PARALLEL IMPORTATION OF HUMAN DRUGS,

THE CASE OF SOUTH AFRICA

by

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(Under the Direction of David Mullis)

ABSTRACT

Most pharmaceutical products have different prices in different markets, with the highest prices being reported in developing countries such as South Africa. Despite the World Health Organization's agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), some member states still oppose its usage. South Africa embraced the idea of parallel importation and passed the Medicines and Related Substance Control Amendment Act in 1997.

This paper evaluated the impact of the passage of the regulations in the South Africa. Data from published literature was evaluated and supplemented with a questionnaire. Parallel importation had not been used in practice but has served as a "Big Stick Diplomacy" tool. Hence, there has been a significant increase in the number of voluntary licenses and price decreases in some essential drugs but no significant change in the regulation or the quality of drugs.

INDEX WORDS: Parallel Importation, Patents, Intellectual Property Rights, Compulsory Licenses, Voluntary Licenses, Arbitrage, TRIPS Flexibilities

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DEDICATION

I would like to dedicate this thesis to: Julianna Tandongfuet, Peter Ngulefac, and Judith Ngulefac. Their moral, spiritual and financial supports have been of great assistance to me in achieving my educational goals.

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CHAPTER 1

INTRODUCTION

There has always been a divide between making profits from the sales of human drugs and actually saving the lives of those who need these drugs. This has led to a battle among drug manufacturers, regulatory authorities, consumers, and advocacy groups. With the amount of money invested in the research and development of drugs, and regulatory approval; most companies would have spent hundreds of millions of dollars before drugs get to the market. This is one of the reasons why companies are given exclusive rights through patents to manufacture and distribute these new drugs for a set period of time, mostly 20 years[50].

Companies have the task to set prices for different markets so that they can recover costs, as well as make profits. This has led to variations in prices from one market to another (*Market segmentation*)[44]. Many consumers, as well as governments on the unfair side of the price designations have looked forward to the idea of parallel importation as a possible remedy to the situation. A parallel import is a non-counterfeit product imported from another country without the permission of the intellectual property owner. Parallel imports are sometimes referred to as *grey products* and are implicated in issues of international trade and intellectual property[4]. Many countries have embraced the idea of parallel importation including the European Union (EU) countries, New Zealand, Kenya, South Africa, etc[7]. Recent industry estimates suggest that lost sales in the EU due to parallel importations currently amount to some $3 billion per year[12]. The practice of parallel importation is often advocated in the case of pharmaceuticals, software, music, printed texts, and electronic products.

A manifestation of the philosophical divide between those who support intellectual property and those who are critical of it is the divide over the legitimacy of parallel importation. Some believe that it benefits consumers by lowering prices, widening the selection, and consumption of products available in the market[22]. However, others believe that it discourages intellectual property owners from investing in new and innovative products[7]. Some also believe that parallel imports tend to facilitate copyright infringement and enable parallel importers to "Free-ride" at the original manufacturer's R&D and marketing expense[7].

This tension essentially concerns the rights and duties of a protected monopoly. Intellectual property rights allow the holder to sell at a price that is higher than one would pay in a competitive market, but by doing so, the holder relinquishes sales to those who would be prepared to buy at a price between the monopoly price and the competitive price. The presence of parallel imports in the marketplace prevents the patent holder from exploiting the monopoly further by market segmentation, i.e. by applying different prices to different consumers like U.S price and South African price[22].

Consumer organizations tend to support parallel importation as it offers consumers more choice and lower prices, provided that consumers retain equivalent legal protection to locally sourced products (e.g. in the form of warranties with international effect), and competition is not diminished[22]. However, such organizations also warn consumers of certain risks in using parallel-imported products such as the use of adulterated drugs. Although the products may have complied with the laws and customs of their place of origin, these products or their use may not comply with those in places where they are used, or some of their functions may be rendered ineffective or not relevant within a specific country's medical needs[22].

