Using Compulsory Licenses to access pharmaceuticals:

A Cross Case Analysis on Outcomes

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Abstract :

Patents pose a significant barrier to accessing innovative medicines, due to exclusivity granted to inventors by the Trade Related Agreement on Intellectual Property Rights (TRIPS), which sets the basis for protection of intellectual property at the international level. The founding of the World Trade Organization and adoption of TRIPS in 1994 brought harmonized intellectual property standards to member states. Compulsory licenses are exemptions to patent exclusivity, allowing a government or a third party to use patented subject matter for commercial, public or emergency use provided certain requirements are fulfilled.

Objective

To evaluate outcomes and policy approaches used by different countries for compulsory licenses under the Article 31 framework of TRIPS, and identify shortfalls and best practices in order to inform policy changes on national, and multilateral levels.

Methods

This retrospective study is comprised of a cross-case comparison of compulsory licensing in varying countries, including Low, Middle and High Income Countries to enable access to generic medications. Each case has been driven by varying contexts and scenarios. After a detailed search for all compulsory licenses threatened and issued after 1994, a database was developed and focus cases selected. Specifics of license and outcomes associated with use were then recorded and compared. Among aspects evaluated were national legislation and delivery instruments for procured generics.

Findings

Following the Doha ministerial declaration on Public health in 2001, there has been more frequent use of compulsory licenses (CL) to procure HIV medications, and increasingly, non-essential medicines such as oncologic agents, anti-inflammatory agents, and prophylactic drugs for heart disease. Approaches taken by countries include an official Government-use policy to compulsory license drugs, use of CLs as a threat, an emergency use for pandemic preparedness, and anti-competitive tool to promote parallel trade. Each case has unique motivators and reveals context specific outcomes.

Conclusions

While use of compulsory licenses is controversial, countries have traditionally used them in case of exceptionally expensive medicines (Cancer drugs, and 2nd line ARV medication), often after failed negotiations (Brazil, Thailand, and Taiwan). The TRIPS Article 31 framework allows significant liberty in issue and use of compulsory licenses, but requires further clarifications of certain provisions to clarify ambiguities passed down from the Paris convention of 1885. Some further policy clarifications are also prudent given the evolving nature of the patent landscape, and current global discussion on impending need for change to the innovation framework has been motivated by conflicting goals between Human rights and Inventors rights.

Acknowledgements:

I began my masters' studies in Innsbruck, Austria in October 2014, shifting from clinical practice to adjuvant health disciplines. The EU-HEM program is structured to immerse candidates in disciplines of health economics and policy from a global perspective, by encouraging mobility between European universities. During an exchange semester at Erasmus University Rotterdam, The Netherlands, I was introduced to compulsory licensing and was intrigued by methods used by countries to promote market access to pharmaceuticals and health technology. Before moving to Oslo for the final stretch of the program, I was granted an internship with the European Union-Delegation to India, and moved to New Delhi, India where compulsory licenses were often discussed in relation to the ongoing negotiations over the EU-India BTIA. The controversial nature of compulsory licensing then led me to settle on a thesis topic, and begin work on a proposal. The process has been highly rewarding, enriching, and eye opening at times.

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1 Table of Contents

1.1 List of Figures

1.2 List of Tables

2 Background

In November 2015, the United Nations Secretary-General, Ban Ki-moon, acknowledging the policy incoherence on inventor rights, human rights, trade and public health in the context of health technology, convened a High-Level Panel (HLP) on Access to Medicines, inviting proposals to resolve gaps in the existing innovation framework. Access to medicines is increasingly affected by costs of patented drugs in both developed and developing countries, primarily due to prohibitive development costs and the patent based reward system. High prices of patented medication give rise to much debate over an optimal solution to the innovation dilemma. The current push for a delinked innovation model, and proliferation of voluntary licensing agreements, encourage innovator firms to shift various stages of R&D and production to smaller contract manufacturers, while retaining control over patents and profits. Within this innovation framework, compulsory licenses represent the final policy tool as a safeguard from prices, drug shortages and abuse.

Compulsory Licenses (CL) allow governments to infringe patent rights of patentees under a variety of circumstances. Among the types of use of patented subject matter described in the Agreement on Trade Related aspects of Intellectual Property rights (TRIPS), are conditions and grounds for using this flexibility. Compulsory Licensing under TRIPS has been controversial and thus, an infrequently used tool for a range of applications.

Aiming to harmonize trade and intellectual property norms in the face of exponential technological and economic progress, the World Trade Organization (WTO), and the Agreement on Trade Related aspects of Intellectual Property rights (TRIPS) was established in 1994 following the Uruguay round of multilateral trade negotiations. In granting 20 years of patent protection to pharmaceutical products, TRIPS allowed access to trade regions in a *sine qua non* package for WTO membership. Developing member countries relented on the basis that certain flexibilities were incorporated into the text as safeguards to public health, and exchanged unmonitored reverse engineering of patented drugs for ”flexibilities” including compulsory licensing. Few developing countries adopted TRIPS Plus provisions that were beyond WTO requirements to appease foreign trade interests without taking advantage of the transition period offered by the WTO (Van Puymbroeck, 2010).

In the 2001 Doha round, the inability of poorer nations to bear the burden of public health crises and strong IP standards gave rise to controversy surrounding HIV/AIDS and unaffordable medication, culminating in the Ministerial Declaration on the TRIPS agreement and Public health (The Doha Declaration) which reiterated the rights of developing countries to use flexibilities to protect public health interests, while reaffirming that TRIPS should not impede public health initiatives in member states(UNAIDS, 2011).

Immediately following the Doha declaration, a number of were CLs issued in LDCs to access anti-retroviral medication (ARV’s), however more recently, compulsory licenses have been used to access to expensive cancer drugs and 2nd line ARVs to support universal healthcare systems, in emergencies, and uncooperative behavior by Transnational companies (TNCs). As developing nations gain capacity in local pharmaceutical manufacture, research and development, many still rely on patents developed in industrialized nations for innovative drugs. CLs are being now selectively used by countries with higher per capita incomes including nations classified by the World Bank as Middle Income Countries (GNI per capita of USD 1,045 - 12,736) and High Income Countries (GNI per capita > USD 12,7436) in order to access patented medication.

Origins:

Origins of compulsory licenses trace back to the Venetian law and the Statute of monopolies which allowed the Crown to use patented subject matter in return for granting inventors exclusivity of sale and immunity from plagiarism, in order to reap financial rewards. Provisions for involuntary use have been passed down from the Paris Convention of 1883 (Art. 5a) and incorporated by reference into the TRIPS agreement of 1995. Developed countries have previously used compulsory licensing extensively across varying fields to promote industrialization, remedy abuse and protect against emergencies, using the theory of Eminent Domain where the government holds the rights to use private property in return for reasonable compensation (C. M. Correa, 1999). The freedom previously available to industrialized and developed countries in establishing IPR systems prior to implementation of TRIPS, is now limited to developing countries in establishing national IP regimes. For example, The United States previously engaged in a broad compulsory licensing policy under the Trading with the Enemy Act (Moser, 2015), and Canada (License of Right system) issued a large number of compulsory licenses prior to amending its patent laws in 1993 (Reichman, 2009).

The Case for Patents as a Social Contract:

Patent theory is premised on incentivizing innovation with temporary immunity from competition. In issuing patents to inventors, an exchange of voluntary disclosure of knowledge and trade secrets for an exclusive opportunity to reap financial benefit is guaranteed. This transaction gives the patentee the exclusive right to discriminate beneficiaries of technological advance on basis of monopolistic remuneration. The temporary block in competition is an accepted tradeoff in the interest of progress and innovation (Reto M & Liu, 2014).

Critics of the patent system argue that monopoly pricing is neither the most equitable nor the most profitable method to finance research and innovation, as costs of restricting use of knowledge associated with the patent system far outweigh any purported benefits. Scholars argue that patents are only the second best method to promote innovation and R&D, but are an accepted compromise for lack of a more workable innovation framework (Stiglitz, 2008). Developmental disparities across countries mean that developing countries would have to abide by trade rules not suitably formulated for their economies (P. Danzon & Towse, 2003).

Industrialized nations rely on IP rights to protect property and promote innovation, while developing nations rely on enforced IP rights to attract technology to their borders. This results in differing perspectives of patents as an inalienable right to inventors, versus a privilege only granted by a government in exchange for disclosure of working (C. Ho, 2011). The detrimental effect of the patent system is extreme when the invention or the right of exclusivity is given to subject matter is a lifesaving or life-prolonging substance, as is the case with pharmaceuticals. Evidence shows that IP enforcement directly affects prices of medicines, and consequently public health Essential goods such as medicines, when monopoly priced translate to deadweight loss, which can then be inevitably measured in lives lost (Reichman, 2009).

While robust IP regimes indicate stable investment environments for firms, compulsory license provisions serve to remind patentees that IP rights are not absolute and subject to suspension. TNCs are often vocal and aggressive in protecting patents given that consequences of compulsory licenses are manifold. Strong patent portfolios are indicative of a firm's investment in R&D and an effective business strategy. Valid patents reflect the market value of firms in terms of stock prices and suggest possible monopolies of products thereby guaranteeing high profits and returns on investment. Infringements of IP rights imply loss of revenues on a high earning product, further compounded by royalties inadequate to cover lost profits. Marketing of blockbuster

drugs in an unsafe IP environment also suggests poor market access planning by TNCs, which often lead to falls in investor confidence and company net worth (Ni et al., 2015).

As exceptions to exclusivity offends the patentee's right, governments hold a moral responsibility to the citizen, and are expected to put human rights above the financial prerogative of TNCs. The infringement of patent rights is seen as a fair tradeoff under the presumption that social and financial benefits that a CL allows greater than any losses in innovation, foreign domestic Investment or through trade sanctions. Threats of compulsory licensing to facilitate generic entry of innovative drugs often necessitate a review of pricing and production strategies, as unavailable medicines have direct implications on public health and human rights, for which governments are held responsible.

3 Methodology

Research Question: : How has Compulsory Licensing been used to enable generic entry and availability in some focus countries, and how use of the flexibility can set a precedent by informing the international regime on patents and the innovation framework?

In this retrospective study I delve into the details and outcomes of pharmaceutical compulsory licenses issued by authorities of focus countries. To identify trends when compulsory licensing has been used as tool to access innovative drugs, circumstances studied include local non-working, unaffordable pricing of drugs, export licenses, anti-competitive behavior and national emergencies. Rather than focus solely on the effects of CL on anti-retroviral drugs, also included are cases of other medications (chemotherapeutic agents, anti-migraine, heart disease, and antivirals) by using a multiple case study approach to arrive at conclusions.

3.1 Literature Search

With assistance from the medical library, a Pubmed search was first performed using the following MesH terms:

("Pharmaceutical Preparations"[Mesh] OR Drug Industry[Mesh] OR "Technology, Pharmaceutical"[Mesh] OR "Legislation, Drug"[Mesh] OR "Drug Costs"[Mesh]) AND ("Licensure"[Mesh:NoExp] OR "Licensure, Pharmacy"[Mesh] OR "Intellectual Property"[Majr:NoExp] OR "Patents as Topic"[Mesh]) AND compulsory AND (("2000/01/01"[PDat] : "2016/12/31"[PDat]) AND English[lang])

The search resulted in 54 relevant articles. Parallel searches were then performed using similar terms in the Oria database which resulted in more useful results. As much of the text is legal in nature, Westlaw and Hein-online legal databases were used to retrieve legal articles and case law where appropriate. Other databases used included Ovid, Medline, Cochrane, WIPO and Google scholar.

3.2 Database

Using leads generated from the search, an excel database of CL threats was compiled (See Appendix), comprising prominent CL threats after implementation of TRIPS (1995- 2015). Existing research on compulsory licenses from multiple sources were referenced at this phase and updated with additions of more recent CL threats and outcomes associated across a range of countries including LICs, MICs, and HICs (R. Beall, Kuhn, & Ford, 2012; CPTech). This process included an extensive search of IP blogs, news sources, legal journals, health

science journals, and each country's legislation. Information was acquired and cross referenced with multiple sources including pricing databases and governmental releases where available.

3.3 Pricing Data and Information

Prices for compulsory licensed products were obtained from various sources, after attempts to contact pharmaceutical firms, governmental organizations and data analytics companies for pricing and procurement data were not successful. Difficulties faced in data collection primarily lies in acquisition of confidential drug costs, which were recovered through indirect sources such as the Global fund database and export data releases, among various others. Some pricing data for HIV medication was recovered from the WHO Global Price Reporting Mechanism. Other barriers to information recovery included language barriers and dearth of data. Other information was acquired from literature, governmental releases, and legal texts of rulings and official statements were also recovered from a range of sources including IP think tanks and national authorities.

3.4 Analytic methods

Using explanation building to thematically highlight commonalities, dissimilarities and guidelines followed by issuing authorities, each focus case was assessed based on the circumstances which led to use of compulsory license mechanisms. Table 1 lists evaluation criteria assessed in each case study. Also argued are the varying schools of thought on CL usage looking at perspective of industry and governments, and its effects on innovation and FDI. Using Thailand's 2007 compulsory licenses for Kaletra and Plavix as a pilot case study, the following cases are then explored in depth and findings described in the results and discussion section. I conclude with a cross case analysis, and end with policy proposals to encourage change and more equitable use of the compulsory licensing flexibility with respect to medicines.

Table 1 Evaluation criteria

Country and World Bank Income Classification	License Type : Open / GUL and Validity period
Healthcare spending (% GDP)	Quantity specified
Drug/s	Geographic validity
Patent Holder/s	Supplier/ Manufacturer
Originator Price before CL	Royalty to Patentee
Indication and Disease Prevalence rates	Generic Product brand and Price ($)
Reason for CL threat	Packaging characteristics
Prior negotiations	Retaliatory measures
CL Provision in local legislation	Delivery instrument
Local Manufacturing capacity	NLEM Inclusion

3.5 Selection of focus cases

Following a compilation of the above mentioned database, focus countries were selected on basis of confirmed compulsory license issued and class of drug. The six case studies including Thailand, Brazil, Rwanda, Italy, India, and Taiwan were thematically selected. As this study aims to compare variations in approaches to drugs being compulsory licensed, focus countries were selected on the basis of circumstances under which CLs were issued, and type of license, policy goals of issuing authority, pricing history, and income status of the countries. Availability of information and analyses also factored in selection of focus countries. Given that certain instances of CL were cited as justification to issue further CLs in third countries, significant consideration was also given to this dimension. Some prominent cases were excluded to allow comparison of varying approaches taken by national authorities to issue compulsory licenses in context to legal infrastructure and availability of evidence. The cross border aspects of CLs were also instrumental in exclusion of cases studied.

Focus studies are first elaborated, followed by cross-case findings and discussion in the following sections to list prominent similarities and difference in approaches. A detailed case description on each of the focus countries and CL specifications was tabulated. Case descriptions were used to build case studies and theme based explanation on outcomes in light of the scenario or circumstances under which CLs were issued. Also observed and recorded are the amendments made to legislation in order to justify the CLs and remain TRIPS compliant. In case summaries, details on royalties set, Originator prices before CL and actual/proposed generic prices after compulsory licenses were issued. Other specifics included validity of license, the outcomes on generic prices and policies were reviewed. Each case study highlights current local trends and updates to the IP Policy and legislation, following a thorough review of available evidence and triangulation to ensure accuracy. Summaries of focus studies provide an overview of key findings in a tabular form.

3.6 Limitations

The Database of CL threats is not exhaustive, as listed cases are limited to instances which have received a fair amount of media coverage and for which evidence exists. Prices were compiled from various sources, and require more research to confirm accuracy. As the number of focus countries is limited, more comprehensive analysis of other cases will be insightful. Given the nature of the research question, the information collected is both qualitative and quantitative in nature and therefore dependent on perspectives of circumstantial evidence.

4 Compulsory Licenses: Framework and theory

4.1 TRIPS Article 31. "Other use without authorization of Right holder"

The WTO defines a compulsory license as "when a government allows someone else to produce the patented product or process without the consent of the patent owner"(WTO, 1995).The Agreement on Trade Related Aspects of Intellectual Property (TRIPS) imbibed Article 5(a) of the Paris Convention for the protection of Industrial Property (1883) acquis to allow for compulsory licenses as a remedy for a variety of scenarios including abusive pricing, anti-competitive behavior and emergencies. Article 31 sets a framework for use of compulsory licenses as an exception to patent infringement, rather than exclusion from patentability (C. M. Ho, 2011).To prevent abuses which might result from the exercise of the exclusive rights conferred by the patent the article allows use of CL by any country, in case of Failed negotiations to obtain a voluntary license under reasonable terms and conditions, National Emergency or Extreme urgency, Public Non-commercial use, and to remedy anti-competitive behavior. Article 31 sets minimum conditions for issue of compulsory licenses, requiring that any CL be:

- Evaluated on a case to case basis on its individual merits - Art.31(a)
- Negotiated with patentee prior to issue under reasonable commercial terms - Art.31 (b)
- Of limited scope and duration - Art.31 (c)
- Non-exclusive - Art.31(d)
- Non transferrable - Art.31 (e)
- Be used predominantly for local use - Art.31 (f)
- Terminable on expiry of deserving circumstance - Art.31 (g)
- Adequately remunerated - Art.31 (h)
- Subject to judicial review - Art.31 (i)

Article 31 exempts prior negotiations in case of emergencies, public non-commercial use, and waives remuneration in cases of anticompetitive conduct, giving precedence to the Privilege view by converting property rights to liability rights for patented subject matter, and does not restrict use of involuntary license to emergencies, or certain disease types (S. Flynn, Hollis, & Palmedo, 2009). Art.31 allows member states the autonomy to decide what constitutes an emergency or public health crisis, on condition that each case is individually assessed and issued under commercially reasonable working terms. As conditions for "reasonable commercial terms" and "adequate remuneration" are not defined in the TRIPS Agreement, the ambiguous nature of the text has left governments and issuing authorities to formulate rulings and national guidelines on an ad-hoc basis.

The Doha declaration Ministerial Declaration on Public Health

In the 2001 Doha round of WTO ministerial talks, the Council reaffirmed the rights of developing countries to use flexibilities to protect public health. The Council acknowledged the barrier posed by Art. 31 by restricting LDC's use of compulsory licenses due to reliance on imports of generics for lack of local manufacturing capability and instructed member states to solve restrictions faced by countries without local pharmaceutical capacity to effectively use compulsory licenses. The Declaration also ensured that countries retained rights in deciding grounds for a National emergency. The declaration despite stating the freedom of members to grant CL's did not condemn external pressure by governments, due to its non-binding nature (Gathii, 2002).

Paragraph 6 of the Doha declaration states 'We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement 1994. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.'

Article 31 Bis: The August 30th 2003 Decision and the "Waiver mechanism"

After prolonged negotiations, the WTO decision of August 2003 proposed an amendment to TRIPS as Art.31bis using a waiver on export limitations by countries on notification of the WTO council and issue of back to back compulsory licenses. The Waiver mechanism creates an exemption for Art.31(f) that limits use of compulsory licenses for local use and allows export of generic drugs, on condition that eligible importing countries and exporting countries issue compulsory licenses and notify the WTO by specifying the validity and quantities for export purposes. The solution also allows for re-exportation of imported drugs to other eligible countries. The mechanism also requires prior negotiation and notification of patentees, along with anti-diversion precautions. A good faith understanding to encourage fair use of the products was also included to avoid profiteering by means of a humanitarian exercise (WTO, 2005).

4.2 Compliance with TRIPS

Clearly reflected in the variation of license use and the circumstances leading to CL issue is the increasing complexity and diversity of national legislation requiring interpretations in context to international law. The ambiguous nature of TRIPS has allowed countries to circumvent rules and obligations as desired while remaining TRIPS compliant (Nanayakkara, 2015), shifting focus to compliance with requirements, rather than justification of provisions (Reto M & Liu, 2014). Cahoy notes that under international law, the obligation to fairly license is almost non-existent due to the ambiguity of TRIPS Art.31 (Cahoy, 2011). The lack of firm directives over remuneration and, increasing use of political clout play a larger role in using flexibilities, leaving both developed and developing countries with little control over benefits and retaliatory losses of using the CL route. This confluence due to sporadic issue of CLs has also resulted in no clear patterns of use.

4.3 Prior Negotiations

TRIPS defines prior negotiations as "demonstrable efforts made by the applicant to request a voluntary license (VL) from the patentee under reasonable terms". The Prior negotiation requirement demarcates the shift of rulings from the Property rule framework to a Liability rule framework, which entitles a patentee to remuneration, without precluding right of use by others. Variations in interpretations stem from perspectives of this requirement as Grounds for initiating a CL versus merely a procedural formality, as it does not require refusal of a patentee to grant a VL, nor proof of rejection of a voluntary request. In essence, it serves as a deterrent against unwarranted use of the flexibility, as use of CL without negotiations encourages marginal pricing while stripping the voluntary ability of patentee to demand reasonable terms and royalties in exchange for a license. Public interest Licenses or Government Use Licenses (GULs) do not require an emergency or crisis to be issued and are the preferred type of involuntary licenses by most governments (C. M. Correa, 1999).

4.4 Local Working

The open interpretation of the "Failure to work" (FTW) clause has caused much debate for lack of a consensus, as each country has a varying definition of FTW. Local working requirements explicitly intend to encourage local production or use of patented matter within borders of a state where a patent is granted in order to promote industrialization. TRIPS and the Paris convention do not define "Local working" and allow member states the discretion to define requirements. The provision has been interpreted in various strengths and has led to WTO disputes between the US, Brazil, and Argentina. For example, the US does not require working of a patent locally to constitute local working requirements. This perspective is not accepted by developing countries like India and Brazil who require local manufacture to be assessed in cases of CL applications. The patent controller of India cited non-working of patent subject matter due to Bayer's importation of sorafenib, explicitly referring to the Paris convention.

4.5 Adequate remuneration

As royalties should cover some part of development costs and lost profits, and serve as incentive for further innovation, royalty obligations should not impede access and be simple to calculate. The lack of an obligatory guideline and definition of adequate remuneration in TRIPS has led to arbitrarily set royalties depending on license type and application. The UNDP and WHO recommend guidelines for a tiered royalty setting ranging from 2-6% under the TRIPS framework that reflects the therapeutic benefit of the licensed drug, and the affordability of the payer (Love, 2005). Low royalties and variations in interpretation of the TRIPS text with corresponding national legislation thereby challenges legitimate use of the flexibility by questioning whether the undefined "Commercially reasonable" requirement is fulfilled.

4.6 Scope of Disease Limitations in TRIPS

TRIPS does not exclude any kind of patent from compulsory licenses when provisions under Art.31 are fulfilled. No text with claims of limitations on types of diseases or instances for compulsory license use, including limiting eligible diseases and drug types through positive and negative lists has been included in the acquis. In response to misleading literature on the Doha declaration claiming that CL use is restricted to epidemics such as HIV, TB, and malaria, Abbott and Reichman note, "[t]here is no public health justification for denying patients access to treatments for certain diseases because trade officials have decided that some diseases should be on (or off) an official list." (F. M. Abbott & Reichman, 2007). On the Doha declaration and Article 31, scholars report that a variety of proposals that were purportedly left out of the final text as safeguard from unforeseen circumstances. These included removal of local non-working as criteria for compulsory licensing, restriction of CLs to epidemics, and removal of patents from pharmaceuticals altogether (Outterson, 2009). However, countries such as Canada have incorporated a positive list into their national amendments complying with the Para.6 Waiver for CLs, limiting eligible drugs to HIV medication, and a few other drugs for infectious disease. The contextual requirements of drugs should be screened as criteria rather than the type of disease and its prevalence, as disease demographics evolve especially in transitioning countries. Given the lack of clairvoyance in predicting future crises, setting inflexible criteria will jeopardize the liberties afforded to WTO members in defining emergency and public use from national perspectives.

