was approved.
b) Drugs listed for fiscal years 2012 to 2015, whose price was determination by **cost calculation method**, meeting either of the following criteria.
i) **The profit premium rate is the highest**.
ii) **The expected peak sales is the highest** among the items for which a premium of 10% or more is approved.
* **Including pharmacological analogues** of the drugs selected based on these criteria.

(Also for newly listed items meeting the similar criteria , data submission is requested for future review, but not for price adjustments.)

	Drugs (7 items)	Medical Devises (5 items)
similar efficacy (functional category) comparison method	Sofosbuvir	Kawasumi Najuta Thoracic Stent Graft System
	Ledipasvir Acetonate/Sofosbuvir	Activa RC
	Ombitasvir Hydrate/ Paritaprevir Hydrate/Ritonavir	Vercise DBS System
	Daclatasvir Hydrochloride	
	Asunaprevir	
cost calculation method	Nivolumab	J-tec Autologous Cultured Cartilage
	Trastuzumab Emtansine	Sapien XT

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Figure 10 Summary of the selectino criteria and target drugs/medical devices

Source: MHLW (2018) Update of Drug Pricing System in Japan

According to the MHLW(2018), the results of the cost-effectiveness assessments by the organization affected the adjustment of the drug price. This price reduction of OPDIVO, which was one of the 7 trial medicine for cost-effectiveness assessment, would have been influenced by this HTA.

Under Japanese Foreign Price Adjustment (FPA), the price of drug price is settled compared to the average price of the United States, France, Germany and the UK and corrected up or down depending on the outcome of the comparison.

Unlike the condition that there was no comparable price of OPDIVO in 2014, there are the list prices of OPDIVO in USA, France, Germany, and the UK. In reality, initial price of OPDIVO in Japan was more than 5 times in UK (JPY 144,000), and 2 times in USA (JPY 296,000)(Nikkei, 2016). This gap would be considered to the re-price of OPDIVO, with the ground of FPA and lowered the price in Japan.

10.5 Outcome

For the reform of the system, the price of OPDIVO was amended to 277,000 yen per 100mg. Comparing with the initial price of JPY 730,000 it was reduced by 60% for 4 years(The Japan Times, 2018).

Recently, OPDIVO has increased the financial burden in Japan due to high-price of the drug and various indication including non-small cell lung cancer, which containing a large patient population. Lowering the price of OPDIVO to 50% in February 2017 with Management Entry Agreement, and 23.8% in April 2018 with Health Technology Assessment and Foreign Price Adjustment would be proper solution among the ways they could have taken place in a situation where drug prices were already high.

For improving the access to the high-cost medicines, various pricing policy could be adapted like this case. The process of setting new drugs is more

complex when there is not the price of the drug for reference outside the nation, and the price policy in a nation could be either beneficial or harmful for the nation.

Taking all into account, the price of OPDIVO with Japanese policy could be valuable lesson for how not to set the unreasonable price initially and how to discount the high cost after the initial price.

11. South Korea : Risk Sharing Agreement

11.1 Introduction

The NHI in Korea was first enforced in 1977 for large-scale workers and then expanded to cover the whole population in 1989.

Korean NHI has achieved universal coverage in a relatively short period of time but was limited in terms of the depth and height of coverage. Some medically necessary services were excluded from the benefit basket, and the co-insurance rate for covered services was relatively high; 20% for inpatient service, 30% for prescription drugs, and 30 ~ 60% for outpatient service depending on the type of institution.

To improve the coverage of NHI, the Korean government has been continuously expanding the benefit basket and has lowered the co-insurance rate for patients who suffer from severe diseases. However, the Korean government also has the goal of maintaining NHI financing in a sustainable manner.

The share of healthcare expenditure among national income was 7.6% as of 2017, which is higher than other Asian countries but relatively low among Organization for Economic Co-Operation and Development (OECD) countries. Medical goods including pharmaceuticals account for 22.5% of healthcare expenditure, which is lower than the number in the past and that of other Asian

countries but is still higher than that of other OECD countries. In Korea, pharmaceutical sales per capita in PPP were 652.6 USD in 2017, which was higher than the average of other OECD countries (OECD, 2018).

In response to rapidly rising drug expenditure, the government announced the implementation of drug expenditure rationalization plan (DERP) in May of 2006 (MOHW, 2006), which focused on the introduction of a “positive list system (PLS)” and price negotiation. In addition, the Ministry of Health and Welfare (MOHW) made a number of price cuts several times in the off-patent market.