In South Africa, the prices of some drugs are very high compared to the price of that of the same drug in other countries. For example, Ceftriaxone is indicated for the treatment of severe infections such as Pneumonia or Septicemia. The South African trade price of 1mg vial of Roche's Rocephin® (Ceftriaxone) was $13.48, while the Rocephin® trade price in Spain, as calculated by the Royal Decree 5/2000 (23rd June 2000), was $8.44 (1.6 times cheaper)[1].

Another example of a drug with significant price disparity is-"Zidovudine". Zidovudine was the first Anti Retro Viral (ARV) discovered in 1964 and the first approved in 1987 for treatment of HIV/AIDS and the prevention of mother-to-child transmission. The South African trade price of 100mg capsule of GlaxoSmithKline's Retrovir® (Zidovudine) was $0.32, while the Brazilian trade price was $0.29 (1.1 times cheaper)[2]. Also, Ciprobay® 250mg an antibiotic mainly used for treatment of Anthrax Infections and Urinary Tract Infections was about $0.3 in South Africa, and $0.06 in India (5 times cheaper)[43]. Parallel importation of this drug from India to South Africa could lead to significant price reduction.

According to a 2001 report to the World Intellectual Property Organization (WIPO) by Keith E. Markus, a professor of economics at the University of Colorado at Boulder[7], developing countries could have high prices due to 3 main reasons:

- The decision to sell low volumes at high markups. These markets have two kinds of consumers. First, high-income consumers with a low degree of price sensitivity, high ability, and willingness to pay for new drugs. Second, low-income consumers who are more price-sensitive and less able to pay. The pharmaceutical companies and distributors decided to serve primarily the needs of the high income consumers.
- Monopolistic nature of distribution systems in developing countries. Most developing countries have a single distributor for a particular brand or the distribution systems are

highly concentrated which may give the distributors extra leverage to pursue higher profits by increasing prices.

- Some affluent nations may have stringent price controls that limit manufacturer's prices to levels below those in poorer nations. Where parallel imports originate in countries with strict price regulations, they have complex potential impacts on economic well-being and research and development performance in both origin and destination countries.

Parallel importation of drugs is expected to highly affect the socio-economic status of those benefiting from it. In countries where out-of-pocket health care expenditure is very high, high drug prices are expected to prevent access to needed drugs. Even insurance companies or national health programs may not have the budget to cover high drug prices, thus leaving the burden on the patients. If patients have to use all their economic resources on healthcare, a drought on other aspects of life, such as standard of living, education, income, etc. can be anticipated.

A major goal in this paper will be to discuss the regulatory challenges that result from the passage of the parallel import regulations. In order for parallel import regulations to be implemented smoothly, industry, regulatory authorities, and consumers which all have different agendas, should be able to agree on its scope. In South Africa's 1997 *Medicines and Related Substances Control Amendment Act (MRSCA)*, there is a provision for parallel importation and compulsory licenses to be granted in the country. This paper will discuss and analyze how this provision has been used and the challenges associated with it. It will also compare the use of parallel importation in the EU and the U.S.

Furthermore, background research and a questionnaire will be used to arrive at conclusions in this paper. Results from the questionnaire will supplement results from the evaluation of data

from the published literature related to parallel importation (background research). It could be expected that parallel importation of drugs would lead to; a decrease in prices of drugs; more drugs entering the market; an increase in the socio-economic status of the nation and a decrease in the quality of drugs. Opponents of parallel import regulations were worried about the abuse of intellectual property rights[27].

CHAPTER 2

BACKGROUND RESEARCH

2.1. PARALLEL IMPORTATION

A parallel import is a non-counterfeit product imported from another country without the permission of the intellectual property owner. Parallel imports are sometimes referred to as *grey products*. They are implicated in issues of international trade and intellectual property. The incentive for its occurrence is sufficient difference in prices between the two countries to cover shipping and transaction costs and still offer gains to both the shipper and the buyer. It is, therefore, a form of arbitrage. The question of the legitimacy of grey marketing does not involve the legality of the products, but the legality of the means by which they are distributed. In general, there are three prerequisites for the evolution of grey markets[6]:

- Gray marketers must have a source of supply;
- Trade barriers between countries must be low enough to provide easy access from one market to another; and
- Price differentials must be large enough to appeal to the profit motives of grey marketers (Arbitrageurs).