5 Preliminary Findings

5.1 Timeline: Compulsory Licenses and Threats of compulsory licensing

Using gathered information, a timeline (Figure 1) was generated to graphically describe the use of compulsory licensing, both as a threat, and as an instrument to procure generic medication, beginning with the creation of the WTO in 1995.

The time trend is reflective of the impact the Doha declaration on encouraging use of the compulsory licensing flexibility, with a significant increase in number of issued licenses after 2001. From 1995 – 2005 multiple developing countries issued Emergency-use licenses for HIV medication such as Zambia, Eritrea and Ghana. Malaysia and Indonesia used Government use licenses to procure HIV medication for national requirements. Of note is the use of CL threats by richer countries such as the US and Canada in response to threats of bioterrorism with anthrax in 2001.

In the 2nd decade of TRIPS from 2005-2016, an increasing number of middle income countries resorted to compulsory licensing for non-HIV medications with Thailand's use of GULs on cancer medication, heart disease medication, and Italy's anti-trust licenses for sumatriptan, finasteride, and imipenem. Also significant are the threats and licenses issued for newer second-line HIV medication such as lopinavir(LPV/r), atazanvir, and most recently a German judicial license for raltegravir. An increasing number of oncology medications being subject to CL in countries such as India, Nepal and Thailand reflect high prices being charged for new medications. Imatinib has been threatened with compulsory licensing in at least 3 countries, namely South Korea, Thailand, and most recently Columbia. Regrettably the Art.31bis waiver solution has only been used once to enable Canada's for export of a generic fixed dose combination to Rwanda.

5.2 Shifting Trend of Threats

Compulsory license threats are gradually shifting towards so called "Ethical drugs" that improve quality of life, including anti-cancer medication, anti-inflammatory agents and COPD drugs, moving from essential drugs like ARVs. Middle Income Countries (MICs) including Ecuador, Peru, and Columbia have used compulsory license as threats to control drug prices as they begin to implement universal healthcare systems. This observation highlights drug pricing as a barrier to access in transitioning countries, rather than infrastructural and resource shortfalls in healthcare systems, while reflecting evolution of disease demographics and the rising prevalence of NCDs in developing countries.

Since Thailand's issue of licenses for Plavix (clopidogrel) and 3 oncologic agents, there have been a variety of threats for non HIV related medications, including India (oncologic, diabetic and pulmonary disease drugs), Italy (migraine, antibiotics), Ecuador (transplant prophylaxis, rheumatoid arthritis), and Columbia (leukemia). As countries establish and expand universal healthcare coverage, rising costs to treatment and shifting burden of disease, the incentives to license expensive medications and reflect directly in IP conflicts. The high costs of innovator drugs even affect developed markets during recessions and economic crises, and in general (Hoen, 2015).Excessively high pricing in developed markets of innovative drugs such as Gilead's Harvoni and Sovaldi also placing tremendous strain on countries with high healthcare spending (Iyengar et al., 2016).

Though the HIV crisis is representative of CL use to promote generic competition, emergence of UNITAID's Medical Patent Pool, and other voluntary patent pools have resulted in fewer CL threats on anti-retroviral medications. Governments have strategically issued compulsory licenses for drugs primarily developed to target profits in high income markets, and have less impact on R&D.

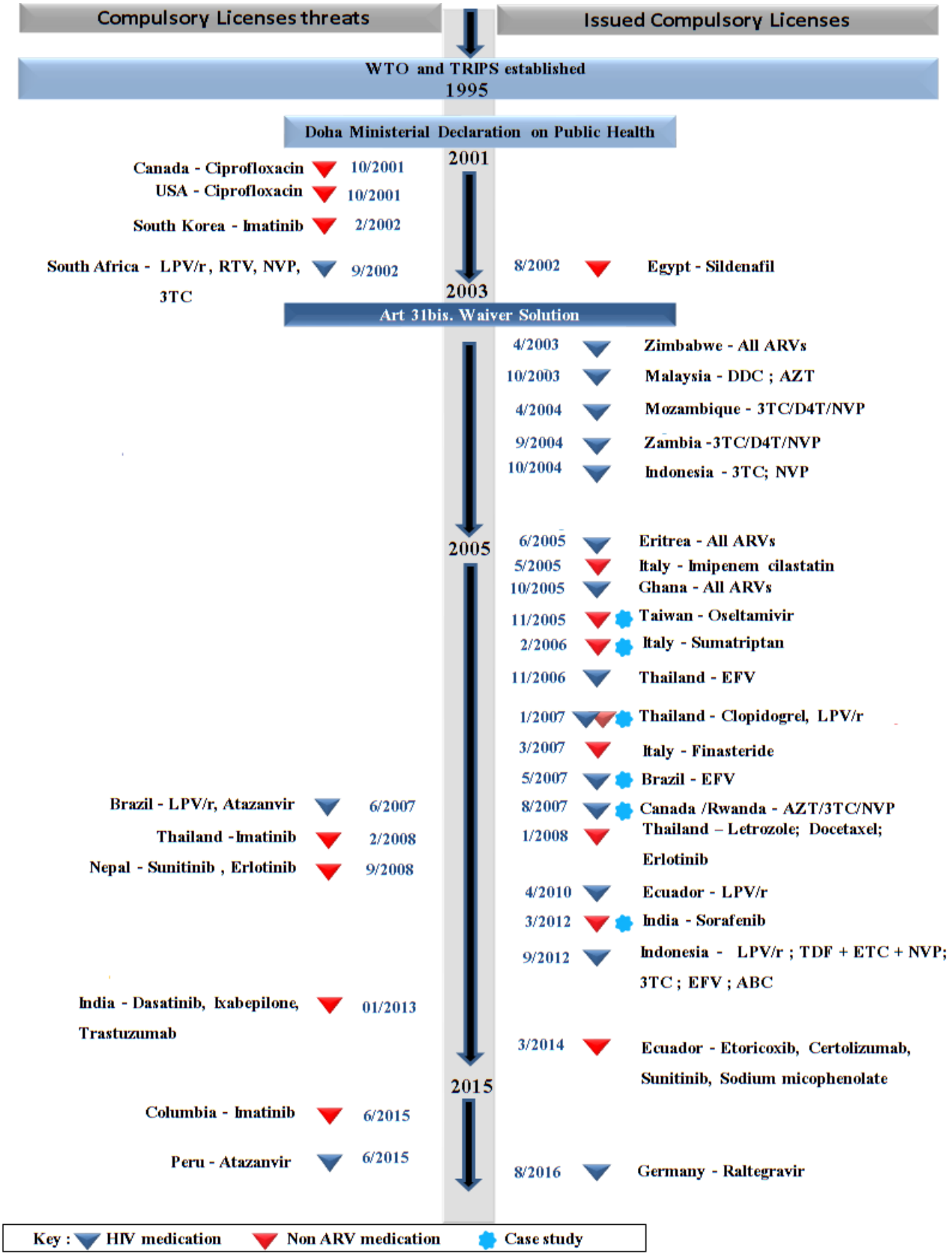
The decreasing frequency of CL threats suggests that the compulsory licensing framework needs reform and clarification, as governments pursue economic growth through foreign investments and technology transfer agreements. Given that TRIPS requires that all compulsory licenses be assessed on a case by case basis, the incidences of new CL have also reduced due to selective avoidance of broad licensing polices such as those adopted by the US with the Trading with the Enemy Act (TWEA), and Canadian policies prior to amending its IP laws for NAFTA in 1992 (J. Reichman, 2003).

Focus cases in this study thematically highlight the divergence in licensing approaches with varying country income group and disease type (Table 2). Cases selected from the timeline include instances of government initiated licenses including the Canadian license to use the Aug 2003 decision "Waiver mechanism", Brazil's public interest license for Stocrin, and Thailand's government use licenses for Plavix and Kaletra. Cases selected to investigate market-initiated licenses include Italy's anti-trust license for sumatriptan, and India's private use license for Nexavar (sorafenib). Taiwan's license for Tamiflu (oseltamivir) was selected to study an emergency use license as a biosecurity issue.

Table 2 Selected focus cases

Year	Income	Country	License Type	Drug	Indication
2005	HIC	Taiwan	Emergency Use	Oseltamivir	Avian Influenza
2006	HIC	Italy	Anti-Competition	Sumatriptan succinate	Migraine prophylaxis
2007	UMIC	Thailand	Government Use	Lpv/R ; Clopidogrel	HIV-AIDS / Heart Disease
2007	UMIC	Brazil	Public Interest	Efavirenz	HIV-AIDS
2007	LIC	Canada-Rwanda	Waiver mechanism	Zidovudine;lamivudine;nevirapine	HIV-AIDS
2012	LMIC	India	Judicial license	Sorafenib tosylate	Cancer

Figure 1 Compulsory License threats and issues; 1994 to 2016 (Compiled from database)



5.3 Case Study 1: Thailand – Government Use Licenses

From 2006-2008, Thailand adopted a Government-Use policy ,using Government Use Licenses (GUL) to procure for 7 patented drugs, including HIV medication, heart disease and oncologic agents. In 2007, amidst a military coup and unsuccessful negotiations with pharmaceutical firms for discounts, Thailand's Ministry of Public Health (MoPH) issued GULs for Kaletra (Lopinavir/Ritonavir- hereafter LPV/r), a 2nd line HIV drug owned by Abbott labs, and Plavix (clopidogrel), a Sanofi drug used in prophylaxis of ischemic heart disease.

With the slogan "30 Baht cures all diseases" universal healthcare coverage was successfully introduced in 2001 under the National Health Security Act aiming to guarantee state funded medical care to 62 Million Thai citizens. The universal healthcare system is cited to effectively cover up to 98% of the Thai population with basic medical care. Under a 3 tier system of coverage using the civil servants medical benefit scheme, the social security scheme, and the universal coverage scheme, the program provides varying levels of care to citizens and also disperses drugs on the national list of essential medicines.

The MoPH expanded the universal access policy to anti-retroviral therapy (ARV) in 2003, with the number of treatment sites increasing from 112 in 2001 to 841 by February 2005. A successful roll out of the universal access to ARV therapy resulted in number of patients increasing from 27,000 in 2003, to 52,593 by 2005. (Glassman & Temin, 2016).

After funding shortages and political turmoil, and a World Bank report predicting unsustainability of the Thai ARV distribution program along with rising healthcare costs, the GULs were a means to reduce reliance on imports of both generic and patented drugs by eventually manufacturing generic drugs for national requirements (Revenga, 2006).

TRIPS Implementation

Thailand adopted TRIPS in 1992, amending the Thai Patent Act (TPA), to recognize patent protection for pharmaceuticals, prohibiting parallel imports, and extending patent validity to 20 years. The TPA was amended again in 1999 (T.P.A, B.E 2542) further diluting local working requirements and abandoning the national pharmaceutical patent review board (Act-2522, 1979). Both amendments were influenced by the United States Trade Representative (USTR) and Pharmaceutical Manufacturers Association of America (PHrMA), in exchange for promised investments. Critics suggest that TPA standards exceed TRIPS requirements, leaving the country with limited discourse in terms remedial measures for unaffordable medicines (Towse, Mills, & Tangcharoensathien, 2004).

National Legislation and Reasoning

The Thai Patent Act B.E 2522 (1979) sets various provisions for compulsory licensing with criterion for issue including local non-working of patents (Sec. 46), dependent patents (Sec. 47, 47bis), Public non-commercial use (Sec. 51), and National emergency (Sec. 52). Sec. 51 of the T.P.A. authorizes any ministry, bureau or department of the government, to issue ex-officio licenses for patented subject matter without need for prior approval from the Ministry of Commerce and the Cabinet in case of urgent public need.

Section 51, para. 1 states *" In order to carry out any service for public consumption or which is of vital importance to the defense of the country or for the preservation or realization of natural resources or the environment or to prevent or relieve a severe shortage of food, drugs or other consumption items or for any other public service, any ministry, bureau or department of the Government may, by themselves or through others, exercise any right under Section 36 by paying a royalty to the patentee or his exclusive licensee under paragraph 2 of Section 48 and shall notify the patentee in writing without delay, notwithstanding the provisions of Section 46, 47 and 47bis."*

The primary motive claimed behind the government use policy of compulsory licenses was to expand coverage of patients under the Universal Coverage(UC) scheme (T. MoPH, 2008). As the Royal Thai Government (RTG) did not issue any private use licenses, use of the generic drugs were limited to citizens covered under the National Health and Security System Act allowing for intentional segregation of higher tier insurance schemes and high income segments of customers who pay for patented originator drugs. That Thailand issued a compulsory license for a non-ARV, also raised doubts regarding the Thai Government's motive to gain popular support during political turmoil. Critics claim that the need for clopidogrel did not constitute an emergency or health crisis (WSJ, 2007) as the RTG did not announce a national emergency or healthcare crisis, but rather maintained that the GULs were issued on grounds of Public interest, reflecting the RTG's perspective of patents as a privilege, is subject to infringements in times of urgency (C. Ho, 2011).

Prior Negotiation and Working groups

A Working group including representatives from Thai Food and Drug Administration, MoPH, Patent Office, and the Ministry of Commerce was established in 2005 to negotiate prices with pharmaceutical firms. During negotiations, discounts were requested without explicit demands for licensing options. With a mandate to achieve prices at the level of 5% higher than the most expensive generics, Thai negotiators aimed to bring prices on par with category 1 tiered prices for Kaletra of approx. USD 500 Per Patient Per Year (PPPY). Abbott labs sold Kaletra in Thailand at a category 2 tiered price of USD 2200 PPPY in Thailand and refused to lower prices (Moon, Jambert, Childs, & von Schoen-Angerer, 2011).With an estimated 50,000 patients requiring LPV/r, the MoPH claimed unaffordability of the tiered price. Sanofi's pricing of USD 2 per day limited Plavix treatment to 20% of the 300,000 eligible patients under the UCS. In an official statement the Thai government stated "Prior negotiation with the patent holders is not an effective measure and only delays the improvement of access to essential medicines. It is only after the threat or the decision to use and implement compulsory licensing or government use of patent that the negotiation will be more successful and effective".

In 2006, a separate sub-committee consisting of national advisors on "Government Use of Patented Drugs and Medical Supplies" was established by the National Health Security Office (NHSO) to nominate drugs eligible for compulsory licensing. The committee was provided eligibility criteria for GULs and tasked with making recommendations to the MoPH for target drugs for up to 15% of all patented drugs. On recommendation from the (NHSO), the MoPH used compulsory licensing pathways to procure unaffordable patented drugs (MoPH, 2007).

License details

The state-owned Government Pharmaceutical Organization (GPO) was licensed as the sole importer and supplier of generics to procure generic medication through issued compulsory licenses. The license for LPV/r was limited to quantities sufficient for 250,000 patients, while the license for clopidogrel was unrestricted with regard to quantity (MoPH, 2007).

Royalty rates were established by the MoPH using a questionable approach, setting the royalty rates at 0.5% of sales for what it termed "high retail value drugs" and an upper limit of 2% for "Low retail value" drugs (MoPH, 2007). The fact that the remuneration rates did not vary for both LPV/r and clopidogrel was also unexplained. In 2014, royalties for the drugs were later revised to 2% to keep consistent with UNDP guidelines of 2-6%. There was no recorded contest on royalty rates from the patentees.

Outcomes

Generic clopidogrel and LPV/r was initially imported (Table2), and later locally manufactured for supplied to the UHS. This allowed for quality assurance as generic manufacturers were required to have WHO prequalified facilities and were subject to TFDA regulations. Critics claim that this was done expressly with the intent of establishing a local generic industry, without having a structured policy in place to utilize TRIPS flexibilities (Lybecker & Fowler, 2009). The generic clopidogrel faced delays in delivery after Sanofi-Aventis threatened to sue the generic supplier in India. In case of LPV/r, the first shipment was delivered 12 months after tender, while clopidogrel took 20 months. The Thai government relied on availability of generics produced in countries and their ability to export to successfully use the licenses (Table 2). In 2011, the GPO began local manufacture of LPV/r which demonstrated bioequivalence to imported generics. With significant reduction in prices of licensed drugs, the MoPH utilized the UHC primary healthcare infrastructure to distribute procured generics.

Table 3 Generic supplier clopidogrel and LPV/r (General Pharmaceutical Organization, 2015)

Generic Suppliers for Lopinavir/ Ritonavir FDC	Generic Suppliers for Clopidogrel
GPO (Thailand)	Apotex Inc. (Canada)
Mylan/Hetero Laboratories (India)	Cadila Healthcare(India)
	Emcure Laboratories (India)
	Ranbaxy Laboratories. (India)
	Sandoz Private (Switzerland)
	Silom Medical (Thailand)

Using Health Technology Assessment to measure outcomes:

In 2007, a national HTA agency was established, and commissioned to measure outcomes of compulsory licensing (Tantivess, Teerawattananon, & Mills, 2009). The Health Intervention and Technology Assessment Program (HITAP) estimated that approximately 40,947 new patients were able to access clopidogrel as prophylaxis for coronary artery disease over a 5 year period following the GUL (Figure 3). This was corroborated by the GPO reporting savings of USD 27 million on clopidogrel alone and 30,000 individuals able to access the drug in 2014 (Yamabhai et al., 2009). HITAP estimated cost savings of USD 78-80.25Mn for (LPV/r) with 3421 new patients in 2012.

Measuring the economic impacts of compulsory licensing, research demonstrated that 1st line drugs such as efavirenz had far more economic benefit as compared to the cancer drugs and more specialized treatments. This was simply due to higher numbers of individual usage, despite wider price differentials between generic and originator cancer drugs. However, the cost benefits for clopidogrel was the least among all the drugs in terms of QALY gain (Mohara, Yamabhai, Chaisiri, Tantivess, & Teerawattananon, 2011).

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Figure 2 New patients using LPV/r after GUL use (Yamabhai (HITAP), 2009)

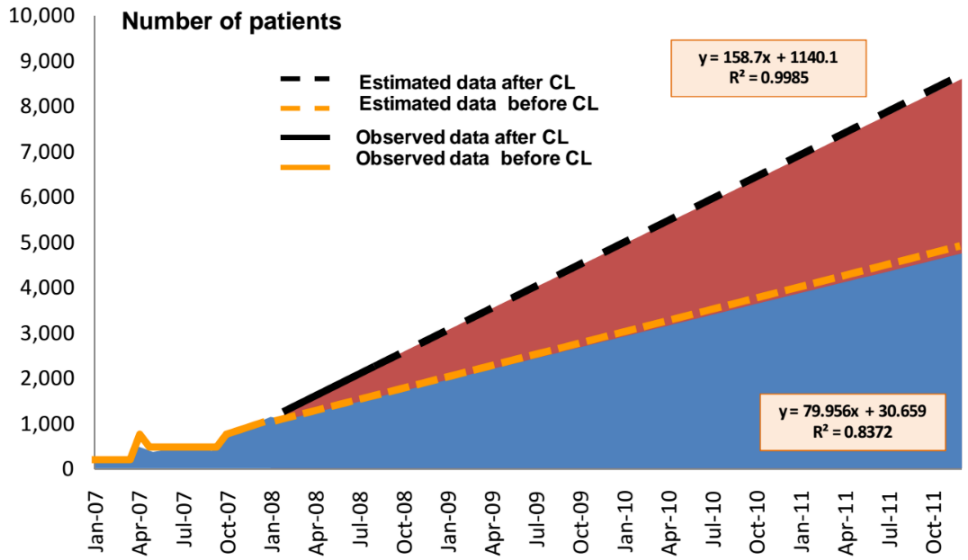
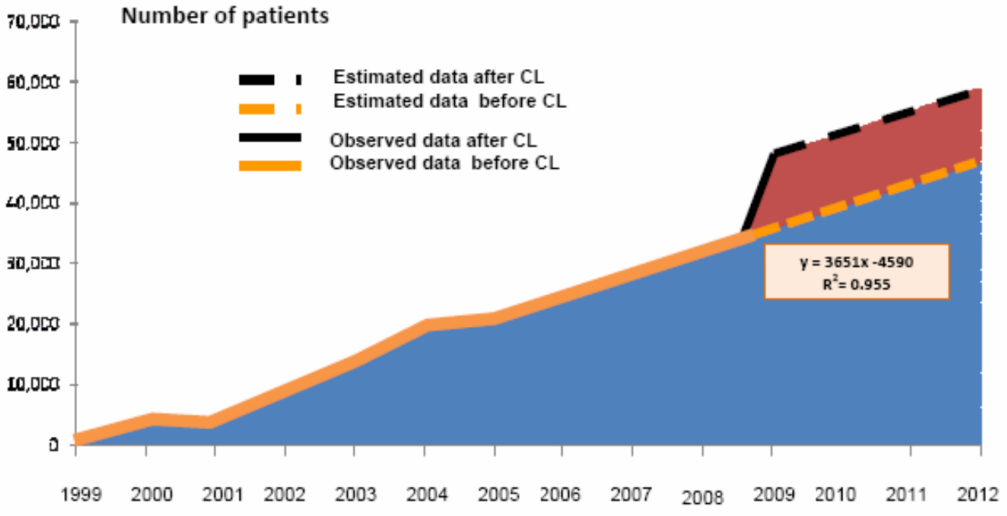


Figure 3 New Patients using clopidogrel after GUL use (Yamabhai (HITAP), 2009)



Retaliation

As a retaliatory measure for loss of exclusivity for LPV/r, Abbott laboratories withdrew 7 new products from the Thai regulatory process, including a heat stable formulation of Kaletra, considered crucial to the tropical country. The USTR also issued a Special 301 Priority watch-list notice for Thailand for its use of compulsory licenses, and withdrawing tariff exemptions on certain exports.

Further Developments

Following the GULs for Kaletra and Plavix, the new Thai government changed approach and confidentially consulted with patent holders for workable solutions to reduce prices prior to issue of GULs for chemotherapeutic agents. In 2008, the MoPH issued licenses for anti-cancer drugs including docetaxel, letrozole and erlotinib after negotiations failed. The licenses for LPV/r and clopidogrel were renewed until patent expiry.

Thailand has not issued any new licenses after a proposal in 2009 to discontinue the GUL policy, amid the new governments push for free trade agreements with the US and EU. In 2011, the GPO reported sales of USD 35 million from compulsory licensed drugs alone (GPO, 2011).In 2009, Abbott labs revised the price for Kaletra globally, offering the discount in Thailand in exchange for cancellation of the GUL, among many other developing countries. Only Novartis conditionally agreed to provide free of cost treatment to eligible patients through its patient access program in exchange for abandoning the CL for imatinib. Sanofi-Aventis also offered a 90% price reduction on Plavix after the Compulsory license was issued.

An established delivery infrastructure has enabled Thais to benefit from savings implemented by CL. As an UMIC, the Thai experience in using compulsory licenses as a tool to augment implementation of a universal healthcare system was an organized attempt to legitimize use of TRIPS flexibilities. In what was a sudden reversal of behavior in opposing business interests, the Thai policy was controversial and highlighted the role of strong political will in countering pharmaceutical corporations. Thailand remains the only country to have comprehensively attempted to evaluate and publish results of its government use policy for pharmaceuticals, setting an example for future applications. Despite criticism suggesting that the intervention was illegal due to non-negotiation and non-emergency nature of drugs, legal experts have clarified that Thai MOPH was fully within its mandate to issue licenses in public interest (S. Flynn et al., 2009),with support from the Director General of the WHO Dr. Margaret Chan (J. P. Love, 2007).