11.2 Reimbursement and Pricing of Drugs

11.2.1 Positive list System

In 2006, the Ministry of Health and Welfare (MOHW) announced the introduction of the positive list of reimbursable drugs. Before that time, all drugs approved by Ministry of Food and Drug Safety (MFDS) had to apply for listing on NHI formulary, and most of them were listed except for drugs used to relieve symptoms of minor illnesses. However, since 2007, the pharmaceutical companies make the initial decisions whether to apply for listing, and only drugs which are able to verify their value in terms of comparative effectiveness and cost-effectiveness can be listed. For new drugs to be listed at a higher price compared to existing drugs, they should be proven to be superior to their comparators and their cost-effectiveness should also be demonstrated based on pharmacoeconomic (PE) data (MOHW, 2006). PLS is a paradigm shift from the cost-based approach to the value-based approach.

11.2.2 Listing process

The process begins with the submission of applications and related documents. Health Insurance Review and Assessment Service (HIRA) staff reviews the submitted evidence, and the pharmaceutical benefit coverage assessment committee (PBCAC), an independent committee, considers the submitted cases and makes recommendations on the listing. If the submission includes full economic evaluation data, an Economic Sub-Committee (ESC) reviews the technical aspects of it before the PBCAC meeting (Bae et al., 2016).

If there is no re-evaluation request from the company, HIRA reports the deliberation results to MOHW, and the price negotiation begins. The National Health Insurance Service (NHIS), not HIRA negotiates the price with the sponsoring company.

If the NHIS and the manufacturer fail to reach an agreement on the price during the negotiation, the submitted drugs will not be listed, even if it was recommended by PBCAC.

However, for drugs that are regarded as essential for treatment, the rule of rescue can be applied. Drugs that meet all of the following conditions are considered as “medically necessary” or “essential”: There are no alternative treatments; The drug is used to treat severe life-threatening diseases; It is used for rare diseases and is considered necessary to treat those patients; The health benefits of the drugs are significant and supported by evidence (Bae et al., 2016).

If price negotiation fails for the above drugs, the benefit coordination committee can determine the price coordinating each party’s interests (compulsory listing). Until now, only 10 drugs have been recognized as “medically necessary”

11.2.3 Access to Medicine

There have been concerns about the accessibility to innovative new drugs since the implementation of PLS.

Under the negative list system, all drugs except for a few were listed, but since 2007, the rejection rate has increased. As of 2014, more than 34.4% of submitted drugs were rejected. Especially, the rejection rate for anti-cancer drugs was higher than that of other categories of drugs (48.4% vs. 28.4%), and the main reason for the rejections was that the submitted drugs were not cost-effective(Bae et al., 2016). This was a somewhat predictable phenomenon as drugs with insufficient value cannot be listed under the PLS. In fact, among the rejected drugs, only a few were regarded as medically important (Bae, 2013).

Nevertheless, to improve accessibility to high-cost drugs, the Korean government decided to increase the upper threshold of acceptable incremental cost-effectiveness ratio (ICER) for several severe diseases in 2013, and introduce a risk sharing agreement (Jan 2014). In addition, the submission of PE data was exempted for drugs for rare diseases in 2015 (Bae et al., 2016).

11.2.4 Price volume agreement

Price-volume agreement (PVA) is a system that adjusts the price as the sales volume increases. It is used to share the risk from unexpected financial expenditure. The extent of the price adjustment is determined through negotiation between the company and NHIS.

The sponsoring company submits the expected sales volume when they apply for listing. If the sales volume exceeds the expected volume by more than certain percentage, the company should lower the price according to the

negotiation results with NHIS. The followings are cases in which price adjustment are required (Lee et al., 2017). ; When drug use exceeds the estimated volume by more than 30% (type I); When the volume has increased by more than 30% in a 6 month period after new indications were added (type II); and when the sales volume raises by more than 60% year on year (type III). However, the extent of price cuts is limited to 10% to minimize the adverse impact on the market. Therefore the cost containment effect of PVA was not large in size.

11.3 Measures to improve accessibility

11.3.1 Risk sharing scheme

Risk sharing agreement (RSA) was introduced for the applicant and the insurer to share the risk (financial risk and the risk of uncertain treatment effects) of listing new drugs. Among the types of risk sharing (Walker et al., 2012), PVA and RSA are in place in Korea.