The European pharmaceutical market is a classic example which encompasses all of these characteristics. Econometric analysis found that the introduction of parallel imports in the EU significantly reduced manufacturing relative prices between 12% and 19% of the original prices. Also, there is further evidence that this effect increases with multiple parallel imports entrants[9].

Parallel importation of pharmaceuticals occurs for several reasons:

- Different versions of a product are produced for sale in different markets. For example Drug A (UK Edition) is officially sold in the UK and Drug A (South African Edition) is officially sold in South Africa. The UK Edition is cheaper than the South African Edition. However, some unofficial distributors in South Africa could also sell Drug A (UK Edition). This is common for generic drugs. Figure 1 illustrates this:

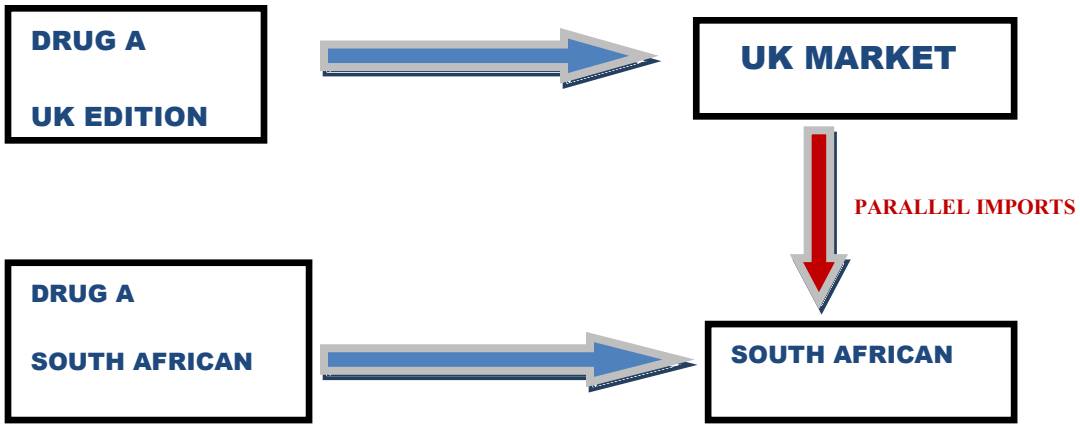

Figure 1: Parallel Trading Mechanism 1

- Companies, either the manufacturer or the distributor, set different price points for their products in different markets. If the price in "country A", is set at P1, and the price in "country B", is set at P2, and the price in A, is significantly smaller than that in B, a parallel importer from B (e.g., South Africa), can import the drug from A (e.g. India), and sell it in country B at a price P3. The P3 will be between P1 and P2. Figure 2 illustrates this mechanism:

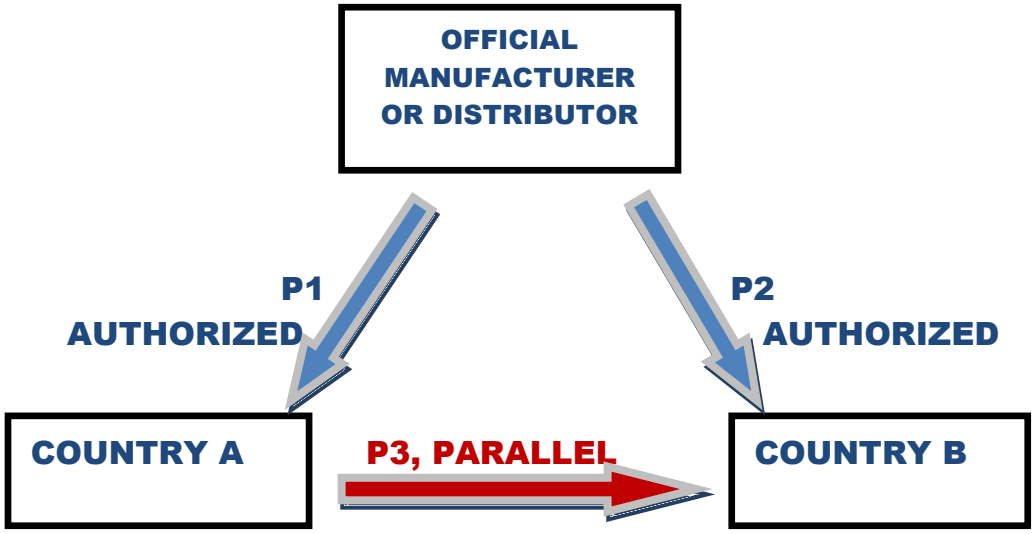

Figure 2: Parallel Import Mechanism 2

- Consumers who are able to obtain more competitively priced items and who may be able to avoid local sales taxes, are placed on even footing with consumers who have less access to overseas sales online.
- Out-of-pocket expenditures on drugs are high in many countries especially developing ones. "Out-of-pocket" expenses refer to those made by patients themselves rather than by the health system (e.g. "Obamacare", Medicaid, Medicare) or paid by private health insurance. A government would be more likely to implement parallel import regulations if it was carrying the burden of high drug prices or its citizens were carrying a heavy price burden. Table 1 gives the percentages of out-of-pocket expenditure for some countries according to the World Bank[3].

Table 1: Percentage of Out-of-Pocket expenditure
World Bank Data[a]

Year / Country	1995 (%)	1997 (%)	2011 (%)
CAMEROON	**93.8**	**94.5**	**94.5**
CHINA	**93.7**	**94.8**	**78.8**
KENYA	**78.3**	**79.2**	**76.7**
SOUTH AFRICA	**23.2**	**18.9**	**13.8**
UK	**67.6**	**59.7**	**53.1**
U.S.A	**26.6**	**26.5**	**20.9**

The longstanding practice of parallel importation costs the pharmaceutical industry $3 billion in sales a year[8], according to industry estimates[b]. Pfizer Inc., for instance, estimates that half of its U.K. sales of Lipitor, its cholesterol blockbuster, come via middlemen who buy the drug in other European countries. The flood of imports, Pfizer officials say[8], has forced it to reduce capacity at a British plant where it makes Lipitor[c]. The pharmaceutical industry has tried to stop parallel trade before and have been overruled by European authorities. Now, drug makers are trying a different approach*: restricting supplies of their wares to meet local need only*, according to formulas based on prior demand and anticipated growth[8]. The idea here was that a country should receive just enough of a drug for needed by its citizens. Wholesalers that order more, with the intention of shipping the drug to higher-price markets wouldn't have enough to do so. Several of the biggest drug makers, including GlaxoSmithKline PLC, Wyeth, Eli Lilly & Co,

a World DataBank, Out-Of Pocket Expenditure[3]. 2013, http://databank.worldbank.org/data/views/reports/tableview.aspx?isshared=true&ispopular=country&pid=17,(Accessed 10/08/2013)

b Fuhrmans V, Drug Makers Try to Curtail Cheap Imports, 11 April 2002, The Wall Street Journal[8], Accessed August 10,2013

c Fuhrmans[8]

Sanofi, etc., have imposed newer tougher quota schemes on national distributors[8]. The tough measures, drug companies say, are intended to streamline distribution, help prevent medicine shortages and curtail excess inventory. However, distributors claim the approach is aimed at thwarting cross-border drug trading, which has been fueled by two seemingly paradoxical fixtures in the European drug industry: the European Union's single market on the one hand and country-by-country controls on drug prices on the other[8].