5.4 Case Study 2: The "Brazilian Model"

Brazil was the first developing country to guarantee universal access to ART through its National HIV and AIDS Program (NAP) by incorporating HIV testing and treatment delivery into its universal healthcare infrastructure (Nunn, 2009). Law 9.313 guarantees universal ART coverage to all eligible patients with no copayments (MOH, 1996). 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.

The Sistema Unico de Saude (SUS) or Unified Health System was established 1988 with active involvement of civil society groups, and decentralized at state and municipal levels to provide universal healthcare coverage (M. Flynn, 2008). The SUS targeted estimated 123 million Brazilians without insurance, in order to work Article 196 of Brazilian Constitution (1988) which holds the state responsible for delivery of universal healthcare. The NAP, which is administered on a centralized level, uses the infrastructure of the SUS as delivery instrument for ART.

Compulsory Licenses as a threat

Combining negotiations, local manufacturing, with threats of compulsory licensing to attain discounts, gives credibility to CL threats has been termed "the Brazilian Model". Having established a robust 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% being imported patented drugs. Brazil was able to attain discounts varying from 40-70% using negotiations (Table 2), with savings of 1.2 billion in ARVs using CL threats (Nunn, 2009).In 2005 ,after negotiations resulting in minimal discounts, tenofovir and efavirenz were targeted for compulsory licensing. Tenofovir was exempted from compulsory licensing due to earlier discounts offered by Gilead, while repeated threats without action failed to attain significant discounts from Merck and led to the CL for efavirenz in public interest. The sustainability of the NAP was also a driving factor behind use of CL to allow generic procurement. In addition to the Generic Law 9.787 (1999) to promote generic quality through demonstration of bioequivalence with originator drugs, industrial capacity buildup has strengthened the bargaining power of Brazil and lent credibility to CL Threats (Shadlen & da Fonseca, 2013).

Table 1 CL Threats and Discounts obtained (Nunn, 2009)

Year	Drug	Patentee	Outcome
2001	Efavirenz *	Merck	Discount (77%)
2001	Nelfinavir*	Roche	Discount(69%)
2005	Tenofovir	Gilead	Discount (5.2%)
2007	Efavirenz *	Merck	CL (2 %)
2007	Atazanavir	BMS	Discount (77-78%)
2007	Lopinavir / ritonavir*	Abbott Labs	Discount (75 %)
2008	Tenofovir	Gilead	Discount (72%)
	*- protected by Pipeline patent		

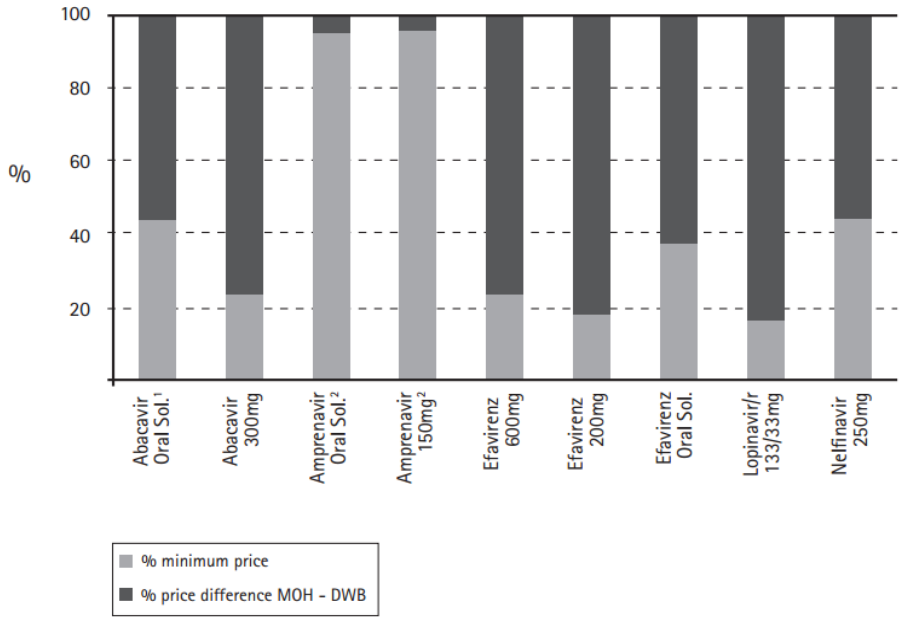
Impact of TRIPS

In 1996, Brazil adopted TRIPS under threat of trade sanctions from the US, without using the *vacatio legis* period offered by the WTO to developing countries (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 deleterious effects on the healthcare budget and on ART access, due to closures of local API manufacturers.

Pipeline protection

As a transitional measure Brazil adopted a revalidation patent mechanism (Pipeline protection) along with TRIPS regime in 1996, allowing validation of foreign patent protection on basis of approvals in third countries. Efavirenz was afforded 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 is 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 CLs were protected by revalidation patents and were attributed to high costs of treatment (Chaves et al., 2015). Brazil spent between USD 420 -519 million on 5 ARVs protected by revalidation patents (Figure 4).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).

Figure 4 Price differentials caused due to revalidation patents in Brazil's NAP (Hansenclever, 2007)



The National HIV and AIDS Program (NAP)

Brazil runs a highly effective NAP that is centrally administered, while using SUS infrastructure to deliver of ART through its AIDS Drug Dispensing Units (ADDU) attached to public hospitals or health centers across the country. With a 0.6% prevalence rate of HIV, Nationwide HIV testing and focus on high risk populations has resulted in fairly high adherence rates and has resulted in a 40% reduction in mortality, and an 80% reduction in hospitalizations due to HIV/AIDS. From 1995-1996 the median survival time of PLHIV increase threefold (Marins et al., 2003). Treatment costs per person rose from USD 1270 in 2004 to USD 2577 in 2005, due to increasing patients accessing ART and high costs of patented ARV's.

Legislation and Reasoning

Brazilian legislation provides instances and provisions for various types of compulsory licenses in Section III, Chapter 7 of industrial property Law No. 9.279 (1996). Article 68-74 describe obligations and exceptions under which varying types of compulsory licenses can be issued including Local non-working (Art.68), Anti-competitive behavior (Art. 73), Dependent patents (Art. 70), and Public interest licenses (Art 71).

In 2001, The United States raised a WTO trade dispute citing TRIPS incompatibility of Local working requirements in Art. 68 of Brazilian patent law. The complaint was withdrawn after an understanding between the parties on the basis of prior consultation in case of compulsory license use under local working conditions, and that compulsory licensing for ARV's could be justified under Public non-commercial use (WTO, 2001).

Article 71 of the Law no. 9.279 states "In cases of national emergency or public interest, declared in an act of the Federal Executive Authorities, insofar as the patentee or his licensee does not meet such necessity, a temporary ex-officio non-exclusive compulsory license for the exploitation of the patent may be granted, without prejudice to the rights of the respective patentee." Art 71 does not invalidate existing patent but only allows government use of subject matter for public use, and was also justified for use by the USTR in a 2001 dispute settlement understanding in order to avoid further dispute.

Prior Negotiations

Lengthy 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, 2007). In 2005, the treatment combination consisting of zidovudine, lamivudine and efavirenz was the most widely used (47%) imported first line ARV (Emily et al., 2011) .

Following Merck's refusal to reduce the price by more than 2%, A Public interest declaration (Ministerial Ordinance 886) preceding issue of a public non-commercial use license was announced on 27 April 2007, followed by Presidential decree 6.108 announcing the of the Compulsory license as prescribed by the Ministry of Health on 7th May 2007. President Luiz Inácio Lula da Silva, signing the decree granting the compulsory license for efavirenz issued in public interest, said "between our business and our health, we are going to take care of our health".

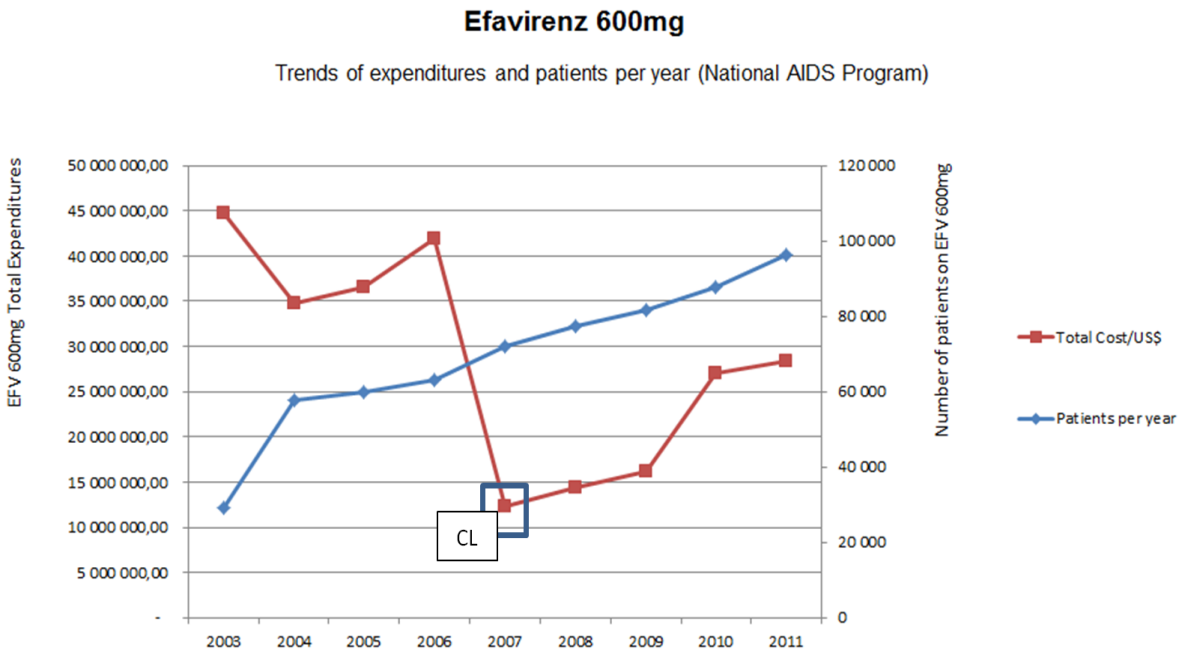
License

Farmanguinos, the largest state-owned pharmaceutical manufacturer was licensed to import and manufacture generic EFV, for public non-commercial use by the NAP. 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. The Ministry of Health received technical assistance from WHO (PAHO) with prequalification of 2 generic manufacturers and UNICEF providing transactional support (UNGASS, 2008). The 1st 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 (Da Silva, Hallal, & Guimaraes, 2012).

Outcomes

The Brazilian MOH reported saving of 58% or USD 104 Million from 2007 to 2012 from generic efavirenz imports alone. Generics were initially procured from Indian manufacturers (Ranbaxy labs, Aurobindo pharma), and later manufactured locally through by 5 national firms namely, FarManguinhos-Rio, LaFepe-Pernambuco, Globequimica, Cristalia, and Nortec (Lago & Costa, 2009). Nationally produced generics were costlier than imported generics due to research and developments costs, and were reliant on imports of APIs from other countries and increase vulnerability to currency valuation rate increases (Meiners, Sagaon-Teyssier, Hasenclever, Moatti, & Boni, 2011).

Figure 5 Cost and use trends of Efavirenz before and after compulsory license in 2007 (Silva 2012)



In 2008, The Ministry of Health 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 (Figure 5). 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(ANVISA, 2015). The CL was renewed by President Dilma Rousef in 2012 and is due to expire in 2017.

Table 4 Price variations for Efavirenz (Silva,2012)

Originator Price Before CL	Imported Generic Price (2008)	Manufactured Generic Price (2010)
1.59/Pill	.46/Pill (600 Mg).22/Pill(200 Mg)	.75/Pill (600 Mg)
580 PPPY	166- 170 PPPY	273 PPPY

Other developments

Brazil has moved towards voluntary licensing approaches with the Productive Development Partnership (PDP) policy (2008) to stimulate local manufacturing capabilities. The program guarantees 5 years of SUS purchases of locally manufactured medicines at fixed prices, in exchange for technology transfer and local production agreements. The program has successfully manufactured a variety of pharmaceutical products including large molecule biologics including filgastrim, and influenza vaccines(Chaves et al., 2015).

The Brazilian approach demonstrates effective use of compulsory licensing as a threat to attain discounts , and by using existing delivery infrastructure for delivery of procured generics . Brazils CL strategy culminated from a confluence of many factors such as political will, active role of civil society groups, compounding prices after implementation of TRIPS, spillover effects of a successful NAP, and threat of legal action at the WTO. The role of the CL to correct the Pipeline mechanism, leads one to criticize the lack of prior diligence in adopting TRIPS Plus standards.

5.5 Case Study 3: Bayer vs. Natco - India

In 2012, the Patent Controller of India issued its first compulsory license for Nexavar (sorafenib), a Bayer drug used in palliative treatment of late stage hepatic and renal carcinomas. Weak national health policy and public health laws impede access to cancer treatment in India resulting in burdensome treatment costs on patients along with a shortage of treatment facilities in rural areas. Cancer treatment in India is widely self-financed, due to a low annual public cancer spending at USD 10/capita (Pramesh et al., 2014). Chemotherapy is minimally covered in schemes and is mainly financed by out of pocket payments, non-profit organizations, and public hospitals offer programs, but is plagued by overwhelming demand, and limited funding. As much of India's population pays for healthcare out of pocket, the judicial license lowered retail prices of sorafenib sold through the private pharmaceutical market.

India's public healthcare spending of 1.1% of total GDP is among the lowest in the world, resulting in out of pocket (OOP) spending of 80% of total healthcare expenditure. Absence of a universal coverage scheme, and decentralized state administration of healthcare has resulted in disparities in health across states, leaving 660 million citizens unable to afford basic healthcare. Nearly 3.1 million additional households face poverty annually due to healthcare expenditure (Van Doorslaer et al., 2006). As a LMIC, India also experiences a demographic shift in diseases transitioning from infectious diseases to non-communicable disease, with NCDs accounting for 53% of all deaths in 2013 (Thakur, Prinja, Garg, Mendis, & Menabde, 2011). Penetration of insurance coverage is slowly progressing with only 15% of the population being insured by some form of basic healthcare coverage.

Paradoxically, Indian generic manufacturers supply up to 20% of the global generic drug market by volume (Perlitz, Just, Ebling, & Walter, 2008), earning the nickname "Pharmacy of the Developing World". India fails to take advantage of homegrown benefits to enable access to medicine, due to low government intervention in healthcare sectors, despite supplying affordable medicines to much of the developing world (Chaudhuri, 2007). The mix of a large private spending on health and good manufacturing capabilities had proven to be a lucrative market for both international and local pharmaceutical firms. Generic versions of expensive drugs set a precedent for supply of affordable medication globally, often to uninsured patients in developed countries - creating an export driven pharmaceutical industry that is highly competitive and profit driven.

Implementing TRIPS

India implemented TRIPS in 2005 after taking full advantage of the transition period for developing nations afforded by the WTO at the time. Its ability to develop and nurture a healthy generic pharmaceutical industry is attributed to non-patentability of products, allowing reverse engineering of patented drugs prior to 2005. The Indian Patent Act of 1970 was amended in 2005 to recognize product patents. Drugs patented prior to 2005 did not benefit from patent protection and continued to be manufactured by generic manufacturers locally. The transition period allowed amending of IPA to a TRIPS compatible regime, including a controversial "Section 3d" amendment to the Indian patent act of 1970. The Indian patent regime is perceived as highly contentious by pharmaceutical firms due to full use of TRIPS flexibilities, including stringent patentability criteria, and the pre- and post-grant opposition framework, which leaves patent holders vulnerable to patent revocation and loss of exclusivity. Indian legislation also does not recognize patent linkage, data exclusivity, and International exhaustion of rights (C. Ho, 2011).

Legislation and Reasoning

Section 84 of the Patents Act (P.A.) sets provisions for issue of a compulsory license on local working grounds. Sec 84 (1) states"(1) At any time after the expiration of three years from the date of the grant of a patent, any person interested may make an application to the Controller for grant of compulsory license on patent on any of the following grounds, namely: (a) that the reasonable requirements of the public with respect to the patented invention have not been satisfied, or (b) that the patented invention is not available to the public at a reasonably affordable price, or (c) that the patented invention is not worked in the territory of India."

Section 84 (6) P.A. sets criteria for evaluation and grant of a compulsory license that mandates reasonable effort in requesting a voluntary license, ability of the applicant to meet local requirements, undertake financial risk to public advantage , and failure to use patented subject matter by the patentee to meet public need.

Establishing Local non-working, non-affordability and non-availability

In 2008, Bayer was granted an Indian patent and regulatory approval for import and marketing for sorafenib tosylate. Investigation revealed that Bayer did not import any quantities of sorafenib in its first year of patent grant in India, and imported quantities of Nexavar sufficient for approximately 2% of eligible patients from 2009-2011, deemed grossly inadequate for local requirements. In 2011, only 593 boxes of Nexavar were sold to an estimated 200 patients, despite Bayer's estimates of 8900 eligible patients. Bayer also did not manufacture the drug locally and imported stock from manufacturing facilities in Germany, claiming to find no suitable need to manufacture the drug locally (Kurian, 2011). In his interpretation of local working requirement, the Patent controller referred to Art.5(A) of the Paris convention citing freedom of local working grounds, to discriminate of foreign manufactured products (Narain, 2012).

Bayer sold Nexavar at INR 280,428 (USD 4100) for a month's treatment, costing the average Indian an equivalent of 42 months of wages for a month's treatment of Nexavar. Nexavar was granted Orphan drug status in both the EU and US markets (Hill et al., 2016), but was rejected for reimbursement by NICE (UK) due to its high price, similar to the price sold in India. Sorafenib is not listed on the National List of Essential Medicines, and does not have a price ceiling under the Drug Price Control Act of 2013, such as other cancer drugs like imatinib (Gleevec).

The case proceedings were influenced by the fact that a 3rd manufacturer (Cipla) was manufacturing and selling a generic version of sorafenib in India. As Bayer had filed a separate case against Cipla, availability of its generic was not considered, on the basis that a separate pending injunction would jeopardize supply of the drug to the Indian market (Kurian, 2011). The court's final ruling gave precedence of public interests over patent rights of the patentee, and was criticized especially due to outright violation of patent rights.

Prior negotiations

Natco Pharma approached Bayer with a proposal for a voluntary license agreement in 2010, offering to manufacture and sell sorafenib at prices more affordable to Indian patients. Bayer was contacted by means of a letter sent to Bayer's office in India, and failed to respond. After a 6 month waiting period prescribed by the Indian patent law, Natco then filed for a compulsory license citing Bayer's refusal to deal. Bayer's legal team claimed that Natco did not make sufficient effort to negotiate a voluntary license, and argued against non-availability citing sales of Cipla's generic.

License Details

The Patent controller of India granted a non-exclusive license to Natco, citing non-availability and non-affordability, on condition that the drug was sold at INR 8800/ Month, and that Natco's product be packaged clearly differentiating it from the originator, and that it takes no advantage of Bayer's marketing and claims on effectivity of Nexavar (Kurian, 2011). Royalties were set at the 6% of total sales in line with the maximum remuneration recommended by UNDP guidelines, and increased to 7% on appeal by Bayer. As the Compulsory license was issued on private commercial grounds, Natco was ordered to reveal details of local working by means of a disclosure form (Form 27), along with provision of free treatment to 600 patients per year.

Retaliation

Bayer appealed the decision at many levels of the judiciary system including the Intellectual Property Appellate Board, the High Court and Supreme Court, all of which were rejected. Bayer's attempt to block Cipla's marketing rights was also perceived as an attempt to implement patent linkage in India and was penalized for the attempt. Bayer also filed for a new patent on a salt derivative of sorafenib that was appealed by Natco and Fresenius pharma in the pre-grant opposition phase, and rejected. The USTR listed India on its Special 301 list for use of CL, but did not take any further action. In a statement Bayer CEO stated that the CL was politically motivated and termed it "Theft".

Outcomes

As a result of the CL issued to Natco, sorafenib is sold in India at the lowest price globally(Hill et al., 2016) (Fig. 1). Natco sells generic sorafenib at the price of INR 8800 (USD 140) per bottle of 120 tablets. Shortly after the ruling Cipla further reduced prices on its generic version by 75% bringing the price of generic down to an estimated INR 5400 (USD 91) per bottle of 120 tablets. Generic sorafenib is available at the price of USD 90-200 through private pharmacies and distributors. Despite being available at a 97% discount at the lowest prices globally, the price is still unaffordable for the average Indian, whose monthly per capita income is USD 110 per month.

Figure 6 Lowest available sorafenib prices globally (Hill et al. 2015)

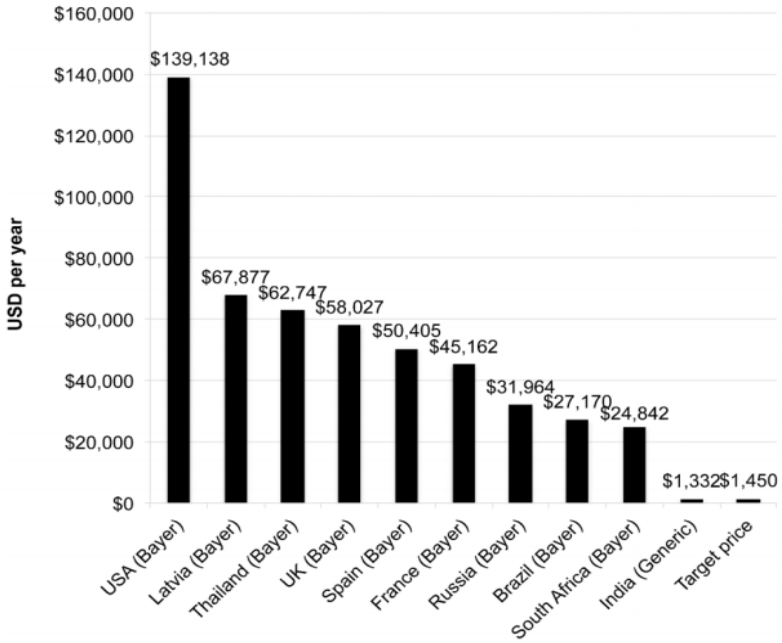


Table 5 Prices offered for Sorafenib Tablets (Monthly Treatment of 120 Tablets)

Originator price (Nexavar - Bayer)	Generic price (Sorafenat- Natco)	Generic Price (Soranib - Cipla)
USD 4100/ Bottle (34/Tab)	USD 140/ Bottle (1.16/Tablet)	USD 91-100/ Month (0.75/Tablet)

Availability of sorafenib

In a survey of 377 Indian physicians treating hepatocellular cancer, Kumar reported that 88% of respondents' hospitals had access to some form of sorafenib, and 67% of physicians willing to prescribe sorafenib to eligible patients (Kumar, 2014). However, the sample was unlikely representative of rural availability of the medicine and did not consider use for other indications. The private market in India ensures availability of quality generics in major cities, where private hospitals sell generic drugs at high margins above maximum retail prices. The abuse of OOP has led to inequitable sale of branded drugs despite generic availability. With 70 % of the population living in rural areas, and concentration of tertiary care centers in urban areas, proximity and travel costs bear heavily on the self-paying patient due to lack of state funded healthcare coverage.