Five different types of RSA plans were suggested by the government; coverage with evidence development, conditional treatment continuation + money back guarantee, expenditure cap, refunds, and per patient utilization cap. According to Walker's classification (Walker et al., 2012), two are outcome-based and three are financial-based approaches (Lee et al., 2016).

In the case a new drug is listed with coverage with an evidence development (CED) plan, the sponsoring company has to collect real-world evidence according to a predetermined protocol, and coverage decisions should be adjusted based

on evidence. Until now, one drug (Evoltra®) was listed with CED and evaluated based on the collected data (Lee et al., 2016).

Conditional treatment continuation + money back guarantee is called the outcome-based approach and is applied at the patient level. The NHIS reimburses the cost only for those who achieved a target effect. If a patient fails to achieve a pre-determined target, the company has to refund a certain proportion of the drug cost to NHIS.

Expenditure cap, a non-outcome based and population level approach, is applied when there is uncertainty in the budget impact. If the claimed cost exceeds the agreed annual expenditure, the company refunds the proportion of the excess amount.

Refund, a non-outcome based and population level approach, is the most frequently used plan, where the company refunds the gap between the effective price and listed price to the insurer.

Utilization cap/fixed cost per patient, non-outcome based and patient level approach, limits the reimbursable length of treatment. If the patient is judged to require further treatment after the agreed cycle, the company refunds the full or partial cost of the extra treatment or the first of several cycles of treatment is provided for free for all patients.

All RSA plans except for CED intend to meet the cost-effectiveness criteria by decreasing the effective price in a way that the pharmaceutical company refunds the gap between the listed price and the cost-effective price, or pays the drug cost of non-respondents (Lee et al., 2016).

Looking at the results of the negotiation over the past few years, both pharmaceutical companies and the insurer prefer a non-outcome based plans to

an outcome-based approach. It is because there is an administrative burden for monitoring outcome indicators. Outcome indicators should be clear and easy to measure, and all stakeholders should agree to use it in decision making. In addition, details of decisions based on the outcome indicators should be determined first. Up until 2017, most drugs that applied for listing with RSA plans chose to refund the price gap (Bae, 2018).

Not all drugs can apply for RSA. Currently, drugs which meet the following conditions can apply for an RS plan: Expensive drugs which are used for life-threatening cancer or rare diseases and which don't have any alternatives or any drugs with the same therapeutic position (Lee et al., 2016).

Table 9 shows the drugs that have been listed with RS plan by the end of 2017. Among the 17 drugs, one was listed with CED, and three were listed with utilization cap per patient and discounted treatment initiation. Other drugs were listed with refunds. For two drugs, Keytruda® and Obdivo®, the expenditure cap was applied in addition to refunds. For three drugs, the RSA was expired (Bae, 2018).

Table 9 The drugs listed with RSA plan by the end of 2017

Product	Indications	RS type
Clofarabine 20mg/20ml (Evoltra®)	ALL in paediatric patients	CED
Cetuximab 5mg/mL (Erbitux®)	Colorectal cancer	Refund
Lenalidomide hemihydrate 5,10,15,25mg (Revlimid®)*	Multiple myeloma	Refund
Enzalutamide 40mg (Xtandi®),	Metastatic castration-resistant prostate cancer	Refund

Crizotinib 200mg, 250mg (Xalkori®)	ALK+ or ROS+ non-small cell lung cancer	Refund
Pirfenidone 200mg (Pirespa® tab)*	Idiopathic pulmonary fibrosis	Refund
Regorafenib 40mg(Stivaga®)	Gastrointestinal stromal tumors(GIST)	Refund
Pomalidomide (Pomalyst® cap)	Relapsed/refractory multiple myeloma	Refund
Pertuzumab (Perjeta®)	HER2 positive metastatic breast cancer (first line)	Utilization cap per patient
Trastuzumab emtansine(Kadcyla®)	HER2 positive metastatic breast cancer (second line)	Utilization cap per patient
Pembrolizumab(Keytruda®),	non-small cell lung cancer	Refund+exp cap
Nivolumab(Obdivo®)	non-small cell lung cancer	Refund+exp cap
Eculizumab inj. 300mg (Soliris®)	paroxysmal nocturnal hemoglobinuria (PNH)	**Refund(pilot project)**
Galsulfase inj. 5mg (Naglazyme®)	Mucopolysaccharidosis VI	Refund(pilot project)
Alglucosidase alfa(Myozyme®, Genzyme Corp.) *	Pompe's disease	Refund(pilot project)
Palbociclib 75mg,100mg,125mg (Ibrance®)	Metastatic breast cancer	Refund
Osimertinib Mesylate 40mg, 80mg (Tagrisso®)	Non-Small Cell Lung Cancer	Discounted treatment initiation

* RS contract expired.