Though drug companies stood to benefit if their strategy worked, the ultimate buyers of prescription medicines will pay more. National governments, which provide most of the medical care in Europe, now benefit from the lower prices of parallel-imported drugs and will have to pay more. Patients who buy drugs on their own also will face higher prices but the most worrisome consumer impact, may be shortages created in lower-priced countries as wholesalers continue to use what supplies they have to profit from exports. Boehringer-Ingelheim GmbH, a German drug maker, applied this actual national demand policy and added an average cushion of 20%. Even after the policy was implemented, parallel trade still consumed drug companies an estimated 40 million Euros in profit -- or 10% of Boehringer-Ingelheim's net income in 2001, says Rolf Krebs, chairman of the company's executive board[8].

Over the years, drug companies have viewed parallel trading to be a result of price controls in various countries. Companies fear that government intervention through price controls will promote parallel trade. However, their strategy to limit supplies based on actual demand in low price countries may lead to drug shortages in these countries, should they engage in such trade[8]. Drug makers say they are the ones shortchanged by parallel trade. According to Hugh O'Connor, president of Pfizer's European Operations, parallel trade went from being a minor annoyance a few years ago to becoming quite a substantial business problem in Europe in recent years. In

Britain, he says, half of all demand for several products is being met by imports from low-price countries[8].

2.2. COMPULSORY LICENSING, VOLUNTARY LICENSING AND TRADE-RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS).

The discussion on parallel importation, market segmentation, and arbitrage cannot be complete without the mentioning of compulsory licensing, voluntary licensing, and the Trade Related-Aspects of Intellectual Property Rights (TRIPS).

Compulsory licensing occurs when a government allows someone else to produce a patented product or process without the consent of the patent owner. It is one of the flexibilities in patent protection included in the World Trade Organization's (WTO) agreement on intellectual property — the TRIPS Agreement. The licensee does not have exclusive rights over the patent. The patent owner still has rights over the patent, including a right to be paid for the authorized copies of the products. The amount of the payment is determined by the government authority involved. Certain conditions had to be fulfilled before a compulsory license could be used, such as; failure of the patent holder to issue a voluntary license under reasonable commercial terms and conditions, or a national emergency situation. As part of the 1997 Medicines and Related Substance Act, the South African government exercised its rights as a WTO member state to grant compulsory licenses where they deemed them necessary for public health emergency reasons. India issued its first compulsory license in February 2012, allowing Hyderabad-based Natco Pharma Ltd to make Bayer AG's lung and kidney cancer drug, Nexavar at one-tenth the price[49].

In many occasions, licenses are granted voluntarily by copyright owners for a negotiated fee and pursuant to an agreed upon terms and conditions. These are called Voluntary (or direct) licenses[49]. Licenses usually take the form of a written contract that specifies the owner of the copyright, what rights are being granted, the term of the license, and the royalties, if any, to be paid to the copyright owner.

The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) is an international agreement administered by the World Trade Organization (WTO). It provides a minimum standard for many forms of intellectual property (IP) regulations as applied to nationals of other WTO Members. It was negotiated at the end of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) in 1994. In January 2005, it initially went into effect[50].

The TRIPS agreement introduced intellectual property law into the international trading system for the first time and remained the most comprehensive international agreement on intellectual property to date. In 2001, developing countries initiated a round of talks that resulted in the Doha Declaration[69]. This was because of their concern that some developed countries were insisting on an overly narrow reading of TRIPS that would have limited the use of parallel importation and compulsory licenses. For the main part, the declaration was necessary for clarifying the TRIPS Agreement's flexibilities (i.e. The Parallel importation and Compulsory licenses provisions) and assuring governments that they can use these flexibilities.