Bayer continues to sell Nexavar at its original prices, while its Patient Access Program to eligible patients charges for 3 days therapy at INR 30,000 and supplied the remaining 27 days free of cost (Hoen, 2015). From 2013-2014 NATCO claims to has supplied free treatment of various cancer drugs to around 20,000 patients through its social responsibility program. (Basheer, 2015).

Grey market exports

As India adopts a national exhaustion principle, generic sorafenib is exported to foreign markets by online pharmacies and shipping agents, proving highly lucrative for NATCO. Export data reveals that sales agents shipped Sorafenat to a variety of countries at the cited costs of USD 150 per bottle. Both Cipla and Natco export significant quantities of generic sorafenib to multiple high, low, and middle income markets like the UK, Singapore, African countries serving as a steady supply of generic medications to uninsured populations worldwide (Zauba.com, 2014/2016). In June 2016, Natco received provisional USFDA marketing approval for its sorafenib Para.IV filing, for first generic entry to the US market.

Other CL applications

Indian patent authorities have rejected four CL applications on various grounds, including CL appeals for dasatinib and saxaglipitin on grounds of inadequate price reduction, and an application for indacterol (Peterson, 2016). An application for export of dasatinib, and sunitinib to Nepal under the Para 6 Waiver mechanism was rejected on grounds of non-notification of the WTO, despite the applicant (NATCO) havng received a compulsory license from Nepal. Coincidentally, Indian generic firms have supplied Brazil, Thailand, Rwanda, and Ecuador for compulsorily licensed drugs, without using the waiver mechanism. Recent USTR reports suggest an understanding between the Indian government and the USTR regarding refraining CLs for non-emergency scenarios, despite the Ministry of Health's recommendation for CLs on high priced patented medicines trastuzumab, ixabepilone, and dasatinib (Sengupta, 2016). Patent oppositions mechanisms have been used more elaborately to allow generic entry, such as the newly rejected patent for enzalutamide (Xtandi), a blockbuster prostate cancer drug by the Indian Patent office for non -inventive step, and non- novelty.

India has not issued a government use license despite struggling with a variety of epidemics, including tuberculosis, malaria and HIV. Research reveals intentional delay in launch of innovator drugs by an average of 5 years in India, attributed to the risk of reverse engineering and production of generics (Berndt & Cockburn, 2014). Social scientists suggest reluctance of the Indian government to issue GULS due to inability to work the patents in state-owned facilities, due to an absent "Shadow of hierarchy", and reliance on civil society and free market competition to enable access to medicine (Eimer & Lütz, 2010). The lack of a comprehensive state funded cancer care program system limits distribution of produced generics in non-urban areas, explaining the reluctance to issue GULs, and reliance on the private market for enable access. As of 2015, NATCO has failed to disclose any information on local sales and working of the sorafenib patent, failing to with fulfill obligations ordered by the compulsory license, without attracting any punitive action (Basheer, 2015).

The judicial license for sorafenib remains the only compulsory license issued by India, but the absence of an evaluatory mechanism has led to violation of compulsory license obligations. Such violations including the non-disclosure of sales and production volumes by the licensee, and grey market exports which potentially invite a WTO dispute. Despite the compulsory license, Natco's generic was neither the first nor the cheapest generic on the market further contributing to the controversial nature of CL use. However, transparency in the judicial proceedings has allowed opportunities for appeal and limited reprisal by the patentee.

5.6 Case Study 4: Use of the Waiver Mechanism - Canada and Rwanda

Rwanda remains the first, and only country to use the Para. 6 Waiver mechanism to procure generic medication using a CL issued by Canada. After discussions with Canadian generic manufacturer Apotex to supply a fixed dose combination of Zidovudine, Lamivudine and Nevirapine (AZT/3TC/NVP) in conjunction with a scale up of the Rwandan National AIDS program. As a low income country that relies on imports of pharmaceutical products due to lack of local manufacturing, the Waiver mechanism was used to procure a first line regimen from Canada, corresponding to revision of treatment guidelines to expand the National AIDS Program in 2007.

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.

Community risk pooling and the National AIDS Program

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 (El-Sadr et al., 2012).

Using the Paragraph 6 " Waiver Mechanism"

Following the Doha Declaration on public health, the WTO's August 2003 decision on TRIPS and Public Health, proposed an amendment to Art.31 allowing exports of compulsory licensed drugs to eligible countries on notification of the WTO council. Under the proposed amendment, restrictions on use of compulsory licenses by countries to import generic medication, due to inability to locally produce medicines, would be waived on the condition that the exporting country also issue a compulsory license for export. Under the system, Eligible countries are required to establish inability to locally produce a compulsory licensed drug, and cease imports once domestic requirements have been met. The Waiver also allows re-export of the imported generics to 3rd countries on issue of import licenses (WTO, 2005).

Among requirements for use of the systems includes distinctive packaging of the produced generic to differentiate it from originator products, and a general notification of the TRIPS Council regarding intent to Import and export, with exemptions for LDCs. The notification requires public disclosure of quantities, and drug specifics such as distinguishing characteristics of products, identification and destination ports. Exporting countries are also required to furnish intent to export and issue a compulsory license for the said drug. The system is also understood to be read in context of a good faith understanding, to prevent profiteering by generic manufacturers.

The Canadian Access to Medicines Regime (CAMR)

The Government of Canada was among the first countries to ratify the WTO decision of August 30th 2003 (The Waiver Decision), passing the Jean Chretien Pledge to Africa (Bill C-9), amending its Patent act and Food and Drug Act in compliance with Art.31bis to establish the Canadian Access to Medicine Regime. The Regime provides conditions for use of the compulsory licensing mechanism for export of medication to eligible countries, purporting to supply medications to developing countries on a humanitarian basis. When permitted by recipient governments the CAMR also allows purchase of medication by NGOs for procurement. Restrictive aspects of the Regime include restriction of exports to LDCs, and requirement of an Emergency declaration by non LDCs to qualify as a recipient. Other measures include a generic price limit of 25 % of originator drug prices and a 4 year limit on the license validity. Aiming to balance patentee rights, the Act allows Patentees to sue the government for wrongful infringement in case of perceived commercial use, as part of its Fair Use provisions. Licenses issued under the CAMR are limited to validity of 2 years, and subject to review prior to renewal. The regime uses a sliding scale to set royalties based on countries UNDP Human Development Index status up to a maximum of 4% (Nkomo, 2013).

Procedural Limitations of the CAMR

The CAMR has many obligations that go beyond requirements of Art.31bis. Eligible drugs are restricted to a positive list and require prior regulatory approval of the Canadian MOH (Rimmer, 2008). In 2005, Apotex composed and formulated a fixed dose combination (FDC) unavailable on the market at the time, branding it Apo-Triavir to comply with CAMR guidelines. As the combination was not available as a FDC on the market, the Bill did not sufficiently make exceptions for fixed dose combinations, and required regulatory approval prior to inclusion of the FDC to the scheduled list of permitted drugs for export, a process that took 7 months. The Regime also mandates partnering with a Canadian generic manufacturer which can place promotion of local industry above the humanitarian visions of the CAMR. The demand driven procurements limit ability of developing countries to stockpile ART due to limits on quantity and validity of the license. Refusal of the Canadian government to amend the CAMR has further contributed to avoidance of use. Drugs produced under the regime are also required to be clearly differentiable from the originator drug, as an anti-diversion measure.

Prior Negotiations and Royalties

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. However, all patentees agreed to waive royalties as Apotex stated the humanitarian motive of the license and the non-profit sales price offered to the Rwandan government. The refusal to voluntary license under reasonable conditions was replaced by non-assert clauses which required further formalities by the CAMR. After negotiations were unsuccessful, the Apotex approached the Canadian patent office for CL's for export (Rimmer, 2008).The multiple patent holders contributed to overall delays in the procurement process.

Rwandan Bidding process and WTO notification

Following discussions with Apotex, the Rwandan Ministry of Health officially notified the WTO council regarding intent to use the Waiver mechanism to import ARTs from Canada. Further complicating the procurement was that Rwandan law required Apotex to participate in a competitive bidding process for a tender as requirement to supply the drugs to ensure the lowest possible price of the FDC, which was also available from other generic

suppliers. As a prerequisite by the CAMR, Rwanda notified the WTO on June 2007 with regards of intent to import a fixed dose combination of AZT/3TC/NVP, followed by a Canadian notification in October 2007. The Rwandan notification specified that reserving the right to modify the specified quantity due to the chronic nature of the disease(W.T.O., 2007).

License details

The Federal Commissioner of Patents (Canada) granted Apotex a royalty-free compulsory license for export, limited to 2 years, as royalties were waived by patentees on a humanitarian basis. The license was limited in quantity to 260,000 packs of ApoTriavir in line with CAMR guidelines. Rwanda was not required to issue a compulsory license for import as Art. 31bis exempts importing LDCs from issuing a compulsory license under the Waiver mechanism.

Outcomes

In 2008-2009, 2 shipments of Apo-Triavir totaling 240,239 bottles (60 Tabs) were delivered to Rwanda(W.H.O.). 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 (Table 4).

The Rwandan MOH mandates 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 receives logistical support from a PEPFAR subsidiary (SCMS) to procure drugs from WHO Prequalified suppliers and then supplies pharmacies nationally. This strategy has successfully protected the program from stock outs of ARVs and ensures quality control. The lack of a Rwandan national drug regulatory authority necessitated this measure to ensure drug quality (El-Sadr et al., 2012).

Scale up of treatment

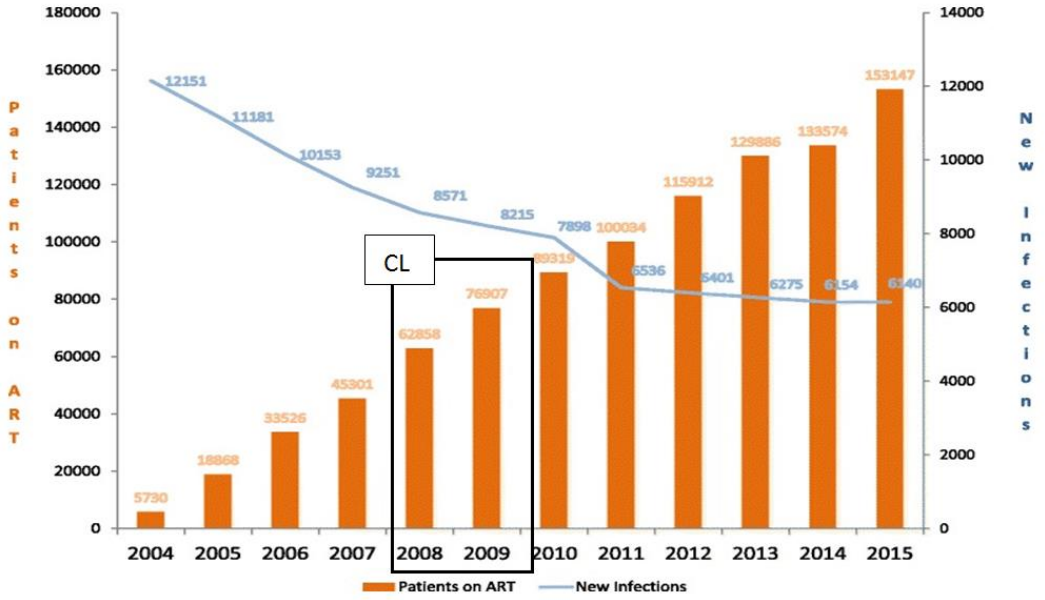
Supporting the procurement of drugs from Apotex, AZT/3TC/NVP was the WHO recommended first-line therapy which was used by approximately 44 % of Rwandan patients on ART (PEPFAR). Total expenditure on HIV and AIDS in Rwanda increased from USD 74.6 million in 2007 to USD 110.8 million in 2008 (an increase of about 33%).The number of people on the regimen was reported to be 56,731 in 2008 and 75,041 in 2009 (UNGASS, 2010). 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 (Figure 7). 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^3.

Access and Availability

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 (PEPFAR, 2012). 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).

Figure 7 ART treatment scale-up of and decreasing incidence rate of HIV infections (Nsanzimana, 2015)



Refusal to renew license

Despite interest to renew the order, Apotex declined to do so, citing complexities demanded by the CAMR, including the 2 year limit on CLs and prior negotiations with patentees. Apotex refused to pursue the CAMR pathway to supply any generics to a country, unless it was amended for less bureaucratic procedures. Rwanda simultaneously procured generics from manufacturers in India at prices similar to the Apotex prices (Table 6). As Apotex's bid was accepted strictly on basis of price competitiveness, Apotex was forced to supply the drugs at cost. Availability of similar products from other generic manufacturers and simpler acquisition pathways both in terms of costs and procedural formalities, allowed acquisition from Indian generic manufacturers, after delivery of assigned stocks by Apotex (W.H.O.).

Other Attempts to use the CAMR

Canadian authorities report difficulty finding a recipient country willing to notify the WTO council fearing retaliation, despite the CAMR's attempt to initiate a humanitarian agenda towards assisting LDCs. Prior attempts to use the regime by Medicins sans Frontiers were rejected by the Canadian govt. due to non-notification of the WTO by the importing country for fear of retaliation (MSFAccess, 2006a).

Table 6 Cost of AZT/3TC/NVP fixed dose combination procured after CL expiry (WHO GPRM)

Year	Supplier	Price per Tab	Buyer	Percent discount
2004	Originator (AZT/3TC +NVP)	0.7916*	UNICEF	*Combined costs
2008	Apotex	0.195	Global Fund	75 %
2008	Aurobindo	0.1982	Global Fund	72 %
2008	Hetero	0.2208	UNICEF	72 %
2008	Cipla	0.2045	UNITAID	74 %
2009	Mylan	0.1965	PEPFAR	75%
2010	Cipla	0.1752	Global Fund	77%

As the only successful use of the Waiver mechanisms, the license issued by the Canadian government for export to Rwanda although a humanitarian exercise, did not offer significant advantages over traditional procurement methods, due to delays and limited cost benefits over generic competition. The process, however serves as a template for prospective users of the mechanism to allow relaxed standards considering that the mechanism was primarily designed for use by countries without sufficient manufacturing capacity, while encouraging use of technical assistance from NGOs and intergovernmental bodies to enable more efficient use of the mechanism by developing countries, including adoption of an official royalty setting method. Further possibilities aspects such as re-export to other eligible countries have yet to be explored.

The Rwandan use of the waiver mechanism was dependent on funding and technical support of philanthropic institutions such as PEPFAR and the Global Fund for procurement of generics. The involvement of humanitarian organizations has discouraged retaliation and avoided funding shortages. The use of the CL approach allowed formulation of a previously unavailable fixed dose combination from 3 different patent holders. However, delays and procedural complexities pose significant barriers to use.

5.7 Case study 5: Anti-Trust license- Italy

Use of compulsory licenses in high income countries have been limited and primarily market initiated. In 2005, Italy opened investigations into anti-competitive behavior by GlaxoSmithKline (GSK) for sumatriptan. The resulting license issued by GSK to Fabbrica Italiana Sintetici (FIS) under order by the Italian Competition Authority (ICA) primarily targeted exports of sumatriptan succinate to Spain. Within the European Economic Area, Italy and Spain are the 3rd and 5th largest pharmaceutical markets by volume, after Germany, UK, and France (4th). With an estimated prevalence of 3,617600 patients with migraine (Badia, Magaz, Gutierrez, & Galvan, 2004), the Spanish market comprised a significant sales market for GSK's Imigran. In parallel, the ICA also open investigations into Merck's refusal to voluntary license generic manufacturers' finasteride and imipenem cilastatin for export purposes (I.C.A., 2005b).

As developed countries benefit from having stricter IP provisions and robust legal infrastructures, competition law in developed countries is used to promote welfare goals while balancing IP rights (Reichman, 2009). The Italian compulsory license cases were among a series of antitrust lawsuits in the EU against large innovator pharmaceutical firms. To avoid parallel trade within the EU, GSK adopted a Dual Pricing strategy for 82 products (including sumatriptan) in Spain, selling drugs to wholesalers at higher tiered prices for export purposes and lower prices for local supply. In 2001, the European Court of Justice deemed this practice illegal and ordered that GSK remedy its behavior. As retention of a dominant position in the Spanish market was strategic to controlling loss of sales in other EU markets, GSK then adopted a market leveraging strategy to avoid losses to parallel trade. Using a similar strategy earlier, GSK had delayed market launch of Imigran into the French markets in order to retain its monopoly status (Inno-group, 2014).

Parallel Trade in the EU

The single market dynamics of the European Economic Area (EEA) plays a key role in competition policy within Europe due to varying patent validities. The EEA adopts a regional exhaustion doctrine that allows free movement of authorized goods within member states, resulting in parallel trade that affects pricing and launches. Pharmaceutical firms often adopt counter-measures to avoid lost sales due to re-export of products sold at cheaper prices, to other higher tier markets. Parallel trade has resulted in drug shortages in some member states such as Greece, leading to adoption of export limits and notification of parallel exports in some member states. Simultaneously, some EEA members such as Germany, Sweden, Denmark, and the UK incentivize parallel imports as part of cost containment policy (Coco, 2008). Studies show that parallel trade in the EU has a detrimental effect on overall welfare as it forces convergence of prices across markets with varying abilities and willingness to pay, making a case for differential pricing in the EU (P. M. Danzon, 1998).

Legislation and Reasoning

As the E.U. legislative infrastructure dichotomizes between IP rights on a national level, and competition law on the European level following harmonization of regulations in 2003, the ICA used EU legislation to argue their final judgment. Article 102 of the Treaty of the Functioning of the European Union (TFEU), provides conditions for "Any abuse by one or more undertakings of a dominant position within the internal market" including (a) Imposition of unfair purchase or sale conditions, (b) restriction production, or technical development, (c) discrimination between trading parties, (d) restrictive clauses in agreements having no connections to subject matter of agreements.

Establishing Abuse under Art 102 TFEU

Application of Article 102 TFEU is conditional on abuse of an existing dominant position in a relevant market, that significantly affects trade between member states. In order to establish a violation of Article 102 TFEU, both markets must be sufficiently independent from each other, to warrant the conclusion of an illegitimate expansion of market power, and simultaneously must be sufficiently related so that causality between the dominant position in the upstream market and the distortion of competition in a downstream market can be determined. Market leveraging is the practice of a dominant company illegitimately expanding a well acquired position into another technically or commercially related, but economically self-contained market, to gain an unjustified competitive advantage in that market and constitute exclusionary abuse (Lamping, 2015).

The Italian Competition Authority found that Italy was the only European country with a valid patent for sumatriptan, allowing GSK to retain a 58% share of Spanish sumatriptan sales despite patent expiry, and 96% of the Italian market through a quasi-monopoly in manufacture of the API, and an injectable form. Sumatriptan was also the only 5HT-1 class of drugs (serotonin receptor antagonists) that was off-patent in other Spanish markets, with other substitutable drugs having valid patent protection (I.C.A., 2005a). In its ruling the Italian Competition authority pointed out that GlaxoSmithKline (GSK) controlled a larger market share than neighboring EU countries due to extended-protection under the supplementary protection system (SPC) system until 2008, and 2012 for process patents.

Supplementary Protection Certificates (SPC) are extensions on patent validity, granted as compensation for regulatory delays, from date of filing the patent, to date of marketing approval for a maximum of 5 years under EU law. Italian SPC's were previously valid for up to 18 years and were required to transition as part of the European community harmonization process. Italian Law No. 112/02 establishes a compulsory licensing framework for export of pharmaceuticals under Supplementary Protection *"only valid for export to countries in which patent protection has expired of its active ingredients, including any supplementary protection certificate, and in accordance with regulations in force in the destination countries."*

Sumatriptan was protected by a SPC and was therefore eligible for a compulsory license for export. The Italian Competition Authority ruled that GSK, indulged in anti-competitive behavior by preventing parallel exportation of sumatriptan succinate to other EU member states where its patent had expired to impede generic entry. By refusing to voluntary license Fabbrica Italiana Sintetici SpA., a primary condition for issue of a CL specified by TRIPS Art.31 was fulfilled. Under TRIPS, anti-competitive behavior allows exemption from prior negotiation and remuneration as punitive action for abuse of fair competition.

Generic Pharmaceutical Policies in Spain

In 2006, The Spanish MOH adopted Law 26/2006 that "Guarantees and the Rational Use of Medicines and Health Products". To control pharmaceutical costs, and alter prescription practices, the law introduced a generic reference pricing system, along with mandatory substitution of generics by pharmacists, and mandatory INN (International Non-proprietary Name) prescriptions. The implementation of this second reference price system has reduced the entry of generics. Sumatriptan is listed on Spain's positive reimbursement list and is therefore eligible for a 60 % reimbursement (Seget, 2003), resulting in originator firms reducing their prices to match the reference price.

Spain uses a combination of external and internal reference pricing to establish price caps for medicines, resulting in low prices for prescription medication within the EU. While low prices and price caps are beneficial for local use, it also poses lucrative incentives for wholesalers who re-export patented drugs to neighboring High Income markets with higher price ceilings. To counter adverse effects of parallel trade, Spain adopts a dual pricing system with unregulated prices (Free Pricing) on exported drugs, and regulated prices for drugs sold locally. This system allows differential pricing between goods intended for local use and exports, while avoiding drug shortages due to excessive parallel trade.

Prior negotiations

In 2005, GSK denied a license to FIS for manufacture and export of sumatriptan succinate API to neighboring markets within the EU where the patent had expired. FIS then applied for a compulsory license to the Italian Competition Authority, after failure of negotiations. GSK held no patent for sumatriptan in Spain, and held a dominant market share, with generic competitors already being present. In defense proceedings GSK claimed that the patent covered under the SPC would not suffice to produce the API, and would also require disclosure of an adjunct process patents with manufacturing specifications, as reason for its denial of license to FIS. FIS initially offered to withhold sale of the generic until expiry of the SPC, which was also refused by GSK stating that the process patent for the production of the API was due to expire only in 2011, further extending the validity of its patent life.

License details

Under threat of penalty, GSK issued a non-exclusive license to FIS for export to neighboring Ex-patent markets at a confidential royalty rate. To avoid a penalty for anti-competitive behavior, GSK also licensed 2 process patents with proprietary information for an expedited production process and compensate for delayed market entry. While the license for export issued by GSK allowed generic entry in a neighboring market to bring down prices of sumatriptan, the local Italian market retained its supplementary protection until 2008.

Outcomes

The ICA reported that the generic had entered Spanish market in Feb 2006, the API manufactured by FIS was exported to Spain for formulation into finished products by Universal Farma SL. Universal farma was the 2nd approved generic supplier after Sandoz (Novartis) to supply the Spanish market with sumatriptan succinate in March 2007 (AEMPS, 2007). The license issued to FIS allowed generic entry, but was limited in ability to counter the monopoly position of the originator due to conflicting policy and cross border barriers.

In 2007, GSK reported a 25% decrease in European sales of Imigran due to generic entry , despite still retaining the largest market share. Studies report limited adoption of generics due to price convergence (Table 7), in conjunction with price caps and reference pricing suggesting that conflicting policy has a deleterious effect on generic entry and competition. Compounding this effect is price pegging of originator drugs which allow retention of market monopolies, limiting benefits of generic competition (del Fresno & López, 2013). The adoption of generics also depends directly on the physician prescription practices in physician driven generic markets and has been evident in Spanish and Italian markets (P. M. Danzon & Furukawa, 2011). (Moreno-Torres, Puig-Junoy, & Borrell, 2009). The sumatriptan market was affected by generic competition with multiple suppliers entering the Spanish market in the same year, resulting in F.I.S. discontinuing producing sumatriptan succinate.