Whether to apply for listing with RS plan is the sponsor's choice. The drug with RS plan goes through the PBCAC deliberation and the price negotiation process with NHIS like other drugs. In the process, the subcommittee of RSA

considers if the drug is eligible for RS and if the type of RS plan is appropriate. PBCAC judges the cost-effectiveness of the drug considering the specific RS plan suggested by the company, and NHIS negotiates both real price (effective price) and nominal price (list price) with the sponsoring company and signs a contract with them.

If the negotiation reaches an agreement, the RS plan will be applied for four years, and during the last year of the term, the company and NHIS negotiate on whether to renew the contract and outline the detailed conditions of contract for an additional 4 years (Lee et al., 2016).

Details of the RS contract are confidential except for type of RSA, which is publically available. For the patient, it is important to determine what price will be the basis for determining the copayment amount. In Korea, after the patient pays the copayment based on the nominal price, the insurer later refunds the patient the difference between the copayment calculated based on the nominal price and the actual price (Bae, 2018).

Early in the introduction of RSA, indication expansion was not permitted, but nowadays, it is allowed except for CEDs (Kim, 2018; Lee, 2018).

If generics or drugs with the same therapeutic position are listed, the contract cannot be renewed. In case the generics are listed before the RS contract term ends, the contract is terminated even if the contract period remains (Kim, 2018; Lee, 2018).

When a contract renewal is possible, the drug is re-evaluated based on updated evidence and contract terms are subsequently negotiated with NHIS.

Until now, only two cases, Erbitux® and Xtandi®, completed re-evaluation. And for Evoltra®, the contract term was extended by one year to enroll a sufficient number of patients in a clinical study (Bae, 2018).

11.3.2 Exemption of submitting PE data

Some drugs are exempted from submitting PE data.

To improve access to new drugs, HIRA newly defined the cases for which the submission of PE data is exempted (May 2015). Drugs that meet all four conditions are exempt from submitting cost-effectiveness data, but instead, their sales volume is restricted (drug expenditure cap is applied), and the price in other countries are monitored after listing. As of December 2017, Caprelsa®, Adcetris®, Imbruvica®, Vimizim®, Zykadia®, Blincyto®, Diterin®, Defitelio®, Zelboraf®, Lynparza®, Meqsel®, Olita® were listed through this route (Kim, 2018).

Table 10 shows the criteria for exemption of PE data

Table 10 Drugs that are exempted for submitting PE data

Criteria	Definition
1.Disease	Ultra-rare diseases (less than 1000 pts.) or cancer
2.Clinical need	There isn't any alternative treatment, or
	There are no comparable treatments that are equivalent in the position of treatment process. Drugs are used for life threatening diseases
	Approved by MFDS with single arm study (without control group)

3.Difficulty in evidence generation (should meet at least one condition)	Approved by MFDS with phase II trial with control group
	Committee admits that the evidence generation is difficult for rarity of disease
4.Number of countries who reimburse that drug	Drug is listed in more than three of the A7 countries (France, Germany, Italy, Japan, Switzerland, United Kingdom, United States). The submitted price must be lower than the lowest level of A7 countries

11.4 Cases of reimbursement and pricing of high priced new drug

11.4.1 Sovaldi ®& Havoni®

Among DAAs listed, Sovaldi® and Harvoni® were listed in May 2016. Two drugs demonstrated their superiority compared to existing drugs, and proved their cost-effectiveness with supporting evidence (Lee, 2018).

Sovaldi® and Harvoni®, known as innovative but controversial in coverage due to the huge budget impact, went through the routine process of reimbursement and pricing of new drugs in Korea. PBCAC made a positive recommendation based on the submitted drugs' comparative effectiveness and cost-effectiveness. The company submitted the comparative effectiveness and cost-effectiveness data according to the sub-genotype of Hepatitis C, and the committee decided to make a different recommendation based on the genotype.