Most governments in developing countries were unsure about how the flexibilities would be interpreted[50]. The Doha declaration is a WTO statement that further clarifies the scope of TRIPS, stating, for example, that TRIPS can and should be interpreted in light of the goal "to promote access to medicines for all". This was to be done by allowing countries unable to

manufacture their needed pharmaceuticals to obtain cheaper copies elsewhere if necessary. The legal means of making the change was agreed on August 30, 2003[d]. The WTO General Council decided to make provisions which allowed generic copies made under compulsory licenses to be exported to countries that lack production capacity. However, certain conditions had to be met, and procedures are followed. All WTO member countries were eligible to import under this decision, but 23 developed countries opted not to import through compulsory licenses[51]. The developed countries who opted out included: Australia, Canada, Denmark, France, Germany, Japan, United Kingdom, the US, etc. plus 10 EU nations which later added to this group. The TRIPS agreement explicitly states that the practice of parallel importation cannot be challenged under the World Trade Organization (WTO) dispute settlement system and so; it is effectively a matter of *"national discretion"*[51]. This gives room for individual WTO member governments to decide if they want to implement parallel importation or not.

The developed and developing countries had to implement the provisions in TRIPS Agreement by January 1, 1996 and January 1, 2000 respectively, but least-developed countries (i.e. countries with Gross National Income per capita less than $1190 in 2012; substantial economic vulnerability and human resource weakness), had at least until January 1, 2006, but this date was later extended to 2013. Least developed countries also have until 2016 to implement these laws into their current pharmaceutical regulations and this date could be further extended.

As the Agreement comes into force in a member state, any inventions of a pharmaceutical product or process that fulfills the established criteria of novelty, inventiveness, and usefulness, will be under the holder's patent for a minimum of 20 years (Article 33). Prior to the TRIPS

[d] WTO, Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health, September 1, 2003. http://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm(Accessed Feb 10,2013)

Agreement, without the patent protection in the process, the local companies could develop the drugs through difference processes than those patented and could make locally developed cheaper versions of the product[51].

2.3. FIRST SALE DOCTRINE AND EXHAUSTION DOCTRINE

Parallel importation of pharmaceuticals and parallel importation of other goods are regulated separately in the United States. This difference has been mainly attributed to public health safety concerns regarding re-imported drugs as well as the quality of such drugs. The first-sale doctrine plays an important role in copyright and trademark law by limiting certain rights of the copyright or trademark owner. The doctrine enables the distribution chain of copyrighted products, library lending, gifting, video rentals, and secondary markets for copyrighted works, (for example, enabling individuals to sell their legally purchased books or CDs to others). In trademark law, this same doctrine enables reselling of trademarked products after the trademark holder put the products on the market. The doctrine is also referred to as the "right of first sale," "first sale rule," or "exhaustion rule"[52]. This doctrine was exercised in the major cases below.

In 1998, the U.S. Supreme Court in Quality King v. L'Anza found that the first-sale doctrine applied to import goods at least where the imported goods are first lawfully made in the United States, shipped abroad for resale, and later re-enter the United States. That case involved importation of hair care products bearing copyrighted labels. A unanimous Supreme Court found that the first-sale doctrine does apply to importation into the US of copyrighted works (the labels), which were made in the US and then exported. However, the Supreme Court did not decide the issue where grey-market products are initially manufactured abroad and then imported into the US. The Court indicated that importation of goods made outside the U.S. could perhaps

be barred under §602(a)[e], since such goods would not be "lawfully made under this title"[70]. Such products might be lawfully made, either by the copyright owner or a licensee, but they would not be lawfully made under US copyright law. Rather, they would be lawfully made under the copyright laws of the other country and the first-sale doctrine would, therefore, not limit the §602 importation restriction[53].

Furthermore, in Kirtsaeng v. John Wiley & Sons, Inc., in 2013, the United States Supreme Court held, in a 6-3 decision, that the first-sale doctrine applies to goods manufactured abroad, even if they were manufactured abroad with the copyright owner's permission and imported into the U.S. The case involved a plaintiff who imported Asian editions of textbooks that were manufactured abroad with the publisher-plaintiff's permission. Without the permission from the publisher, the defendant, imported the textbooks and resold them on eBay. The Supreme Court's holding severely limited the ability of copyright holders to charge vastly different prices in different markets due to ease of arbitrage. The decision does remove incentives to U.S. manufacturers to shift the manufacturing abroad to attempt to circumvent the first-sale doctrine altogether[52].