Figure 8 Generic market share and Price differences of Sumatriptan in EU markets(Vogler ,2012)

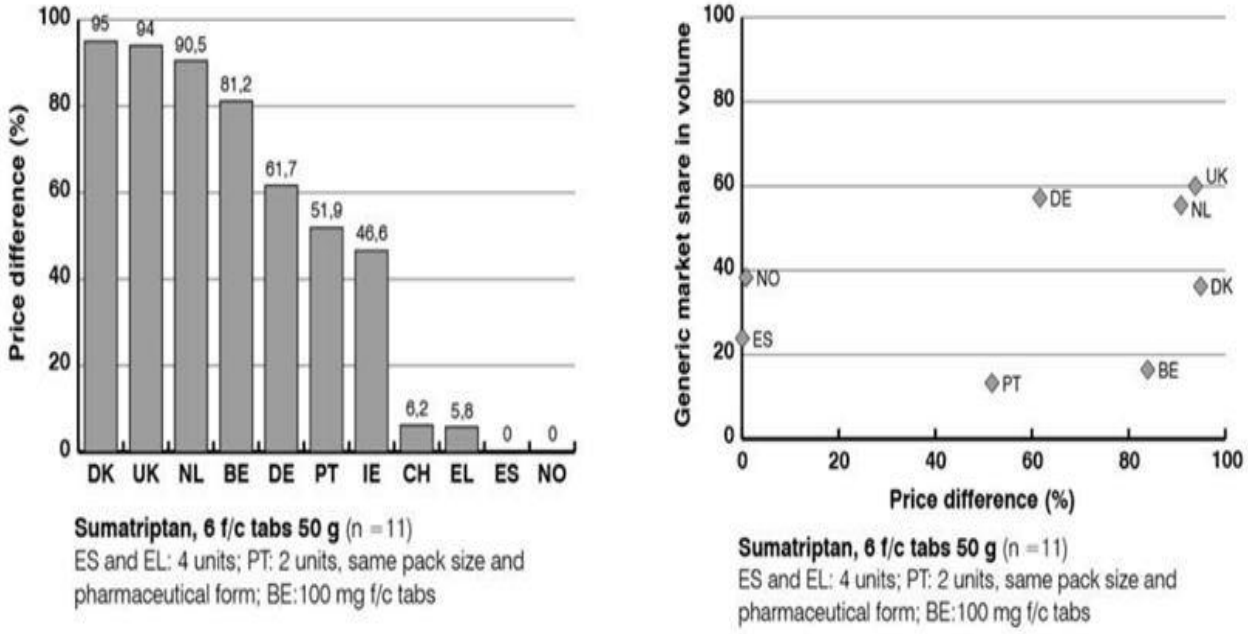


Table 7 Prices convergence of originator and generic drugs (Spanish medicines agency, 2013)

Drug	Price / Pill(€) 2010	Price / Pill (€) 2013
(Originator) Imigran 50 mg (4 Tabs)	5.63	3,0675
(Generics)Teva/ Ur/ Sandoz/ Mylan 50 mg	4.40	3,0675
Imigran (Originator) 6mg SC injectable	-	26,21
Sun Pharma 6 mg SC injectable	-	26,21

Well-regulated markets such as E.U., often restrict the benefits of generic entry due to conflicting policy between National and EU law (P. M. Danzon & Furukawa, 2011). This likely suggests a disincentive to compulsory license a drug, where lack of adoption by the market would deem the procedural and legal costs useless. The Italian CL was necessitated due to conflicting patent validities within a trade region, patent extensions, and compensatory behavior by pharmaceutical firms. As there is no regulation against price convergence in well regulated markets, allowing price pegging by originator firms comes at the cost of discouraging generic competition.

5.8 Case Study 6: Taiwan - Tamiflu

In October 2005, following a threat of an Avian Influenza pandemic and WHO working group report stating insufficient global stockpiles of antivirals, Taiwan (R.O.C.) was the first country to use CL to ensure a stockpile of Oseltamivir for emergency use (Hille, 2005). Taiwan lies in migratory pathway of birds that exposes the country to various strains of the H5N1 virus, and frequently experiences annual influenza epidemics due to centrality of tourism and trade routes (Chou, Chen, Chou, & Chang, 2008).

Taiwan (Republic of China) is politically recognized by the UN as a province of the Peoples Republic of China (P.R.C). However, its membership of the W.T.O. as Chinese Taipei, is crucial to establish its sovereignty from China (P.R.C). In 2003, Taiwan implemented TRIPS on condition that it is classified as a HIC, without using the transition period and other trade concessions. The W.T.O. is the only intergovernmental organization that recognizes Taiwan as a state. As a result of this "Anomalous" arrangement, Taiwan does not qualify for W.H.O. membership and is restricted in taking full advantage of W.H.O. interventions and assistance. Beijing recognizes Taiwan as a province of China and has blocked Taiwan's applications for WHO membership. In a 2005 MoU, the WHO and China, agreed not to invite high ranking Taiwanese participants to the WHA or other meetings. The 2003 SARS epidemic saw a delay of technical assistance by 4 weeks, including delayed official notification of W.H.O. due to political lobbying. In 2014, Taiwan was granted observer status at the WHA after amending its request from full membership to observer status (Charnovitz, 2006).

As compensation for political isolation, the MOH, and Taiwan CDC have used the WHO's Pandemic Preparedness program (2004) framework and International Health Regulations (2005) to establish an independent emergency response system that parallels WHO pandemic response protocols. In November 2005, the WHO reported 62 casualties due to the Avian (H5N1) Influenza epidemic in neighboring countries of Vietnam, Thailand, Cambodia, and Indonesia and issued an imminent threat of pandemic avian influenza. Oseltamivir is one of the 2 WHO recommended antivirals for influenza treatment, preferred over zanamivir due to its longer shelf-life and administrative route. In light of growing global demand, Roche was unable to meet supply requests of Tamiflu (oseltamivir). The Taiwanese government issued the CL to complement its pandemic preparedness program as a biosecurity initiative to prevent against stock outs. A W.H.O. report in 2004 stated that "Stockpiling of drugs in advance is currently the only way to ensure sufficient supplies at the start of a pandemic. Governments with adequate resources should consider pursuing this option as a precautionary measure."

Legislation and Reasoning

Section 5 of the Taiwanese Patent Act lists grounds and provisions for CL (TIPO, 2014). Following the SARS outbreak of 2003, the TPA was amended in 2003 to include national emergencies and broadened its scope of use beyond TRIPS Art.31(c), for failure to acquire a voluntary license in an emergency.

Art 87. states "In response to national emergency or other circumstances of extreme urgency, the Specific Patent Agency shall, in accordance with an emergency order or upon notice from the central government authorities in charge of the business, grant compulsory licensing of a patent needed, and notify the patentee as soon as reasonably practicable."

In May of 2005, Taiwan Ministry of Health (MOH) and the National Health Research Institutes(NHRI), approached Roche for a voluntary license to manufacture oseltamivir locally after inability of Roche to deliver the required amount 2.3 million doses to cover 10% of the population. Roche denied the license instead offering

to guarantee delivery of stocks by diversion from other countries. Unsatisfied with the response, the MOH applied for a compulsory license in October 2005 having failed to negotiate a voluntary license for manufacture of oseltamivir. Roche also cited inability of the NHRI to manufacture oseltamivir due to a complex formulation process. As response, the NHRI demonstrated ability to manufacture generic version of oseltamivir that gave credibility to the threat by manufacturing 100 Kgs of the API as proof of competence (Dean, 2005). NHRI Director Su Ih-jen stated "We have tried our best to negotiate with Roche. But to protect our people is the utmost important thing."

Legitimacy and Necessity of a National Emergency:

In 2004, following the SARS epidemic, the Taiwanese Communicable Disease Act was amended to declare Avian Influenza a Category 1 epidemic, constituting a threat to national security and requiring notification to the CDC (CDC, 1944). Given only anticipated pandemic and not an existing national emergency, the TIPO cited the Precautionary principle of the Rio declaration on Environment and development, 1992. The H1N1 influenza was deemed a threat to national security due to the high mortality rate of 50%. Comparing the American and Canadian CL Threats for Ciprofloxacin in light of the Anthrax attacks in 2001, there were no requests for discounts on the prices for the drugs. Citing the unique political position of Taiwan (R.O.C), the TIPO issued a CL to NHRI for local manufacture of oseltamivir, in addition to placing an order with Roche for 2.3 Million doses of oseltamivir.

Citing Emergency use under Paragraph 5(c) of the Doha Declaration which states "Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency."

Supporting policy

Not being a WHO member, Taiwan does not benefit from WHO sponsored surveillance, stockpiling and information sharing, calling for added prudence in issuing a CL for emergency use. The Influenza Pandemic Preparedness Plan consisted of 4 strategies including Early Detection, Interruption of Transmission, Antiviral stockpiling, and Vaccine Stockpiling, in conjunction with the WHO Rapid containment strategy and Stockpile (2005) and the WHO International Health Regulations (2005), which instructs countries to maintain stock of antivirals for emergency use and surge protection. The Taiwan CDC Established a National Influenza Center in 2006, in line with WHO guidelines and IHR (2005).In 2007,the system was independently audited by WHO advisor Dr. Robert Coker who ranked it on par with HIC pandemic plans (Chou et al., 2008).

License

TIPO issued an ex-officio compulsory license on Dec 8, 2005, to the NHRI to locally manufacture Oseltamivir for local use, citing the 68 confirmed deaths in Indonesia, China, Vietnam, and Thailand, along with para 5(c) of the Doha declaration to establish a National Emergency Under the compulsory license, valid until December 31, 2007, manufacture was restricted to domestic use in response to shortage of supply from Roche (AvianFluWatch, 2005). NHRI was also ordered to pay a fair compensation royalty, in case of use of patented subject matter for local use. The License was subject to revocation if Roche met its supply commitments within the agreed timeframe (江亮頡, 2007).

Roche stated that it was “Puzzled and Surprised” at the ruling and cited concern regarding the production and quality of generic oseltamivir by the NHRI, given the global shortage of the API for Tamiflu. However, there was no further appeal by Roche.

Outcomes

In issuing the license the NHRI demonstrated the ability to manufacture by partnering with Scinopharm Taiwan to manufacture and acquire the active pharmaceutical ingredients for Oseltamivir. The license was not used, as Roche was able to deliver a stockpile 2.3 million doses of Tamiflu capsules and powder by 2007 – following WHO guidelines to cover 10% of the total population (CDC, 2009a). In 2009 Taiwan CDC purchased another 2.68 million doses of Tamiflu from Roche, and 900000 doses of Relenza (GSK), and released 250000 doses into the public healthcare system for distribution following a Swine flu epidemic (CDC, 2009b).

Production Scale- up

In response to the CL threat by Taiwan, Roche entered into multiple voluntary licensing agreements in China (Shanghai Pharmaceutical Group, HEC), South Africa (Aspen), India (Hetero), for supply to neighboring countries and local stockpiles (Wright, 2005). It also increased production of Tamiflu in its own production facilities to 400 million doses. In 2005-6 Roche donated 5 Million doses of oseltamivir to the WHO for distribution to countries unable to afford the drug followed by another 5.65 million doses 2009 (WHO, 2005, 2006a). In response to the threats, Roche initiated a Tamiflu Reserves Program that sold Tamiflu to developing countries at 5-6 euros (/75mg pack). The 70% discount was offered to developing countries, when a pandemic warning was announced by WHO (Roche, 2009). Roche’s strategy of not registering Tamiflu patents in LDCs, delayed generic entry in these countries due regulatory delays, while maintaining control over global supplies through VLs’ (B. K. Baker, 2016).

The Taiwanese use of a CL in conjunction with frameworks set by the WHO allowed successful stockpiling to augment a pandemic preparedness plan. Taiwan (R.O.C) remains the only country to issue a Cl for a pandemic scenario, while encouraging voluntary behavior form Roche in terms of global supply, and prices. While Taiwan’s CL was used to protect against lack of technical assistance for pandemic response from the WHO, highlighted are the procedural restrictions faced in issue of Emergency use licenses. One questions whether threats from high income countries hold more credibility and attract less retaliatory behavior.

Scholars have suggested the possible use of the Waiver mechanism to permit exports of Tamiflu in case of a pandemic of avian influenza, and also highlight the lost opportunity of using the Waiver to acquire oseltamivir for emergency stock piles (F. M. Abbott & Reichman, 2007).

5.9 Summary of country cases

Table 8 Case summary table

Country (Year)	Thailand (2006)	Brazil (2007)	Rwanda (2007)
Policy goal	Sustainability of UHC	Sustainability of NAP	Use of Waiver mechanism
WHO Classification	UMIC	UMIC	LIC
Drug/s	Plavix(Clopidogrel) / Kaletra(LPV/r)	Efavirenz (Stocrin)	ApoTriAvir (AZT/3TC/NVP-FDC)
Patent Holder/s	Sanofi / Abbott Laboratories	Merck	GSK, Shire Pharma , B.I.
Indication	IHD(Plavix) /HIV (Kaletra)	HIV/AIDS	HIV/AIDS
Originator Price	Plavix US$ 2 PPPDay/ ; Kaletra US$ 2,060 PPPY/	US$ 580 PPPYear	US$ 6 PPPDay (Combination of originator drugs)
Reason for CL threat	Unaffordable under National Healthcare coverage	Non-working / Prohibitive pricing	FDC unavailable on market, Humanitarian basis
Negotiations	No	Yes- Insufficient discounts	Yes, Failed
National legislation cited	Section 51 Thai Pat. Act.	Article 68, Para. 3 and 4 of LPI	CAMR ,
TRIPS Legislation Cited	Doha Declaration	Doha Declaration	Para. 6, TRIPS Art. 31bis
Supporting Policy	Universal Healthcare coverage	NAP, Generic Preference	NAP
Geographic Validity	Thailand only	Brazil only	Canada and Rwanda only
Open / GUL	Public non-commercial use	Public Non-commercial Use	Public Non-commercial use: for Export (Canada)
Quantity	Unlimited / 250,000 patients	Unspecified	15,600,000 Tablets. 21,000 Patient treatments
Validity	Indefinite (Plavix) / 5 year(Kaletra)	5 years, Renewable, Extended in 2012	2 years, Renewable
Supplier/ Manufacturer	GPO- Multiple	FarManguinhos Brazil, Hetero	Apotex - Canada
Royalty	0.5% of total sales	1.50%	Royalty free
Generic brand	Generic GPO	Generic FioCruz	ApoTriAvir (AZT/3TC/NVP)
Generic Price ($)	Clopidogrel .20 US$ PPPDay ; LPV/r US$ 595 PPPY	US$ 166 PPPY	USD 146 PPPY (0.195/tablet)
Price Regulation	Free pricing	Free Pricing	Free pricing
Anti-diversion measure	Branded Generic	Unique packaging	Branded Generic
Retaliatory measures	Products withdrawn, Generic supplier threatened, Special 301 Listing	None , Merck offers discounts	None
Outcomes	75-90% saving on drug costs	ARV expenditure reduces - 48% savings on EFV alone.	75% savings on costs. Delays in entire process
Prevalence	200000(IHD)/ 600000 (PLHIV) Public sector only	0.5% (660,000 PLHIV)	200000 Individuals with HIV/AIDS
Delivery Instrument	Universal Healthcare system	National AIDS program	National AIDS Program
Payer	Thai Government	Brazilian MOH	Global Fund, Rwanda MOH
NLEM Inclusion	Yes	Yes	Yes
Other Factors	Revision of tiered pricing strategy, discounts	PAHO – prequalification, UNICEF – logistic support	NAP funding by PEPFAR
Associated Outcomes	CLs renewed @ 2% Royalty	CL renewed in 2012	Renewal declined by Apotex
Evaluation	Economic and cost impact studies conducted	Financial savings disclosed USD 103 Million	None

Table 9 Case summary table

Country	India (2012)	Italy (2005)	Taiwan (2005)
Policy Goal	Price reduction	Generic entry- Spanish market	Pandemic Stockpiling
WHO Classification	LMIC	HIC	HIC
Drug/s	Nexavar (Sorafenib)	Sumatriptan (Imigran)	Tamiflu (Oseltamivir)
Patent Holder/s	Bayer Corp.	Merck	Gilead / Roche
Indication	Renal, & Hepatic Cancer	Migraine	Avian influenza H5N1 virus
Price before CL	US$ 4500 /Patient /month	N/A	USD 60/ dose
Reason for CL threat	Non-working of patent, "Not reasonably affordable"	Anticompetitive- Market leveraging	Anticipated pandemic, National Emergency
Negotiations	Yes- Rejected by Bayer	Yes- Rejected by Merck	Yes- Rejected by Roche
National legislation cited	Section 84,Patents Act	Art.102 TFEU, Lei 112/02	Art 87, Section 5, T.P.A.
TRIPS Legislation Cited	Art.31, TRIPS.	Art. 31, TRIPS	Doha Declaration
Supporting Policy	None	Generic substitution	Pandemic Preparedness
Geographic Validity	India only	Italy, EU/EEA	Taiwan only
Open / GUL	Non Exclusive Judicial	Judicial license	Emergency Use - Conditional
Quantity	Unlimited	Unlimited	2.3 million doses
Validity	Until patent expiry	Until patent expiry	31st December 2007
Supplier/ Manufacturer	Natco Pharma – India	Fabrica Italia Sintetici spa.(IT)/ Universal Farma S.L(ES)	National Health Research Institute - Taiwan
Royalty	7%	Undisclosed	Undisclosed
Generic brand	Sorafenat	Sumatriptan Universal Farma (ES)	Unbranded
Generic Price ($)	USD 150 / Patient / month	N/A	N/A
Price Regulation	Unregulated, (Non-NLEM)	Regulated , Reference pricing	Free pricing
Anti-diversion measures	Branded Generic	Branded generic	Unspecified
Retaliatory measures	USTR Special 301 Listing	None	None
Outcomes	Generic competitor lowers price to 90 US$	GSK cooperates , licenses adjunct patents for	CL Expired – conditions
Estimated patients	20000 Liver cancer/ 8900 Renal Carcinoma	3,617600 patients (Spanish population)	10% of population
Delivery Instrument	Private self-pay market	NHS – Prescription drug	Universal Healthcare system
Payer	Private customer	40% Patient Co-payment	Taiwan MOH
NLEM Inclusion	No	Yes	Yes
Other Highlights	Free generic treatment to 600 Patients	Generic competition leads to price convergence	Epidemic Controlled - CL expires
Other factors	Prior generic on market	CL used to invalidate Supplementary Protection	No appeal against decision, multiple VL agreements
Associated Outcomes	Grey market exports due to national exhaustion regime	FIS stops production of API	Global production scale up by Roche
Evaluation	None conducted, non-disclosure by licensee	None conducted, EC antitrust investigation 2008	None

6 Cross-case results and Discussion

6.1 Choice of License type

The choice of CL instrument has varied with respect to policy goals and ease of use (Table 10). Countries with robust legal infrastructure are increasingly capable of using competition law and local working provisions to issue CLs. While Judicial CLs have the benefit of isolating government intervention from competition policy, they cannot be fast tracked and require extensive insight and evaluation of facts, contributing to lengthy proceedings and delayed delivery times. As a result, market induced licenses have been limited, with the majority of CLs being government initiated in interest of Emergency or public health goals. On the other hand, the Government Use route demands state accountability and transparency in terms of procurement and delivery of generics. This approach bypasses lengthy procedures of a judicial license, but restricts the use of patented matter to public non-commercial use.

Table 10 License type and details of selected case studies

Country	Type	Propagation Instrument	Policy Goals
Taiwan	Govt. Use – Emergency	National Pandemic response	Emergency Stockpiling
Italy	Market initiated	Anti-Trust law	Generic entry for export
Thailand	Govt. Use - Public non commercial	National Healthcare System	Sustainability of NHS
Brazil	Govt. Use - Public interest	National AIDS program	Sustainability of NAP
Rwanda	Waiver mech.	National AIDS program	Sustainability of NAP
India	Market initiated	Local Working provisions	Local availability and price

6.1.1 Government Use licenses

The variation in institutional dynamics and ideologies contribute to the different approaches in selection of license type. In cases where initiating authorities were the Health Ministries (Taiwan, Rwanda, Thailand, and Brazil), the primary motive was sustaining healthcare systems. The payers in these cases were the governments themselves with incentive to reduce costs in light of rising demand, and avoidance of stock shortages. Procured drugs were then supplied to citizens through nationally funded and monitored healthcare programs.

GULs are unlikely to be isolated events as circumstances leading to the issue of compulsory licenses are influenced by ideological motives, financial and market dynamics. Public interest licenses often complement generic preference policies adopted by governments to ensure sustainability of the national healthcare systems. Government use license and Emergency use licenses were issued to complement generic preference policies or pandemic preparedness programs in the case of Taiwan. Change of governments has also affected use of CL policies as evidenced in Brazil, India and Thailand where authorities have followed stricter requirements and higher royalties when issuing new licenses, representing shifting ideologies as governments change. India has refrained from issuing CLs despite recommendations from the MoH for expensive medications after a new government was elected. International pressure and industry lobby groups have also had a significant deterrent effect on number of CLs issued.

Due to ability to waive the 'Prior negotiation' requirement set by TRIPS, government use licenses are preferred for ease of procedural formalities and discretionary mandates, and is often criticized for lack of transparency and influence from local lobbies. Following development of local production facilities for self-reliance for medicines; countries such as Brazil have often expanded local production to other drugs after compulsory licenses. Ironically, the emergence of new generic manufacturers has increased opportunities for voluntary agreements further reducing dependence on imports. Critics suggest camouflaged use of Government-use-licenses (GUL) as a pro-Industry policy (Lybecker & Fowler, 2009), and claim that compulsory licensing has been used for other purposes than access to medicine, especially in the case of Thailand, and Brazil where CL use was used to garner political support from citizens prior to elections. Both countries claimed segregation of public market segments to justify policy approach, as the originator product continued to be sold in the private markets. In the absence of technology transfer agreements, and an inability to reduce reliance on imports of medicine, a pro-industry policy would be in line with the Public health safeguards the Doha declaration intends to promote and should be supported.

Government use licenses should be used in conjunction with existing national frameworks both for manufacture and delivery of procured drugs in order to demonstrate accountability as in the cases of Brazil, Thailand, and Rwanda. Brazil, having existing generic manufacturing capabilities, used CLs as threat to attain discounts and voluntary licensing agreements on multiple high burden medications. Thailand used the flexibility to broaden access to national healthcare systems and HIV programs, while Canada's government license was issued exclusively to take advantage of the Waiver mechanism. If sustainable use of compulsory licenses is to be justified, significant support from high levels of government is prudent to counter risks of reprisal by industry and foreign governments.

6.1.2 Art.31bis "The Waiver mechanism"

The Canadian Rwandan case allowed the licensee (Apotex) to generate a scope economy through the combination of 3 patented drugs into a fixed dose (MSFAccess, 2006b). However, the process compliance with both importing and exporting country requirements proved to be excessively cumbersome for the licensee. The case further lacked reason due to availability of cheaper versions from competing manufacturers and simpler acquisition pathways. Compliance with the Canadian Access to Medicine Regime requiring mandatory negotiations with multiple patentees led to delays, as patentees set excessive conditions for voluntary use. The WTO notification issued by Rwanda was merely a formality to comply with the CAMR regime.