Sovaldi® was not recommended for genotype 3, 4 and 1b, because the PE data was not submitted for genotype 3, 4, and there was uncertainty on clinical effectiveness for genotype 1b (Lee, 2018).

Harvoni® was not recommended for genotype 1b, as it was not cost-effective for that subgroup when it was compared to Daklinza + Sunvepra (Lee, 2018).

For both drugs, the indication was expanded in Aug. 2016, three months after they were listed. Following the indication expansion, the price of Sovaldi® has been lowered by 5%, which is required by MOHW. For Harvoni®, the company voluntarily lowered the price by 16.67%. Only one year after listing, claimed expenditure of Sovaldi® totalled 140 billion won, and the price was lowered by an additional 5% according to price volume agreement. Because the maximum price adjustment is limited to 10% under the current price-volume agreement formulae, Havorni® didn't have to lower the price further as it had already lowered its original price by 16.67%. In Korea, a 12-week treatment cost of Sovaldi® is 21.6million won, and a 24-week treatment cost is 43.2 million won. For Harvoni, a 12-week treatment cost is 25million won (Lee, 2018).

Drugs used for hepatitis C cannot apply for risk sharing as they are not included in the range of diseases that can apply for RSA. And, NHIS did not limit the cap on spending, as there is no rule for controlling the total expenditure of drugs except for the price-volume agreement in case the drug is listed through a routine process. For drugs listed with a risk-sharing plan or drugs listed without PE data according to PE exemption criteria, NHIS can limit the total expenditure in the contract.

11.4.2 Opdivo® and Keytruda®

Immune checkpoint inhibitor is a new type of anticancer drug that attacks cancer cells by activating immune cells of a patient. It targets immune checkpoints which regulates immune system of a patient.

Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®) is the first immune checkpoint inhibitor listed in Korea. Both are PD-1 inhibitors that keep immune responses by blocking the binding of PD-L1 to PD-1.

Among the patients who were treated with these drugs, some showed long survival rates, but the response rate was not high. On the other hand, the treatment cost per patient was very high, and the indication is expected to expand in the near future, which means it may not be affordable to reimburse these drugs. At the current price level, the annual treatment cost of Opdivo® is 69 million won and 99 million won for Keytruda®(Lee, 2018).

Both Opdivo® and Keytruda® were listed in Aug. 2017 with a risk-sharing plan. Both have to refund the gap between the list price and actual contracted price, and the total expenditure cap is imposed on each drug. The price will be re-negotiated when the indication is expanded (Lee, 2018).

In the case of Opdivo® and Keytruda®, a distinctive feature is that, unlike other drugs, both drugs have restrictions on prescribable institutions. That is, only medical institutions with a multidisciplinary team can prescribe two drugs.

11.5 Challenges

South Korea is actively using health technology assessment (HTA) for reimbursement and pricing of new drugs, which is rarely used in Asian countries. In addition, the insurer is making aggressive efforts to purchase value through negotiation. Intermittent price cuts in the off-patent market also contributed to the stable management of total drug costs.

However, there were concerns that the accessibility of new medicines had deteriorated since the PLS was introduced. Although there is no evidence that the acceptance rate of new drugs in Korea is lower than that in other countries with similar policies (Clement et al., 2009; Bae, 2011; Bae et al., 2015), the government took some complementary measures to cope with the accessibility issue. RSA is one of them.

Stakeholders from industry were generally positive about RSA's performance. They thought that RSA improved access to high-cost new drugs at a price that is acceptable to NHI. They expressed this as a win-win strategy; a situation where no one loses. Even though all stakeholders agree that the accessibility has improved after the introduction of RSA, some disagree about broadening the range of drugs to apply for RS plans (Lee et al., 2016; Bae, 2018).

The industry insists that other diseases should also be allowed to apply for RS, and even for drugs that have alternatives listed, re-signing a contract should be permitted.

Patient and citizen group took a conservative stance on the expansion of scope for risk sharing even though they also recognize the contribution of RS in improving access to high-cost new drugs. They worry that the transparency of the pricing system will deteriorate if RSA is expanded because the price of RSA-

listed drugs is confidential and not publically available. Their argument is that RSA should be applied in limited conditions, even though they also oppose limiting RS applications only to cancer and rare diseases.

Between accessibility and affordable prices, RSA was adopted as a compromise, but instead the pricing system had to suffer a loss of transparency.

In addition, there is criticism that the PE submission waiver policy does not require active efforts of the manufacturers to solve the uncertainties of the evidence but opens the way that can be easily listed. Some insist that listed drugs should be re-evaluated periodically based on updated evidence, as there are many uncertainties surrounding the efficacy at the time of listing.

Although there are claims by the pharmaceutical industry that the price level of Korea is lower than that of other countries, it is difficult to trust the results of price comparison between countries based on published data. Price transparency has already declined globally, and therefore the published data is far from the actual price paid by the national health authorities.

12. Conclusion

Pharmaceuticals play a vital role in the health system, representing the third largest expenditure of health care spending and managing a number of diseases and, in some circumstances, they replace the use of costly health care services(Jacobzone, 2000). However, the sky-rocketing prices of new medicines, especially in oncology, hepatitis C, multiple sclerosis or for rare diseases, have raised questions and challenges. First of all, in a number of countries, particularly LMIC, these drugs are not affordable, or not accessible to all patients who really need them. Accordingly, payers, providers and the public are questioning the rationale for such high prices and their legitimacy(Howard, Bach, Berndt, & Conti, 2015).

Among other things, the impact of IPR protection, patents in particular, on product prices is straightforward. Patents, by providing monopoly power to the patent-holder, enable the latter to raise the price of the patented good above the level that would have prevailed in a competitive market. This is the immediate effect of patents. TRIPS has strengthened this phenomenon through perpetuating the patent impacts on pharmaceutical prices. On the other hand, given ethical and economic issues brought about by pharmaceutical products, TRIPS is carrying flexibilities to nullify or circumvent patents, which should be strategically utilized by countries.

Compulsory Licensing can be conceived of as solutions to access patented products and the Paragraph 6 System is only a solution for products patented in the exporting country. Given the price impact of patents, which strongly influence overall access to health care, these solutions are crucial for patented products. Furthermore, the full implementation of TRIPS in all major exporting

countries, including India, will reduce the future production of generic versions of new medicines. If patents are granted, there must be no generic copying unless Compulsory Licenses are issued. This report presented several case analysis to help explore the lessons needed to tackle related challenges : Brazil(Compulsory Licensing), Rwanda(Paragraph 6 System), Malaysia(Government Use), Kenya(Parallel Imports)

However, to implement such methods requires certain prerequisites. In order to successfully implement Paragraph 6 System, it should make economic sense for importer and exporter. The compulsory license will only attract a regular for-profit company, if it can expect reasonable returns on the investment. The importer, on the other hand, will only conclude a deal if the new producer can offer a price below the patent holder's price. Economic condition should improve, if the importing market is large enough to cover production costs and (Iyengar et al., 2016)provide a margin for risks and reasonable returns to investments. However, most developing country markets are small, so apart from the more advanced among the developing countries, the new rules will only be useful if importers can use donor money to buy medicines under compulsory licenses.

Even though economic condition is satisfied, Paragraph 6 System can only be used if they are legally implemented and not contradicted by other international commitments. It may become impossible to use the new rules if the countries in question have implemented provisions that go beyond the TRIPS (so-called "TRIPS-plus"). This type of provisions enables the patent holder to exercise more control over the use of data from clinical trials of a new medicine than mandated in the TRIPS. Even though the provisions do not always address compulsory licenses directly, they may still make such licenses impossible to use effectively. If the producer with the compulsory license is not allowed to rely on these data when developing their copy of the medicine, all clinical trials would have to be

redone. This would increase costs and delays to such an extent that the compulsory license would not be able to contribute to lower prices. This limitations are also applicable to Compulsory Licensing or Government Use.

It looks difficult to fulfill all prerequisite. Developing country authorities may be more hesitant to grant compulsory licenses on the grounds of safeguarding foreign investment. From an economic perspective, using the new rules will be easier the larger the market, but politically, it may instead become more difficult. There is a risk that an importer that is large enough to attract potential new producers also is large enough to raise concerns among patent holders and their governments. If these actors voice criticism or even employ threats of trade sanctions, any importer might hesitate using a compulsory license.