The Waiver decision of Art.31bis of 2003 aiming to ease restrictions on exports of compulsorily licensed medicines provides a complicated solution for developing countries, with only 77 of the required 111 WTO member states ratifying the amendment into local legislation. Reluctance of governments to implement the proposed solution into national law, and the single use of the system is a testament to the bureaucratic complexity of the dual CL mechanism for export purposes. Other attempts to use the mechanism have been rejected by governments for varying reasons, suggesting that it is unlikely to be used to procure drug for NCD given the complexity of the framework to remain TRIPS compliant. For example, Indian courts refused a CL for export, as Nepal declined to notify the WTO, despite being exempted as an LDC. Similarly, the Canadian regime declined a Chilean request to export generic imatinib using the CAMR regime.

Abbott & Reichman suggest that the Waiver mechanism could be used in case of an epidemic to allow regional procurement of vaccines on a larger scale to offset high political, legal, and economic costs in countries that recognize national exhaustion of rights (F. M. Abbott & Reichman, 2007). Despite having provisions for pooled procurement and re-export, the formalities requiring multiple issues of CL in importing countries, makes use of the waiver unlikely. The mandatory notification to the TRIPS council exposes applicant countries to pressures of retaliation and is a further deterrent to elective use of the facility. Despite being formulated especially for developing countries, there have been no regional applications to use the Waiver mechanism. Fear of retaliation and pressures from the World Bank (in case of Rwanda) have also played a role in avoiding use of the Waiver mechanism (MSFAccess, 2006b). Correa suggests that the dual notification system causes a potential clash between data exclusivity and implicit suggestion of a patent linkage system in countries where these provisions are not recognized (C. Correa, 2004).

As threat of trade retaliation is significant for LDCs, notification by either importing country or exporting countries should suffice as grounds for use of the Waiver mechanism. If such a change was adopted, LDCs or other eligible countries will be able to use the mechanism without fear of reprisal in case if emergency or public need, and would increase instances of use.

6.1.3 Emergency Use licenses to complement Pandemic Response

Taiwan opted for an Emergency use license after the Department of Health projected 14,000 causalities as a result of the Avian influenza epidemic. As part of its surge protection strategy, the threat elicited a response by way of increased global production capacity and voluntary discounts, while also allowing development of local manufacturing to establish independence from imports. The conditional license was not put into practice, as the grounds for a public health emergency was contained. Taiwan's Emergency use license for oseltamivir was successful in attaining the stockpile quantities from Roche through increased production (江亮頡, 2007). Roche offered a pandemic price of 16 USD per course for Developing countries and delivered an extra 1.3 million doses to avoid use of patent matter. Previous use of CL threats was also used by the US and Canada to gain discounts and increase production of ciprofloxacin, in response to a bioterrorism threat of anthrax in 2001.

Balancing interests of both patentee and applicants in the case of emergencies have been favorable in the case of Taiwan's conditional license with Roche for Tamiflu (oseltamivir) allowing use of patent matter in case of inability to deliver guaranteed volumes. Future applications of CL in such a pandemic scenario may not result in favorable response, as capacity of governments and pharmaceutical firms are limited by financial and technical constraints and unpredictability of pandemics.

6.1.4 Market Initiated licenses

The two study cases including market induced licenses revealed higher levels of transparency and inclusion of parties in the royalty setting and judicial process, requiring a thorough review of circumstances, events, and behaviors of actors. Although issued in public interest, licenses in India and Italy were Initiated by private companies, and issued by the Patent authority and Competition authority respectively, to promote generic competition. The Indian patent controller invited settlement proposals from both parties during the proceedings for the sorafenib case. Similarly, the Italian competition tribunal proceedings were more inclusive regarding the issue of licenses on establishing grounds for issue.

As motives for a market induced license vary, market dynamics, free market competition and minimal government intervention play a role to successfully work patent matter and outcomes. This is reflected in the potential profitability of the drug being licensed and costs borne by applicant. Judicial CLs in both the case of India and Italy, have hastened generic price erosion despite not being the first generic entrants in targeted markets. In both cases, the applicants were not the first generic entrant in respective markets. In case of Italy, generic entry also led to drop in originator prices as a market retention strategy, while the Indian example saw discounts on a competing generic brand. If Private generic manufacturers depend on price differential between originators to profitably sell cheap generics, one questions whether sufficient regulation negates the need to compulsory license a drug once suitable prices have already been attained due to prior generic entry.

Academics suggest the Indian government's non-intervention as market driven neglect that leaves private enterprises to assume responsibility for local supply, reflecting the inability of the government to work the patent in case of a government use license (Eimer & Lütz, 2010). In case of India's compulsory license, generic sorafenib was exclusively supplied through the private sector, as it is not listed on the NLEM. The public healthcare system poses a barrier to access and availability, even in the presence of cheaper medication. A fragmented healthcare system has also led to concentration of available stock in urban settings while other infrastructural shortfalls result in ineffective use of compulsory licensed drugs. In countries with high out of pocket expenditures, the private generic market has stepped in to ensure delivery in urban areas, while rural areas have experienced neglect.

In case of CL use to remedy anticompetitive behavior, such as Italy's CLs for sumatriptan, the offending company intentionally refused to license manufacture of an active ingredient for supply to a parallel market. Along with the Italian license for sumatriptan for exports to Spain, the patentee (GSK) voluntarily disclosed proprietary information and related process patents to expedite generic production and regulatory procedures in order to avoid penalties. The licensee (Fabricca Italia Sinthetica.Spa) initially exported the generic product to markets where the patent was invalid where research shows that generics did not attain a greater Spanish market share, with originator drugs retaining sales through price matching to de-incentivize generic use (Vogler, 2012). Studies suggest the limitations of adoption in a physician driven market, which is influenced by prescription behavior and absence of incentive to use generics (P. M. Danzon & Furukawa, 2011). While there were generic substitution policies in place, conflicting policy has had a limiting effect on outcomes. Nonetheless, cross border enforcement has influenced benefits of the CL proceedings, due to the market leveraging strategies adopted by the originator firm, allowing retention of market dominance after expiry of patent protection.

Reichman notes that competition law in developed countries requires "complex economic analysis, high transaction costs and skilled regulators", explaining why the numbers of judicial licenses have been fairly limited, with governments opting for the fast track approach to supply urgent public health needs (J. Reichman, 2003). Market initiated licenses are dependent on licensees with sufficient capital and expertise to successfully implement patented subject matter into a marketable product while making a margin significantly above costs. As this aspect involves considerable risk, the non-exclusive nature of CL further increases the risk of investment and litigation. The non-transferrable nature of compulsory licenses also increases risk associated with of investing into R&D for individual license applicants limiting options for sub licensing agreements to further leverage scale economies, explaining the limited applications for market induced CLs for highly profitable innovative drugs. In study cases, the licensees such as F.I.S. (Italy), and Natco (India) were large generic manufacturers with ability to reverse engineer and formulate the product prior to applying for a CL.

On 1st September 2016, Merck was granted a judicial license by the German patent court for local manufacture of HIV drug raltegravir (Isentress). The license was issued after negotiations for a voluntary license failed, citing the public interest of pregnant women, infants and children dependent on raltegravir who could not safely substitute the medication without health risks and increased risk of infection to others.

In regulated markets such as Europe, the confluence on multiple regulatory policies along with appropriate anti-trust policy may substitute the role of market initiated CLs on generic competition. Such CL applications require licensees with sufficient prior capacity to work the patent, reducing reliance on disclosure of technical knowledge and proprietary information by patentees. Further research into this aspect would be prudent to tailor competition policy and further applications.

6.2 Pricing strategies;

Pricing issues were the primary drivers of CL use in Brazilian, Thai and Indian cases. In the case of Brazil, and Thailand tiered pricing strategies of Abbott, Merck and Sanofi were clearly unable to sustainably offer prices suited to local capacity to pay, while a market skimming approach adopted by Bayer for Nexavar in India was explicitly targeted at high income segments, resulting in CL threats and use.

Innovator firms adopt price discrimination strategies intending to reconcile patents with affordability and access in developing countries. In practice, tiered prices are subject to a variety of preconditions, requiring firms' autonomy to freely price their drugs in order to maximize profits, optimal functioning of differential pricing requires voluntary abstaining from parallel trade and external price referencing in price negotiations on behalf of governments. This implicitly calls for transparent price setting by pharmaceutical firms, whose motives are primarily profit-seeking. The conflict of interest impedes efficient functioning of the tiered pricing model (P. Danzon & Towse, 2003).

Theoretical economics argues that restriction on competition to incentivize innovation is required, by allowing static inefficiency through sub-optimal use of existing innovation, in interests of promoting dynamic efficiency by encouraging investment in R&D for future innovation (P. Danzon, Towse, & Mestre‐Ferrandiz, 2015). Allowing monopolistic behavior by the patentee in order to recover sunk costs accrued during development is an accepted trade-off in interest of innovation as high prices of patented medicines limit equitable distribution. This loss of welfare, despite available knowledge and capability to replicate the drug at marginal costs especially distorts distribution of new products in a market without social healthcare systems with insurance or state funded healthcare resulting in skewed distribution of resources and equity failures. As a result, monopolies have little incentive for innovation due to absence of competition, betraying the non-rival nature of knowledge (Arrow, 2000) further delaying gains in manufacturing efficiency.

Price discrimination has proven challenging in practice for a variety of market failures including the inability to restrict parallel trade and reference pricing. For example, the EU follows regional exhaustion of rights, to allow free movement of goods within the Union, with member states adopting compensatory pricing mechanisms such as free pricing for exported products. Spain allows a dual pricing strategy, which allows higher prices for pharmaceutical products sold outside the Spanish market through legal parallel exports, while using reference pricing to limit prices locally. Certain EU members (DE, DK, UK and SE) allow free (Unregulated) pricing that allows pharmaceutical firms to set prices for certain products, while encouraging use of parallel imports to promote competition (Vogler, 2012). Other countries such as India and Brazil follow National exhaustion

principles that enable parallel imports. While TRIPS Art.31(f) limits use of compulsory licensed drugs to local use, Art.31bis allows exceptions for exports to other countries within a trade union. Regulation of prices in markets without sufficient government interventions has varying outcomes on pricing strategies of pharmaceutical firms.

Prices set by tiered strategies are often relatively referenced to high income market prices, resulting in insufficient prices reductions that remain unaffordable to large segments of the population who earn below the average income. As tiered pricing strategies often do not account for income inequalities within developing countries, an optimal pricing strategy for countries without universal healthcare systems has proven challenging. Bates and Danzon report that many LMICs refuse to acknowledge their income status and claim prices set for LDCs further distorting pricing discrimination mechanisms. Non-uniformity of economic classification by the WTO, WB and other UN bodies also hamper systematic differential pricing mechanisms from functioning as intended. Reference pricing in HIC markets such as the EU/EEA also results in non-uniform prices due to varying approaches taken by national authorities.

Differential pricing has been successful in allowing medicines to be priced equitably, in case of low demand, monopsony buyer drugs such as vaccines (Plahte, 2005), XDR-TB, and malaria treatment. However , this does not apply to MICs where the overall GDP has risen, but income inequality is drastic; A good example would be Merck's and Abbott's tiered pricing strategies for efavirenz and lopinavir in Brazil and Thailand that neglect heterogeneity in prevalence of AIDS within income subgroups. Sachs noticed that pharmaceutical companies have neither priced products to gain maximal profits or maximal access, to compensate for reference pricing in secondary markets for a variety of reasons (Sachs, 2013). The phenomenon leaves the lower income groups in Low and Middle Income Countries unable to afford "affordably priced medicine" due to higher average income (Table 11).

Hollis describes a "Convex demand curve problem" where a rational profit seeking firm takes a High-margin Low-quantity approach to sell smaller quantities of patented drugs to high income segments in countries without UHCs and high inequity (S. Flynn et al., 2009). This market skimming approach is taken in developing countries, where pharmaceutical companies price new innovative drugs at high prices, as in the case of Nexavar, selling the drug as a luxury good. In this scenario it is more profitable to sell smaller amounts of a life-saving/prolonging drug as a luxury good, rather than take a low-margin high-quantity approach while claiming to offer tiered prices. In markets with high income inequality, large sections of non-insured population pay for innovator medicine out of pocket, resulting in perverse levels of deadweight loss which "translates into dead bodies" (Reichman, 2009).

Table 11 Treatment costs in local currencies as percent of average monthly wage (Converted from USD)

Country	Drug	Price / month	Av. Monthly wage	% of Monthly wage	Payer
Thailand	Kaletra	5163 ThB	13386 ThB	38,57	State funded
Thailand	Plavix	7251,0 ThB	13386 THb	54,16	State funded
Brazil	Stocrin	156,00 BR	1600 BR	9,75	State funded
Rwanda	AZT/NVP/3TC	149482 RWF	108000 RWF	138,41	State funded
India	Sorafenib	299848 INR	7479 INR	4009,19	Private payer

6.3 Value based differential pricing: A potential solution?

As drug development costs are prohibitively high, reaching USD 2.5Bn per successful drug (DiMasi, Grabowski, & Hansen, 2016), much of the debate around CL use stems from issues with pricing. The emergence of Health Technology Assessment and cost-effectiveness techniques gradually reduce reliance on external reference pricing, by shifting towards equitable pricing strategies better tailored pricing for individual countries. Rather than the cluster approach of common tiered prices for groups of LICS, MICs, and HICs, this also allows better segregation of markets and encourages transitioning countries to increasingly contribute towards R&D costs as their ability to pay rises. Equitable pricing models also encourage transition towards delinked innovation models by setting the lowest sustainable prices, taking into consideration the consumers' ability to pay (Moon et al., 2011). Driving costs lower to leverage both scope and scale economies, through expansion of voluntary licensing agreements to further offset direct manufacturing costs on licensees for reasonable royalties, and outsourcing R&D and production operations to smaller and more efficient firms. Rather than using recoupment of R&D costs as the primary driver of price setting, availability of CL provisions as a policy instrument promotes use of the voluntary pathways and technology transfer, and corrects the imbalance in number of patents granted to foreign firms in developing countries.

Two prominent proposals to further develop differential pricing to address inequality are put forward by Danzon, and Moon. Danzon suggests adoption of differential pricing within countries, to allow better affordability in countries without universal healthcare systems and high income inequality, while Moon suggests tiered pricing between government and private sector markets to address distribution inequities (P. Danzon et al., 2015; Moon et al., 2011). Danzon proposes a Value based differential pricing by measuring willingness to pay in self-pay markets to allow inter-segment differential pricing. Taking advantage of absent insurance systems maintains the price elastic nature of consumers, and therefore allows for payers to express their true willingness to pay for expected benefits (ideally measured in QALYs), potentially allowing for optimal price tiers within income segments, provided quality of drugs are assured and the market is well regulated. While these suggestions are potentially a solution, implementing such a segment specific delivery system, and limiting cross segment infiltration poses a significant challenge due to technical and financial investments required to introduce Health Technology Assessment into a market.

6.4 Affordability

In cases of CL issue and threats, the price savings have been beneficial and often substantial both in terms of purchasing costs and avoided hospitalizations (Table 12), but dependent on imports and availability of generic manufacturers. It bears to note that price reduction may not always be the primary goal of authorities as in the case of Taiwan and Italian licenses. Issuing a CL with intent of local manufacture is unlikely to result in maximal savings if generic copies are available on the market from large scale generic manufacturers. In cases of Thailand and Brazil generic supplies were initially sourced from large generic manufacturers in foreign countries with well-established manufacturing capability prior to local manufacture. Due to non-availability of proprietary information and limited local capacity development of local expertise and R&D for formulation of drugs raised production costs for local produce, while remaining dependent on imports of Active Pharmaceutical Ingredients (API). Beall,Kuhn and Attaran note that compulsory licenses are mainly useful when used with a repertoire of other strategies like bargaining, pooled procurement to bring down prices (R. F. Beall, Kuhn, & Attaran, 2015).

Affordability was better addressed in countries with state funded healthcare where governments were monopsony buyers and distributed medication through national distribution networks. In cases of Brazil, Thailand, and Rwanda, drugs were distributed using a functioning delivery instrument to enable use of procured drugs. The substantial challenge faced by many developing countries in establishing a state funded healthcare system, is key to address unaffordable prices of medication and limit out of pocket healthcare spending. As the ability of a generic manufacturer to generate profits relies on scale economies, guarantees of large purchases by monopsony buyers are essential to incentivize generic production, while efficient delivery requires a functioning state managed instrument to eliminate requirement of individual capacity to pay, along with reducing production and procurement costs.

In the case of India's judicial license, the benefits of price reduction was limited to private payers as the generic was not procured for distribution through a functioning healthcare system. In a market with high out of pocket expenditures and high inequality, where low income levels restrict individual to capacity to pay for essential medicines, a CL is therefore less likely to have substantial benefit in public interest. The lack of an efficient monitoring and delivery system limits distribution of price benefits, and highlighting the need for a Universal healthcare system to reduce dependence on civil society bodies, philanthropies, and aid organizations.

Table 12 Cost Savings on Compulsorily Licensed Drugs (In USD)

Country	Drug	Originator	Generic	% Savings	Unit
Thailand	Lpv/R	2060	500	75,73	/Patient/Year
Thailand	Clopidogrel	26280	2555	90,28	/Patient/Year
Rwanda	Apotriavir FDC	0.6	0,195	67,5	/ Pill
Brazil	Efavirenz	580	166	71,38	/Patient/Year
India	Sorafenib	4500	150	96,67	/Patient/Month
Taiwan	Oseltamivir	60	16 (Discount)	73,33	/ course

6.5 Outcomes on Access

With strong political support, in conjunction with healthcare policy reform and implementation of universal healthcare delivery systems, countries have used compulsory licenses to ensure sustainability of universal access programs including HIV programs. Outcomes have been in terms of immediate cost benefits, but also in sustaining universal coverage systems. Developing Countries like Rwanda, Thailand, and Brazil have maintained robust delivery programs through financial crises, coups, and stock outs. Cost savings from CL use have been diverted to procurement of larger quantities of generic drugs. Generic preference policies have enabled use of compulsory licenses both as a threat and tool, to reduce costs of drug procurement.

Successful use of acquired generics requires well established and functioning delivery mechanisms to ensure availability of compulsorily licensed drugs after implementing universal healthcare coverage with significant access benefits. In cases of Thailand, Brazil and Rwanda the government was the primary buyer. With developing countries in various stages of implementing universal healthcare coverage, although CLs do not always guarantee the lowest prices, they inevitably promote generic self-sufficiency through import or manufacture in the long term. In the cases of Brazil, Thailand and Rwanda, CL threats indicate successful adoption and increasing adherence rates of ART use. Results of increased access and delivery of ARVs in Thai

and Brazilian use of CLs demonstrate that governments face to gain substantial cost benefits in resorting to CL use if retaliatory outcomes are offset. Adoption of generics was generally better in low resource settings like Thailand, Brazil and Rwanda where adherence to treatment regimens was indicative of good adoption rates. While the lifesaving nature of medicines plays a role in this dynamic, barriers to adoption were primarily cost and proximity of delivery units.

The role of large generic manufacturers is crucial to enabling the beneficial aspects of the both CL use and universal coverage systems. India has played a major role in supplying generic medicines to AIDS programs globally, accounting for up to 80% of the annual purchase volume of ARVs in LMICS and LICS (Waning, Diedrichsen, & Moon, 2010). Compulsorily licensed drugs such as LPV/r, and clopidogrel to Thailand, and efavirenz to Brazil, were initially supplied by Indian manufacturers. Other countries such as Ecuador have also procured compulsorily licensed medicines such as etoricoxib from India (Zauba.com, 2014). In 2016, Venezuela, and Nigeria entered into discussions with the Indian government to exchange crude oil for essential medications in light of the economic crisis and currency devaluation (Reuters, 2016). Adoption of TRIPS standards by India jeopardizes the ability of generic manufacturers to manufacture newer generation HIV and TB medication, and calls for prudent provision of policy space to accommodate requirements of countries without capacity to pay and develop medicines for local use. As generic manufacturers grow and invest more towards R&D, activists criticize the export-focused Indian pharmaceutical industry of increasingly behaving similar to innovator firms and fiercely protecting IP standards to suit evolving business plans and growth.

6.6 Compulsory Licenses as a threat

Repeated threats of CL in emerging markets can encourage pharmaceutical companies to price their patented drugs fairly. A good example of this is Brazil's successful use of threats to achieve discounts on patented medications. The Thai MoPH also successfully negotiated with patentees prior to its 2nd wave of compulsory licenses.

Reichmann and Hazenzahl state that "the mere threat of a non-voluntary license may obviate the need to issue it in practice" because "it usually induces the grant of contractual licenses on reasonable terms. If so, it would mean that the real obstacles to the granting of non-voluntary licenses under article 31 of the TRIPS Agreement are usually of an economic and political nature, and do not necessarily derive from the codified international minimum standards as such" (J. Reichman, 2003). Voluntary licensing has been demonstrated to encourage profitable sublicensing of innovator drugs to ensure access to medicine in developing countries at low costs, while allowing patentees to retain control over patent rights and market shares (Amin, 2007). Voluntary action of innovator firms after CL threats remains the most optimal outcome when using CL threats balanced social welfare gain, as price savings and long term benefits in terms of technology transfer to licensees (Frederic M Scherer, 1977). Voluntary Licensing (VL) agreements project secure investment markets and improve publicity of both pharmaceutical firms and pro-industry policy of governments. Ladas noted "The practical value of the existence of compulsory license provisions in the Patent Law is that the threat of it usually induces the grant of contractual licenses on reasonable terms, and thus the objective of actually working the invention is accomplished." (Ladas, 1975).

However,licensees need to be wary of covert agendas that limit distribution to protected markets and impede access to essential medicine. VL agreements such as Gilead's access program for sofosbuvir intentionally

excludes markets such as Thailand, and China from its voluntary licensing agreements with generic contract manufacturers, among other restrictive clauses(Amin, 2007).

6.7 Revision of prices

In response to Thai and Brazilian threats against Kaletra (LPV/r), Abbott revised its global tiered pricing strategies to offer discounts to a number of developing countries. The cases of Stocrin (Efv) and Kaletra (Lpv/R) have been especially good examples of global price reduction of originator drugs. Repeated threats force patent owners to reconsider pricing strategies to allow more equitable access. Merck offered substantial discounts and free pediatric doses in Thailand and Brazil (30%) after a compulsory license, while Abbott offered global price reductions for developing countries after compulsory license threats in Thailand and Brazil(Moon et al., 2011). The case of Kaletra pricing strategies adopted by Abbott labs is a prime example of transparent price setting in MICs. Following India's license for Sorafenib, another generic manufacture (Cipla) also reduced its prices for its generic version simultaneously to approximately USD 100 per month's treatment. In Response to Taiwan's CL for Oseltamivir, Roche established a Tamiflu Reserves Program offering tiered pandemic pricing discount for developing countries (Roche, 2009).

Countries with histories of CL have been able to negotiate prices to a higher degree than others, as evidenced with the Brazilian and Thai strategies, where authorities used threats to achieve discounts on multiple occasions. As less developed countries often hold lesser bargaining strength in terms of economic power and manufacturing capacity, the unpredictability of CL use and threat is key to limiting its effects on innovation while simultaneously allowing price reductions and reduced likelihood of retaliatory action. Desired voluntary action by the patentees is also limited when a CL threat lacks credibility in terms of local manufacturing capacity and import options. Retaliatory action by infringed firms stand to have greater consequences, as offended firms may simply choose not to patent a drug in a country not considered to be a safe IP environment. In countries with lower manufacturing capability, dependence on imports from large generic manufacturers further weakens bargaining strength (Ramani & Urias, 2015).