From Indian case, we can understand various strategies taken to lower prices in one place. Also, large pharmaceutical companies played a partial role for patient accessibility through patient access program, of course ultimately to improve their marketing activity. Despite the reputation of being a generic factory, India has a problem of accessibility to drugs for people in India. High out-of-pocket money, low insurance rate, and the absence of sophisticated price control systems would be the reasons for that. Indian drug pricing policy, which controlled only essential drugs on DPCO list, and Health Insurance System, is facing reform for achieving universal health coverage recently. Indian IPR law was made in favor of producing cheap generics, utilizing the IPR law, patent opposition and compulsory licensing could be applied for lowering the cost of drugs in India. In a wide range of political and economic situations around the world, the pricing of medicines in each country would be vary. Nonetheless, this case would be important to introduce strategies that can be taken in countries where income levels are very low for most people. In the current situation, where patents and expensive new drugs are emerging, it would be a clue to how to ensure that price is accessible to more people.

On the other hand, for improving the access to the high-cost medicines, various pricing policy can be adapted even though fully acknowledging patents. Regardless of income levels, pharmaceutical financing, pricing and strategic purchasing policy are crucial in all countries(S. Kim et al., 2017). Fundamentally, inadequate competition and monopolistic power of pharmaceutical manufacturers make pricing policy necessary(OECD, 2008). Especially in countries with weak pharmaceutical systems, price affects affordability and access to medicines directly due to OOP pay(Kwon et al., 2014).

Korea assesses the value of high-priced drugs through HTA and decides whether to reimburse the costs based on the criteria. Furthermore, the national insurer tries to obtain drugs at good prices using their position as a single insurer. HTA does not primarily aim to reduce costs, but it contributes to get value from a given budget with the number of new drugs entering at an excessively high price despite the slight improvement in effectiveness.

However, negotiations with monopolistic suppliers are not always successful. Unlike in the past, MEAs are emerging as an important part of price negotiations as more and more countries are increasingly confidential about the outcome of price negotiations. Korea also introduced RSA, which is a type of MEA, and is taking the initiative to reduce the actual price instead of yielding to the nominal price. However, MEAs have reduced price transparency globally and have made external reference pricing difficult.

The weakness of the Korean drug price system is that the price adjustment mechanism is very weak once it is listed. Although prices are adjusted based on market transaction prices, there is no incentive structure to promote price competition in the pharmaceutical market. These results of the price reduction based on the survey of actual transaction price is negligible.

The PVA system is used to negotiate price cuts in case the volume increases by more than originally expected. However, the financial savings with this are not significant as the maximum price cut is limited to 10%.

The OPDIVO case of Japanese policy could be valuable lesson for how to set the drug price initially and to discount the high cost after. Unique drug pricing policy which considers the cost for the drug development and provides premium to innovative drugs in order to encourage the development of new drugs made the initial price of OPDIVO in Japan higher than any other countries. OPDIVO increased the financial burden in Japan, because its high-price was also applied to the treatment of non-small cell lung cancer, for which there is a relatively large patient population. They lowered the price of OPDIVO to 50% in February 2017 with Management Entry Agreement, and 23.8% in April 2018 with Health Technology Assessment and Foreign Price Adjustment.

Countries should use appropriate pharmaceutical pricing policies selected based on the objective, context and health system. According to the WHO (2015b) and lessons from two case review in this report, external reference pricing and value based pricing would be recommended rather than cost-plus pricing. With legislative, administrative, technical support, pricing policy and price should be regularly reviewed, monitored, evaluated and amended as necessary.

This report contributed to the current knowledge in that various measures and methods have been explored and combined in the form of case analysis in order to help overcome the access problems brought about by high price medicines. Case study would be the preferred method in situations when (1) the main research questions are “how” or “why” questions; (2) a researcher has little or no control over behavioral events; and (3) the focus of study is a contemporary (as opposed to entirely historical) phenomenon(Yin, 1994). So,

through case study, we can obtain more holistic knowledge. Various strategies employed by broad spectrum of countries were researched to provide appropriate understanding from LMIC to developed country like Japan and from compulsory licensing to managed entry agreement.

Additionally, for proper analysis of each case, negotiation theory has been utilized to better understand the negotiation process and draw working knowledge. Given tremendous differences between official prices set by pharmaceutical companies and the willingness-to-pay of LMIC countries, negotiation process is inevitable and already well established negotiation theories can be of great help. Thus, this study introduced key concepts of negotiation such as BATNA to identify the nature of negotiation processes.

This study, hopefully, will help better understand challenges countries face in terms of high price medicine and develop appropriate strategies. Nevertheless, more detailed data from various sources such as survey, interview, primary/secondary data and more rigorous adoption of case study methodology and application of negotiation theory will help better understand policy and negotiation processes in the future studies.

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