Using game theory, Bird & Cahoy simulate a hypothetical situation where regional trade agreements could be used the maximize welfare gain though coordinated compulsory licensing (Bird & Cahoy, 2008). Although such an approach has not been put to practice and needs much technical advice and policy analysis, sharing of a country's economic strength with a less powerful country could theoretically be used to protect against retaliation for CL use.

6.8 Increased production capacity by originator firms

In response to Taiwan's threat, Roche increased production capacity of oseltamivir globally to meet global demand and prevent stock outs in an unprecedented ramp up of production to cover 10% of the global population. Roche also informed the Indonesian government to begin manufacturing oseltamivir without fear of litigation through a non-assert declaration. As an outcome, global supplies of Tamiflu were bolstered through voluntary licensing agreements in the US, South Africa, China, India. After stocks were delivered, the Taiwanese NHRI donated 600,000 doses of oseltamivir to Vietnam on a humanitarian basis. Roche also assumed a non-assert stance in Thailand and the Philippines and also donated a stockpile of 5 Million doses to the WHO for distribution to LDC's. CL threats and issue for biosecurity have succeeded in provide security against stock

outages in Taiwan, and other countries such as Indonesia and Argentina. The threat factor of CL has also allowed countries such as Canada and the United States security from stock-outs in case of biological threats and pandemics, amidst the anthrax scare of 2001.

While production capacities of originator firms were bolstered in case of Taiwan, national manufacturing capabilities were used to manufacture compulsorily licensed drugs. The NHRI demonstrated the ability to manufacture the drug along with a request for a voluntary license. Even emergency use licenses such as Taiwan's case has required demonstration of local manufacturing capacity to make a credible CL argument and encourage voluntary action by the patentee.

6.9 Use of CLs to remedy adoption of excessive IP standards

In Brazilian and Italian cases, compulsory licenses were instrumental to remedy patent extensions imposed by local legislation. While LDCs have been afforded repeated extensions on transition period for pharmaceuticals until 2033, MICs who did not use the full transitory period to adapt local legislation have experienced deleterious effects on local pharmaceutical capability. Estimates suggest that Brazil spent between USD 420-519 million on 5 ARVs alone due to its patent revalidation system (Meiners et al., 2011). Approximately 340 other medications were granted pipeline protection in Brazil on implementation of TRIPS. Similarly, Thailand included a Safety Monitoring Program which allowed marketing exclusivity to patented drugs for 2 years. Both Thailand and Brazil adopted of TRIPS and TRIPS plus conditions without use of transition period.

Brazil's license was corrective action for the pipeline patent on efavirenz, which granted patent protection to efavirenz on basis of a valid American patent without local examination by Brazilian authorities, despite being ex-patent in other countries, impeding access to generics. Brazil witnessed a drop of foreign investment in the pharmaceutical sector from USD 91 Million (1994) to 31 million (2003). Technology transfer agreements fell by 70% in the pharmaceutical sector (1992-2001) after implementation of TRIPS. In conjunction with TRIPS and other trade policies 1700 pharmaceutical factories were closed (M. Flynn, 2008).

Italian licenses for Sumatriptan and I/C were also remedial for the Supplementary Protection Certificate system (SPC) that prolonged patent validity and allowed segregation of EU markets to delayed generic entry in ex-patent markets. The SPC system allow extensions on exclusivity lost due to regulatory delays, and extended patent validity of drugs by 5 years in the case of Glaxo's Imigran. One must consider that both Brazilian and Italian licenses could have potentially been avoided by abolition of excessive IP standards during adoption of TRIPS (Brazil) and the EU harmonization process (Italy).

6.10 Royalty variations

Authorities have adopted varying approaches to royalty setting (Table 13). In case of the Italian license royalties were set by the patentee without disclosure. The Indian patent controller used UNDP guidelines for establishing remuneration rates, while Thailand's MOH set remuneration rates taking into consideration the retail prices of drugs. As most originator drugs were high earning products, royalties did not compensate for lost sales and avoided healthcare burden. Considering that cost savings range from 50% to 97%, royalty rates set by some countries have been miniscule considering the avoided costs of hospitalization and other treatments. Although a

variety of recommendations establish sliding scales of royalty setting, they remain recommendations and not binding legislature. Savings in terms of purchasing costs and avoided hospitalizations are not reflected in royalty rates, with the highest royalties levied in India. Remuneration guidelines could also encourage disclosure of R&D costs to allow fair calculation of rates. The suggested 2001 UNDP remuneration guideline of 2-6% of total sales has not been adopted by other countries further contributing to the non-conformity of CL use.

Royalties issued in Government use licenses have been low compared to judicial licenses and Voluntary license agreements. The "Non-commercial" use aspect has been used to justify low remuneration rates despite being procured from for-profit firms. Chien suggests royalties that match original demands of the patentee likely offsets retaliation after compulsory licenses. Reward to the patent holder needs to be more substantial than low rates set in case of Thailand and Indonesia (0.5%) that is often not representative of development costs. Revised royalty rates according to type of license are also necessary as the circumstances of CL issue vary (Chien, 2003). Cahoy argues the case for more equitable rate of remuneration to further legitimize use of Compulsory licenses as TRIPS Art.31 does not specify whether the adequate remuneration is required to cover sunken development costs, or forfeited sales to the patentee (Cahoy, 2011). As marginal costs of drug production are significantly low, generic manufacturers avail of savings on R&D costs, regulatory barriers and clinical trial data (Bate, 2007).

Table 13 Royalty Rates in study cases

Country	Royalty calculation	Drug	Royalty rate
Taiwan	Unspecified	oseltamivir	Unspecified
Italy	Patentee proposal	sumatriptan succinate API	Undisclosed
Thailand	Scale % of Retail price	Lpv/R(Kaletra); Clopidogrel(Plavix)	0.5% of purchase (revised@ 2%)
Brazil	Government set	efavirenz (Stocrin)	1.5% of purchase/sales
Canada	Sliding scale	ATC;3tC;NVP Fixed dose	Royalty free
India	UNDP guidelines(2001) (2-6%)	sorafenib (Nexavar)	6% of sales (revised to 7%)

Often overlooked is the fact that generic suppliers also sell drugs above marginal costs and make substantial profits, implying that higher royalty rates could also serve as deterrent to frivolous use of compulsory licenses by private licensees. In the Indian example, Natco lists its generic sorafenib as a blockbuster drug with annual sales of INR 10 Million. Similarly, the Thai GPO listed sales of 33 Million USD from compulsorily licenses drugs alone. The Royalty setting process should therefore invite proposals from parties involved to ensure more transparent process, ensuring fair remuneration of sunk costs to the originator. This process could potentially allow for further transparency into development costs of drugs. Low royalties can also potentially be used as a retaliatory measure, to question legitimacy of CL use. In the case of Thailand's GUL, Abbott labs and Sanofi did not appeal for higher royalties despite an extremely low rate of 0.5% of sales. Similarly, GSK and BMS have declined royalties of 6% in Malaysian GUL use. Some patentees have not claimed remunerations due to low royalties such as Malaysia 4%, and Indonesia's 0.5% for Nevirapine (7 years), Lamivudine (8 years) (de Morais, 2010). Adoption of a binding guideline in TRIPS is therefore essential to strengthen the argument for CL use and legitimize action taken by governments.

6.11 Parallel Trade

Some cases of compulsory licenses demonstrated evidence of parallel exportation of compulsory licensed pharmaceuticals. The Italian license was specifically intended to promote legal parallel exportation to the neighboring Spanish market, while the Indian compulsory license enabled (unintended) parallel exports to third markets due to a national exhaustion doctrine. Parallel trade through the grey market channels is often incentivized in well regulated markets, where generic entry is restricted until data exclusivity and patent validity has expired, in contrast to less regulated MIC and LDC markets where early generic entry (often intentionally and necessary) allows profiteering. In Italian investigations against Merck, licenses were issued for sumatriptan and finasteride explicitly for export to neighboring markets with expired patent protection within the EU, while retaining exclusivity in the Italian market until patent expiry. There have been exports of generics to HICs, MICs, and LICs markets through grey channels in case of sorafenib from India. Failure to implement sufficient anti-diversion methods required by TRIPS Art.31.6 could potentially lead to a WTO dispute, and negate any benefits gained. While poorer countries benefit from parallel trade, loss of potential profits in higher income markets make a strong argument against CL use when generic leakage into high income markets distort differential pricing measures in target export countries (Maskus, 2000).

6.12 Policy Diffusion

Research suggests growing evidence of south-south diffusion of policy approaches through more informal means, with evidence of similarities between Implementation of compulsory license laws and amendments into legislation. For example, Andean nations such as Columbia, Ecuador, and Peru which have socially funded healthcare systems, and where the government is the primary buyer and payer to innovator firms, seem to have emulated Brazil's example of CL threats. It bears to note that similarities in legislation, political structures and regional proximity might have a role to play. Use of compulsory licenses has also been cited by 3rd countries in making a case for price reduction (Columbia cited the Thai and Indian imatinib cases as basis to issue a CL for Gleevec). Indonesia's issue of 7 compulsory licenses in 2012, showed similarities to Thailand's approach in exercising government use provisions.

Civil action groups and NGOs are instrumental in garnering public support and legitimizing compulsory license use by assisting governments with procurements, negotiations, and logistics of generic Advisors from NGOs were consulted in Brazil, Thailand, India and Rwanda, while epistemic bodies such as think-tanks promote use of flexibilities, strategies and policy tools on global platforms. Civil action groups such as Essential action and KEI have provided advisory support for compulsory license appeals in Romania and Peru for HIV medication (Brook Baker, 2007; KEI, 2015).

In a comparison between Brazil's and India's compulsory licenses Serrano and Burri found little evidence of policy similarities in procedures and approaches. However, both were elementally different as initiators were government (Brazil), and private market competitors (India). Similarities can be found in the wave of emergency use licenses issued by a number of African nations for the HIV epidemic including Zambia, Zimbabwe, Cameroon, Ghana, Eritrea, and Rwanda where government use licenses were issued in a state of emergency to significant access benefits. Similarities in types of drugs also suggest informal diffusion across countries. Efavirenz has been compulsorily licensed in five countries, and LPV/r compulsory licensed in three countries. Some aspects of

royalty settings have also been similar as evidenced by Thailand's royalty rates of 0.5% on all GULS issued, similar to Indonesia's rate of 0.5 %.

Due to the controversial nature of CLs, convergences of CL approaches due to frequent discussions of on multinational fora and the supporting framework set by TRIPS are inevitable. The role of civil society organizations has been crucial in promoting diffusion of ideologies and should be supported by governments, with complementing national policy. Emulation of CL approaches should be encouraged, as limited expertise and experience in using TRIPS flexibilities poses a barrier to successful use and implementation of the afforded policy space.

6.13 General discussion

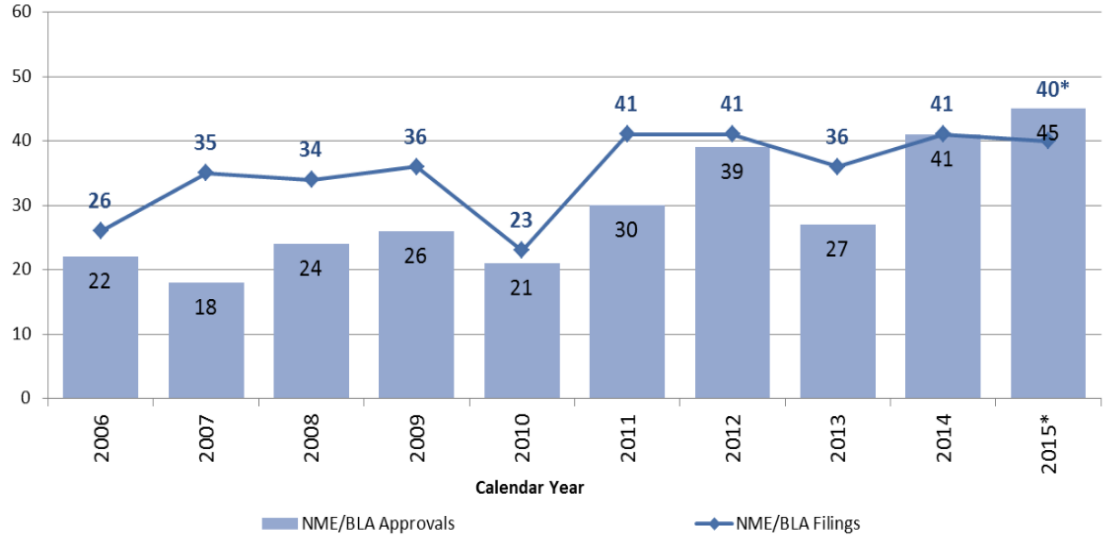
6.13.1 Effects on innovation

Among commonly raised arguments against compulsory licensing, are its deleterious effects on innovation. Contradicting this perspective, multiple studies show that loss of IP rights promoted innovation in order to remain competitive (Moser, 2013; Frederic M Scherer, 1977). Moser and Voena, studying the American market, demonstrated the increase in inventions, after a broad compulsory licensing policy with the Trading with the Enemy Act (TWEA) following WWI. In their analysis, they note that compulsory licensing is highly effective in promoting innovation in fields with relatively less competition, and that many affected German companies, increased R&D spending to compensate for lost exclusivity (as is often the case with blockbuster drugs).

Earlier research by Scherer examined cases of compulsory licenses in the US to measure effect on R&D spending, and found no conclusive evidence to suggest decreased spending, as constant R&D was key to maintaining a firm's competiveness in the long term. Reduced R&D spending on a high burden disease was demonstrated to have detrimental effects on stock prices, establishing a positive effect on R&D spending by companies affected by compulsory licenses. Conversely, introduction of patents was not accompanied by any increase in R&D expenditures or on the introduction of new chemical entities in Italy (Fredrick M Scherer & Weisburst, 1995).

Scannell attributes the declining overall R&D efficiency due to large efficiency gains in preclinical selection phases of NME's, leading to fewer molecules reaching clinical trials phases, and hence an overall decline in number of approved drugs per Billion USD spent on R&D, in a phenomenon called Eroom's law (A reverse phenomenon of Moore's Law). Stricter regulation, Incremental innovation, and the tendency to over-estimate the ability of advances in research also lead to drop in NME/NCEs despite increased spending on R&D (Scannell, Blanckley, Boldon, & Warrington, 2012). In 2015, the USFDA showed a gradual increase in approvals for NME reaching levels similar to the 1990s, that suggests increased spending, supporting Scherer's argument on increasing R&D in interest of remaining competitive (Figure. 9).

Figure 9 New Molecular Entity (NME) and Biologic License Applications (BLA) and approvals (USFDA, 2015)



Further research has revealed little evidence of compulsory licensing negatively affecting R&D spending. Describing the impact of compulsory licensing on innovation and the market value of the segment affected, Chien suggests that CL use for HIV medication is unlikely to affect innovation in other segments, and that licensing innovator orphan drugs and were more likely to de-incentivize innovation within the segment. Predictable use of compulsory licensing in high income markets plays a direct role on innovation while countries with less significant markets attract less retaliation in cases of IP infringement, despite having stronger IP regimes in place. (Chien, 2003)

As portfolio management techniques dictate spending priorities based on profit maximization, reduced R&D spending for type 1 and type 2 diseases are not in the best interests of any rational pharmaceutical company, a fact confirmed by Bayer CEO Marijn Dekkers when discussing India's license for Nexavar (KEI, 2014).The approach taken by offended firms is either to delay launching innovative drugs in low income markets, or enter into voluntary licensing agreements with local firms, implying that limited instances of compulsory licenses in middle-income and low-income countries are yet to affect R&D spending of companies which specifically target research towards diseases of high income countries. Confirming this aspect is a WHO sanctioned study that found no evidence that adoption of IP by developing countries resulted in increased R&D on diseases predominantly affecting developing and LDCs (WHO, 2006b).

Although compulsory licensing of drugs for orphan disease or regional endemic diseases could possibly affect R&D spending, no CL has been issued for such an orphan drug to date. Given the relatively few numbers of CL after TRIPS, there is little evidence demonstrating adverse effects on innovation, and holds no substantive argument against CL use, with no adoption of broad compulsory licensing policy on scales similar to previous American and Canadian models. Ecuador has announced such a policy, and has only issued 9 licenses to date, possibly due to interference by trade partners and stakeholders (Andia, 2014). Kuhn suggests that CLs will cease to be used due to more favorable pathways to procure affordable generic medicines (Kuhn & Beall, 2012). However, this may not be the case with expensive cancer drugs with no generic competitors. As compulsory licenses stop short of patent forfeiture, rational companies are more likely to attempt to capitalize on their remaining market share by reducing prices to competitive levels, while using branding exercises and loyalty programs to promote drug usage. The ambiguous nature of Art.31 contributes to the unpredictability, lending a protective effect on innovation.

Despite being TRIPS compliant, broad use of CLs by a UMIC country is questionable, given better ability to pay, and capability to structure stronger IP frameworks and better use other TRIPS flexibilities. Infrastructural gaps and poor governance in middle income countries pose greater barriers to access than unaffordable prices and availability, as lack of clinical guidance and counselling renders availability of affordable medication useless, especially in HIV and cancer treatment. CL use by such countries also contributes to distortion of differential pricing strategies, allowing short term discounts, but reflected in delayed launch of newer drugs. Countries with significant local pharmaceutical capacities have experienced significant launch lags of innovator drugs when compared with US, and German markets due to fear of infringements. The ability to enforce stricter patentability standards, and more comprehensive regulation could be a better strategy to develop local markets by attracting technology transfer agreements, and resorting to CL use only as a final step.

6.13.2 Effect on Foreign Domestic Investment

Apprehensions that CL use might discourage foreign investments for risk of IP infringements have generated significant literature to estimate effects. Factors of correlation between FDI and Innovation rely on predictability of CL use, and economic significance of the market. Research suggests that perception of a well enforced IP environment is directly proportional to foreign investments, an effect that affects middle income countries to a greater extent than low income countries (Lee & Mansfield, 1996). Other studies suggest that a compulsory license in one field is unlikely to affect FDI in other segments due to the vertical nature of FDI, and that an accepted loss of FDI in a certain segment is buffered by increased gains in other segments (Bird & Cahoy, 2008). In contrast to compulsory licenses, voluntary licensing agreements usually allow for more FDI through technology transfer and capacity building in the recipient country. Goyal, in his study of CL on FDI observed reductions in foreign domestic investments in countries that used CL and found little significant correlation between CL use and FDI (Table 13).The study attributed much of the decrease in FDI to the economic downturn of 2008-2009, rather than CL use, suggesting that losses incurred due to CL is distributed by price rises in the product portfolio. Thailand's seemingly extreme use of CL did not have a significant effect on FDI, despite a slowdown due to the economic crisis of 2008. Other countries did not report any significant loss of FDI due to CL use. A 2007 study by the HITAP found no relation between Thai use of GULs and level of foreign domestic investments from 2002-2008. Conversely, Brazil and Thailand saw significant FDI reductions in the pharmaceutical sector following implementation of TRIPS.

Table 14 Changes in foreign domestic investments after use of CLs (Goyal, 2015)

Country	Year of CL grant	Change in FDI, net inflows (in % terms, with falls in FDI mentioned in parenthesis)									
		2002–2003	2003–2004	2004–2005	2005–2006	2006–2007	2007–2008	2008–2009	2009–2010	2010–2011	2011–2012
Egypt	2002	(0.63)	4.28	3.29	0.87	0.15	(0.18)	(0.29)	(0.05)	(1.08)	(0.63)
Zimbabwe	2002–2003	(0.85)	1.29	10.82	(0.61)	0.72	(0.25)	1.03	0.58	1.33	(0.85)
Malaysia	2003	(0.23)	0.87	(0.15)	0.96	0.18	(0.17)	(0.98)	78.95	0.31	(0.23)
Zambia	2004	0.16	0.12	(0.08)	0.73	1.15	(0.29)	(0.26)	1.49	0.15	0.16
Mozambique	2004	(0.03)	(0.27)	(0.50)	0.51	1.25	0.34	0.60	0.12	1.07	(0.03)
Ghana	2005	1.32	0.02	0.04	3.39	1.17	0.96	(0.13)	0.07	0.27	1.32
Thailand	2006–2007	0.57	0.12	0.37	0.17	0.20	(0.25)	(0.43)	0.88	(0.15)	0.57
Brazil	2007	(0.39)	0.79	(0.15)	0.25	1.30	0.14	(0.38)	0.69	0.34	(0.39)
Rwanda	2007	0.78	0.65	0.05	0.40	4.98	0.54	0.15	(0.64)	1.50	0.78
Ecuador	2010	0.11	(0.04)	(0.41)	(0.45)	(0.28)	4.18	(0.68)	(0.51)	2.59	0.11
India	2012	(0.23)	0.34	0.26	1.76	0.26	0.72	(0.18)	(0.26)	0.21	(0.23)
Indonesia	2012	(5.11)	(4.18)	3.40	(0.41)	0.41	0.34	(0.48)	1.82	0.32	(5.11)
World		(0.09)	0.25	0.93	0.23	0.46	(0.11)	(0.47)	0.16	0.23	(0.09)

Patterns would thus suggest that sporadic use of compulsory licensing have limited effect on FDI and innovation and that the occasional CL in MICs is unlikely to have substantial effect on foreign investments. As TRIPS explicitly requires case to case evaluation on CLs, frequent use of the flexibility is unlikely, and therefore poses little threat to long term innovation, unless used indiscriminately. The threat of retaliation and a WTO dispute therefore serves as a safeguard against frivolous use of compulsory licensing. Attributing low innovation and large decreases in foreign investments to use of compulsory licenses therefore pose a weak defense against use of this crucial flexibility.

6.13.3 Response to CL and Threats of CL

Experiences from case studies imply that foreign governments and pharmaceutical firms have been vocal against CL use in economically significant markets, especially true in "Pharmerging" markets with increasing local industrial capacity like Thailand, Brazil and S.A. Repeated use of retaliation by stronger countries through extra judicial tactics such as the USTR Special 301 list and threats to trade benefits is also an open violation of WTO rules, as use of flexibilities is entirely legal and subject to judgment by the WTO dispute settlement tribunal. Bird says the total social costs of CL licenses — "secondary effects" – may "negate any benefits from increased access" (Bird & Cahoy, 2008). In case of the WTO dispute between US and Brazil, the final ruling was deferred due to an understanding between both parties. The publicity garnered by the complainant states namely the US, and the EU has been negative as in the WTO disputes against Brazil, South Africa and Argentina.

Abbott's retaliatory measures in Thailand have been the most vocal measure to decry government infringement of IP rights. Ironically, Abbott applied for a compulsory license for HCV genotype testing kits in the US in the same year it withdrew products in Thailand as retaliation for CL use (J. Love, 2007). The Wall Street Journal has also published a range of editorials that criticize Thai CL use, often framing it as theft . In Thailand's case, Sanofi threatened to sue the Indian generic exporter of clopidogrel, while Abbott labs withdrew all new products from regulatory processes. In response to Thailand's CL use a "USA for innovation" lobbying firm was established by American businesses to explicitly criticize the GU policy (MoPH, 2007). EU trade commissioner Peter Mendelson intervened in Thai GUL announcement for cancer drugs calling Thailand's GUL policy "detrimental to the patent system". The USTR also intervened with a Section 301 Priority watch list notice.

Similarly, after Indian CL for Nexavar, led to the establishment of a coalition of business groups and – the Alliance for Fair trade with India - that lobbies for pro-business IP policy in India. Ostensibly, the majority of countries opting to use CLs have earned places on the USTR Special 301 List for a variety of IP violations including CL use. The 2016 Columbian CL application for Novartis's Gleevec was abandoned after the US government threatened to suspend funding for peace talks between rebel factions to resolve a civil war, a striking example of using economic might to strong-arm trading partners.

Broad use GULs policy have elicited restrained responses by big pharma, such as the Ecuadorian Decree by President Rafael Correa to license over 2000 drugs involuntarily while establishing a local generic manufacturer. Response to the announcement of CL use policy was fairly restrained with big pharmaceutical firms "accepting the democratic decisions to use this extraordinary legal measure, observing rights and responsibilities laid out in international law" (PharmaLetter, 2010).The US mission in Quito attempted to form a consortium of pharmaceutical companies to oppose Ecuador's CL policy, but received little enthusiasm from industry for unclear reasons . Similarly, Indonesia's broad use licenses for 7 ARV drugs in 2012 did not attract any retaliation besides media reports.

The Humanitarian motives behind the Canadian-Rwandan use of the Waiver mechanisms has discouraged retaliation by innovator firms, despite patentees' demanding terms beyond required by TRIPS Art.31bis for voluntary licenses during negotiations. Similarly, emergency use licenses have not attracted any retaliatory behavior.

There have been no challenges raised against use of compulsory licenses using the WTO dispute settlement to date, as retaliation has shifted to para-legal pathways such as trade barriers and proxy wars waged through media channels. The lack of WTO trade disputes challenging TRIPS compliance of compulsory licenses and reflect avoidance of pursuing WTO sanctioned penalties, due to the negative publicity garnered when richer nations intervene in public health initiatives of developing states. Due action must be taken to address and limit such reprisals on a high level, as developing countries are more vulnerable to trade shocks and financial penalty. Active inclusion of civil society organizations and public support from the WHO could also help in limiting effects of reprisals in justified cases of CL use. Other tools used to push agendas, include lobbying by pharmaceutical firms, prescription rewards, media editorials, and application of diplomatic and trade pressures are often brought to light by civil society organizations and activism.

6.13.4 Counter retaliation

Governments have also used varying approaches to counter retaliatory action. Brazil, in a public reversal of retaliation raised a dispute to counter accusations made by the US at the WTO Dispute Tribunal (Kogan, 2006), in contrast to Thailand's approach of countering negative press and a Special 301 listing by justifying CL use through a series of government releases of economic evaluations and explanatory white papers in an attempt to challenge the withdrawal of new products from case filed against Abbott. To counter the negative image projected by opponents, both Thailand and Brazil used media platforms to publically announce issue of compulsory licenses. The controversial nature of compulsory licenses often initiates discussion on pricing on international fora and highlights undesirable behavior, often reinforced by developed countries governments.

Thailand sets a good example by establishing its national Health Intervention and Technology Assessment Program (HITAP) exclusively with the intent to support its Universal Healthcare system and induce pharmaco-economic evaluation into its reimbursement process. In 2008, cost-effectiveness analyses were included for all drugs on the Thai NLEM. HITAP now conducts cost-effectiveness studies on behalf of the MoPH and guides reimbursement decisions for the Thai government (Tantivess et al., 2009). In the white papers released by Thai government, results from HTA's were used to justify use of CL with budget impact analyses of compulsorily licensed drugs .

Unfair or unjustified uses of CL carry negative social costs in terms of lost investments, as seen in the case of Egypt's CL for Viagra, hardly an essential drug (Allam, 2002). Countries such as India, Brazil, and China have amended their patent laws to further increase patentability standards for novelty and inventive step, choosing to avoid the perils of trade retaliation resulting from CL use. Having stringent patent criteria also has the benefit of projecting competence of authorities to scrutinize patent applications, and suggest a safe IP environment for investments. However, these provisions are also subject to criticism by stronger nations. India's rejected Novartis' patent for imatinib citing lack of inventive step earned it a USTR Section 301 listing, as did Brazil's rejection of Gilead's tenofovir patent application for lack of novelty.

6.13.5 TRIPS+ measures

As countries aim to develop economies by promoting trade through trade agreements and regional treaties, the risk of stringent IP obligations threaten ability to use TRIPS flexibilities. For example, in U.S. free-trade agreements, compulsory licenses are restricted to emergencies, as an anti-trust remedy, or for public noncommercial use, permitting appeals against compulsory licenses on grounds of unwarranted circumstances. Some TRIPS-Plus provisions mandate "reasonable and entire" remuneration for patent owners rather than "adequate remuneration" as prescribed by TRIPS. Further scrutiny of text reveals undefined "emergency situations" or "public non-commercial use". By confining a government's ability to issue compulsory licenses and providing an opportunity for the patent holder to challenge the issuance of compulsory licenses, TRIPS-Plus compulsory licensing provisions diminish a generic producer's ability to compete and enable the patent holder to retain control over drug pricing.

Scholars note that purposeful non-inclusion of text on use of regulatory data in relation to compulsory license use, limits practical use of flexibilities through covert means. Despite limiting provisions in FTAs, developing countries are offered lucrative access to export markets that are crucial to economic growth and fiscal stability. FTAs often enforce TRIPS plus clauses and "side notes" that allow exceptions to infringements in interest of public health. This leaves LDCs with limited advisory and technical expertise vulnerable to more stringent interpretations of fine text (F. M. Abbott & Reichman, 2007). Agreements such as the Trans-Pacific Partnership (TPP) include provisions for data exclusivity and patent linkage, which potentially affect public health in less powerful signatory nations. Studies warn of trade agreements with TRIPS Plus obligations that effectively diminish bargaining power of trade partners though incentivizing trade relations to a greater extent than possible benefits of compulsory license use(Bird & Cahoy, 2008).

Among case studies, both Thailand and India are in varying stages of negotiation trade deals with the US and the EU, under which data exclusivity and limited CL provisions were proposed. The Indian delegation has deferred data exclusivity provisions for the text of the EU-India BTIA and has agreed to refrain from issuing licenses for drugs in a non-emergency scenario (Sengupta, 2016). Thailand, similarly has refrained from issuing any new licenses after its 2nd wave of GULs on cancer medications, as discussions on a US-Thai FTA continue (Kittitrakul, 2016). The evidence of pressure of countries to refrain using TRIPS flexibilities, on bilateral and global platforms is immense. Ironically, the US does not allow injunctions on involuntarily licensed patent matter when used by the government.

Premature adoption of TRIPS Plus provisions with insufficient prior evaluation in trade agreements are further burdening situations in LDCs, and TRIPS flexibilities are now rendered unusable through imposition of data exclusivity, patent linkage, and CL limitations and investor state dispute settlement mechanisms. Overeager negotiators from developing countries should be advised against accepting agreements that result in detrimental long term effects on public health and therefore risk losing crucial ground in exercising afforded flexibilities.

7 Policy suggestions

While my findings are not unique, I make some suggestions based on conclusions derived from case studies. My recommendations are addressed at national, multilateral, and civil institutional levels to promote simpler and justified use of compulsory licensing under appropriate circumstances. The TRIPS framework has tactfully taken shape to give ample freedom in interpreting and issue of compulsory licenses, while explicitly discouraging large scale adoption of general compulsory licensing policies by requiring issue on a case to case basis. Countries should therefore be prepared to support decisions to license patented medications with sufficient evidence, often requiring willingness to defend use of CL on multilateral fora with proper evaluation of outcomes. Given the costs of implementing and successfully using a compulsory license, significant amounts of resources also need to be allocated exclusively for its use. CLs remain a measure of last resort against non-cooperative patentees, emergencies and crises, and should be used as such. Preferred use of other flexibilities afforded by TRIPS also limits retaliatory action and maintains investment friendly climates that developing nations are eager to promote. Use of CL has been dependent on use of existing legal and delivery infrastructure, and now calls for adoption of policy that encourages transition to more progressive innovation system while remaining conducive to the existing framework.

On the National Level, some economically transitioning governments have relatively little experience with compulsory licenses, and face challenges in exploring and navigating TRIPS flexibilities due to dearth of technical and legal expertise. Potential users of the compulsory licensing flexibility therefore should:

1. Selectively issue compulsory licenses, considering impacts on innovation and possible long term consequences including local market dynamics and delivery mechanisms. In order to retain credibility of threats and maximize benefits of the procured drugs, results of threats and issued licenses should be published on media platforms.
2. Design strategic voluntary escape mechanisms for innovators threatened with compulsory licenses, such guaranteed purchase quotas for discounts and voluntary licenses, providing desirable outcomes for both innovator firms and national capacity.
3. Order disclosure of proprietary information and clarify positions on regulatory data in case of Government use, Emergency and Urgent use licenses for expedited access to required products. As governments often rely on third parties to manufacture generic medications, availability of manufacturing specifics, and regulatory data could shorten delivery times.
4. Allow expedited regulatory processes of generics with proven bioequivalence to hasten availability of compulsorily licensed generics, by use of existing data to fast track approvals.
5. Encourage social activism to raise and highlight pricing issues at a grassroots level. While the end goal of activism and lobbying is to reform the current R&D model, transition to equitable distribution is dependent on leveraging public moral support of citizens, and its effect on publicity of pharmaceutical firms. Social activism has been essential in balancing retaliatory effects when raised on multilateral forums
6. Actively consult with multilateral organizations, civil society bodies and think-tanks for policy advice on compulsory licensing to ensure TRIPS compliance and transparency to avoid retaliatory action. Current

trilateral cooperation between WTO-WHO-WIPO has been limited to a framework for future amendments (WHO, 2006b).

7. Promote regional cooperation to take advantage of the Waiver mechanism for collective procurement of essential medicines through diligent use of Art.31bis, which allows for re-export of essential drugs to other LDCs that are signatories of a regional trade agreement.
8. Give preference to WHO prequalified suppliers to ensure quality of procured drugs. Given the absence of technical capacity in LDCs, WHO GMP guidelines must be mandated for generic suppliers, to protect quality of procured drugs.
9. Actively include the WHO in the CL process to legitimize use, while also discouraging retaliation. Technical assistance in procurement and logistics can be provided to developing countries through cooperation agreements with the WHO and other philanthropies.
10. Reject trade agreements with restrictive clauses that potentially affect public health such as limitations on CL use, prolonged data exclusivity, and limits on parallel imports. While benefiting from better trade relations, protection of public health should receive appropriate priority during the negotiation stage.
11. Amend patent application procedures to remedy excessive patent extensions and demand more stringent inventive standards, to avoid perennial extensions of patent validity. More careful IP policy making negates resorting to CL use, and also promotes capacity building of local legal systems.
12. Higher tiered royalties for judicial licenses to balance interests of patentees and de-incentivize abusive behavior by generic producers through fair use obligations. When paid by licensees, higher royalty rates increase marginal costs of production and avoid free riding on marketing by originator firms.
13. Implement compulsory licenses in conjunction with functioning delivery programs and policy changes to ensure maximal benefits by providing instruments to deliver procured generics. Measure and publish outcomes such as price benefits and improved access attributed to CLs, along with long term effects of changes both in cases of GULs and Private licenses.
14. Formulate national obligations for licensees and authorities to work patent matter through an established delivery mechanism as part of the compulsory license framework. This would encourage transparent and measurable distribution of procured medication, while generating information for future research and improvement.

On the Multilateral Level: The WTO council should now highlight the delayed ratification of the Art.31bis and call for certain updates to the TRIPS acquis. Such updates could include the following:

1. Attain a consensus on definition of “Prior negotiation” periods and terms to avoid delays in issue of licenses. Interpretation of prior negotiations has caused delay, and also set a standard to reduce ambiguity in issue of CLs.
2. Amend Art.31 to clearly differentiate between Judicial and Government use licenses, to clarify responsibilities and exceptions to licensees and issuing authorities, and encourage transparency of the compulsory licensing framework.
3. Encourage patent discrimination of life saving subject matter for Compulsory licenses, through an Art.30 exception. This would essentially allow an exemption of patentability on life saving technology or substances as is currently allowed for LDCs, and can be used as a step beyond Compulsory Licenses,

taking into consideration endemic orphan diseases. Countries such as Belgium and France have used Art. 30 to frame national CL provisions, rather than the Art.31 framework (Reichman, 2009).

4. Amend Art.31bis to require notification after use of CL's rather than prior to avoid prohibitive behavior by governments and pharmaceutical companies. This would also aid in creating a registry of issued CLs for future research and contribute to case law. Limiting notification to a single country is also essential to encourage use of this mechanism.
5. Include a Fair use clause for Government Use licenses to ensure judicious use of patented subject matter. In order to prevent abuse of the flexibility, fair use criteria could strengthen the case against leakage of patented drugs and allow segregation of markets, and avoid (unintended) parallel exportation.
6. Adopt the tiered sliding scale for royalties proposed by the WHO/UNDP on life saving patents to adequately reflect health gains and lost profits from a human rights perspective. This would decrease ambiguity of financial compensation and promote transparency.
7. Create provisions for automatic compulsory licenses in case of pandemic, emergencies, and biosecurity threats with higher royalties, to avoid delayed availability of essential drugs due to negotiations in a crisis scenario.
8. Create provisions for expedited repeated CLs application after initial non-exclusive non-transferrable licenses have been issued to promote generic competition. Such provisions would validate the non-exclusive clause and non-transferability requirements of Art. 31 by maximizing use of the framework.
9. Mandate audits of issued compulsory licenses for reporting to the WTO panel after use within a set time frame, to encourage accountability of governments, and licensees to originator firms.
10. Acknowledge the extra judicial trade retaliations taken by stronger governments to bypass TRIPS flexibilities through trade agreements, by publishing reports of texts prior to WTO approvals. This would allow LDCs further freedom in negotiations without compromising crucial liberties.
11. Re-align the mission and vision of the WTO to correspond with the UN Sustainable Development Goals, by acknowledging the current policy incoherence and giving priority to human rights over intellectual property, as raised in 32nd session of UNHRC and the UNHLP on ATM.

Studies have reported biased policy technical and capacity building assistance to developing countries from the WTO and WIPO ,due to influence of the collective North (Deere Birkbeck & Roca, 2011). In the current climate of hesitant CL use, absence of an unbiased advisory body calls for establishment of an independent consortium of experts from civil action bodies, autonomous from influence of UN bodies such as the W.T.O and W.I.P.O. to provide guidance to National authorities on implementation and procedural formalities for application of compulsory licenses when required. This role is currently played by civil society bodies and activist organizations, and such an institution has been proposed at the UNHLP on ATM (B. Baker, 2016), and could:

1. Provide policy guidance to governments on amending IP legislation to accommodate compulsory licensing provisions and diligent use of flexibilities, and in case of trade agreements evaluate outcomes of TRIPS plus provisions in trade agreements. LICs and LMICs could especially benefit from the Waiver decision (Art.31bis) given the complexity of the solution.
2. Serve as a platform for dialogue between able generic manufacturers and governments to propose licensing strategies for generic versions of on-patent drugs, and mediate negotiations between capable

generic companies and innovator firms for licensing agreements on patented drugs, and provide request guidance on CL applications in case of failed negotiations.

3. The advisory can provide official proof of “Prior negotiations under reasonable commercial terms” to national authorities in case of judicial license applications to expedite proceedings, and serve as expert witness to judicial proceedings in case of National judicial licenses. Currently the burden of proof lies on the patentee and applicant, leaving the fulfillment of the criteria to be judged on an ad-hoc basis.
4. Represent governments on the WTO dispute tribunal in cases of challenges against of Government use, Public Interest and Emergency compulsory licenses. If CL’s are to be used within the TRIPS framework, active use of the dispute tribunal is in best interests of issuing government, to defend and justify use of flexibilities. Provide support and advice on retaliatory measures, and guidance on counter retaliation when necessary.
5. Conduct research into more equitable and effective compulsory license models under existing TRIPS legislation, given the broad nature of Article 31, to encourage more dynamic use of market initiated licenses along with the regional procurement strategies.
6. Conduct further research into Article 30 exceptions that could potentially bypass the Article 31 framework on a Human rights basis. Such pathways might alleviate procedural burdens for countries with limited technical resources
7. Create a platform for collective bargaining using compulsory licenses as a threat. Guidance on the type of license to be issued with further exploration of the Art.31bis. Waiver mechanism for regional procurement and exports.
8. Conduct economic analyses of issued licenses and outcomes, to measure outcomes of compulsory license use and avoided burdens on life saving patents. This could potentially be integrated into a prize fund for averted costs and savings gained.
9. Create a registry for compulsory licenses and outcomes for further evidence-based policy guidance, through collaborating with civil action bodies that promote awareness of compulsory licensing worldwide.

8 Conclusion

As an advocate of public health, I find it disturbing that Access to Medicine is governed by a trade framework with financial interests as its imperative. The WTO and TRIPS has encouraged countries to strengthen IP frameworks to harmonize standards of intellectual property, and countries are adopting stringent patentability standards as a primary safeguard for public health, along with other flexibilities such as national exhaustion regimes, and exclusion of patent linkage and data exclusivity. As the TRIPS framework ensures selective issue of CLs, proper use of the guidelines is essential to avoid reprisal and ensure justification if challenged. The Doha declaration and Art.31bis experience is testament to the lengthy periods for policy decisions to come to fruition, and serves as a strong argument to justify prudent research and investigation prior to formulating legislation. Repeated extensions on the transition period for LDCs to adopt patent protection for pharmaceuticals (up to 2033), makes a case for inability of some developing nations to adopt harmonized IP standards.

As many countries (including the US) gradually implement universal healthcare coverage, along with recent instances of price gouging behavior for essential medicines such as pyrimethamine and epinephrine in the US, and drug shortages in Greece due to inability to pay bills highlight the requirement for a more responsible

innovation framework. I believe that such instances will result in a steady frequency of CLs over the coming years, unless the innovation model evolves to allow sustainable prices of new medication.

Addressing the policy conflicts between the Right to Health and Inventor's rights is the first step towards reform of the innovation framework and eventually to TRIPS. On 27th October, 2016 the Delegations of Brazil, India, China and South Africa requested a dedicated agenda on the November 2016 session of the TRIPS council meeting to discuss findings of UN Secretary-General's High-Level Panel on Access to Medicines (UN HLP). Responses to following discussions will shed light on how the innovation framework will evolve to accommodate public health needs of citizens globally, and will dictate policy choices of governments and corporations. Until a point of reconciliation is reached, compulsory licenses represent the last resort to ensure access to protected inventions, and serve as a looming reminder of its significance in the policy toolbox, remaining far from obsolete.

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10 Appendix.

Appendix : List of CL threats and outcomes (compiled from multiple sources)

Year	Status	Country	Drug	Indication	Outcome
1995	HIC	Israel	hepatitis B vaccine	Hepatitis B	CL
1997	UMIC	South Africa	multiple ARVs	HIV-AIDS	Discount
2001	HIC	USA	ciproflaxin	Anthrax	Discount
2001	HIC	Canada	ciproflaxin	Anthrax	Discount
2001	UMIC	Brazil	efavirenz	HIV-AIDS	Discount
2001	UMIC	Brazil	nelfinavir	HIV-AIDS	Discount
2002	UMIC	Dominican Republic	clopidogrel	Heart Disease	Rejected
2002	HIC	South Korea	imatinib	Chronic Myeloid Leukemia	Rejected
2002	LIC	Egypt	sildenafil	Erectile Dysfunction	CL (Public interest)
2003	UMIC	Malaysia	didanosine; zidovudine	HIV-AIDS	CL (GUL)
2003	LIC	Zimbabwe	All ARVs	HIV-AIDS	CL (Emergency use)
2004	LIC	Mozambique	lamivudine/stavudine/nevirapine (FDC)	HIV-AIDS	CL (Emergency use)
2004	LIC	Zambia	lamivudine/stavudine/ nevirapine (FDC)	HIV-AIDS	CL (Emergency use)
2005	LIC	Indonesia	lamivudine/ nevirapine	HIV-AIDS	CL (GUL)
2005	UMIC	Brazil	lopinavir/ ritonavir	HIV-AIDS	Discount
2005	UMIC	Brazil	tenofovir	HIV-AIDS	Discount
2005	LIC	Ghana	All ARVs	HIV-AIDS	CL(Emergency)
2005	UMIC	Argentina	oseltamivir	Avian Influenza H5n1	Non-assert
2005	HIC	Taiwan	oseltamivir	Avian Influenza H5n1	Conditional CL
2005	HIC	Italy	imipenem cilastatin	Bacterial infections	CL (Anti-trust)
2006	HIC	Italy	sumatriptan succinate	Migraine prophylaxis	CL (Anti-Trust)
2006	UMIC	Thailand	efavirenz	HIV-AIDS	CL (GUL)
2007	HIC	Italy	finasteride	Prostatic Hypertrophy	CL(Anti-Trust)
2007	UMIC	Thailand	lopinavir/ritonavir ; clopidogrel	HIV-AIDS / Heart Disease	CL (GUL)
2007	UMIC	Brazil	efavirenz	HIV-AIDS	CL (GUL)

2007	LIC	India (For Nepal)	sunitinib and erlotinib	Renal and lung cancers	Rejected (Waiver mech.)
2007	UMIC	Brazil	atazanavir	HIV-AIDS	Discount
2007	UMIC	Brazil	lopinavir/ritonavir	HIV-AIDS	Discount
2007	LIC	Rwanda	zidovudine; lamivudine; nevirapine (FDC)	HIV-AIDS	CL (Waiver mech.)
2008	UMIC	Thailand	letrozole; docetaxel; erlotinib	Breast and lung cancers	CL (GUL)
2008	UMIC	Brazil	tenofovir	HIV-AIDS	Discount
2008	UMIC	Thailand	imatinib	Chronic Myeloid Leukemia	Discount
2010	UMIC	Ecuador	lopinavir/ritonavir	HIV-AIDS	CL (GUL)
2012	LIC	Indonesia	ABC; LPV/r ; TDF/ETC/NVP; 3TC ; EFV	HIV-AIDS	CL (GUL)
2012	LMIC	India	sorafenib	Hepatic and Renal Carcinoma	CL (Private use)
2012	UMIC	Ecuador	abacavir/lamivudine	HIV-AIDS	CL (GUL)
2012	UMIC	Thailand	rituximab	Non-Hodgkin's Lymphoma	None
2012	LMIC	China	tenofovir	HIV-AIDS	Discount
2013	UMIC	Ecuador	ritonavir , lamivudine , abacavir	HIV-AIDS	CL (GUL)
2013	LMIC	India	trastuzumab	Breast cancer	VL
2013	LMIC	India	dasatinib	Chronic Myeloid Leukemia	Rejected - GUL Threat
2013	LMIC	India	ixabepilone	Breast Cancer	Rejected - GUL Threat
2014	UMIC	Ecuador	sunitinib, sodium micophenolate	Cancer, Renal transplant prophylaxis	CL
2014	LMIC	India	indacterol	COPD	Rejected - GUL Threat
2014	UMIC	Ecuador	etoricoxib, certolizumab	Rheumatoid arthritis	CL
2015	LMIC	India	saxagliptin	Diabetes	Rejected
2015	UMIC	Columbia	imatinib	Chronic Myeloid Leukemia	On hold
2015	LMIC	Peru	atazanavir	HIV-AIDS	Rejected
2016	HIC	Germany	raltegravir	HIV-AIDS	CL- pending appeal

Abbreviations :

ABC – Abacavir, 3TC-Lamivudine , TDF – Tenofovir, LPV/r Lopinavir+ritonavir, NVP- Nevirapine, EFV- Efavirenz, AZT – Zidovudine, RTV – Ritonavir, ATV – Atazanavir, RTG- Raltegravir, FTC –Emtricitabine, FDC – Fixed Dose Combination