Alternatively, the Exhaustion Doctrine, which is a common law patent doctrine, limits the extent to which patent holders can control an individual article of a patented product after an authorized sale. Under this doctrine, once an unrestricted authorized sale of a patented article occurs, the patent holder's exclusive rights to control the use and sale of that article are exhausted and the purchaser is free to use or resell that article without further restraint from

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[e] Cornel University Law School, Quality King Distributors, Inc. V. L'Anza Research, Http://Www.Library.Mun.Ca/Guides/Howto/Mla.Php, Nov 12, 2013

patent law. However, under current law, the patent owner retains the right to exclude purchasers of the articles from reproducing the patented product, unless it is specifically authorized by the patentee. Procedurally, the patent exhaustion doctrine operates as an affirmative defense, shielding authorized purchasers from infringement claims concerning the use or sale of a patented good after the patent owner authorized its sale. Because the doctrine is only triggered by a sale authorized by the patentee, it is often difficult to figure out if the exhaustion doctrine applies in a particular case. For example, when the patentee restricts or conditions the sale itself or restricts the use or sale of the patented article, once purchased and in the hands of the end user. The 2008 Supreme Court decision in Quanta Computer, Inc. v. LG Electronics, Inc. leaves unclear the extent to which patentees can avoid the exhaustion doctrine through limited licenses. Since its development by the courts in the late 19th century, the patent exhaustion doctrine has raised questions regarding the scope of exclusive rights granted by patents and the extent to which a patent owner may extend those rights to control downstream use and sales of patented articles[54].

In the pharmaceutical industry, exhaustion of rights could be national, regional, or international, depending on the laws of a particular country. The concept of National Exhaustion does not allow the Intellectual Property (IP) owner to control the commercial exploitation of goods placed on the domestic market by the IP owner or with his consent. However, the IP owner (or his authorized licensee) can still oppose the importation of original goods marketed abroad based on the right of importation. National exhaustion promotes market segmentation and price differentiation among various countries. The U.S. practices national exhaustion within the pharmaceutical industry.

In the case of regional exhaustion, the first sale of the IP protected products by the IP owner or with his consent exhausts any IP rights over these given products, not only domestically, but within the whole region and parallel imports within the region can no longer be opposed based on the IP right. The European Union allows exhaustion of rights within the Euro Zone.

Where a country applies the concept of international exhaustion, the IP rights are exhausted once the product has been sold by the IP owner or with his consent in any part of the world. This type of exhaustion is practiced in Australia, Malaysia, and most developing nations like Kenya and South Africa. The U.S practices international copyright exhaustion rights are evident in the case of Kirtsaeng v. John Wiley & Sons, Inc., in 2013[52].

CHAPTER 3

COUNTRY SCENARIOS

3.1. UNITED STATES (U.S.) SCENARIO

The long history of the regulation of pharmaceuticals began in the U.S. in 1902 with the Virus, Serum, and Antitoxin Act. Shortly thereafter was the passage of the Pure Food and Drugs Act of 1938, which took action against fraudulent remedies and unlabeled products. The Federal Food, Drug, and Cosmetic Act (FDCA) were the first attempts to require drugs to be tested for safety and labeled for use. These acts were passed in order to ensure that the products were healthy and safe for consumers. The Prescription Drug Marketing Act of 1987 (PDMA) and the Prescription Drug Amendments of 1992 amended the FDCA to prohibit prescription drug re-importation. This legislation was proposed based on Congressional hearings regarding serious potential problems relating to the efficacy and accountability within the system of the re-importation of prescription pharmaceuticals to be sold to American consumers[55]. After five days of hearings, a formal report issued by the subcommittee noted the following concerns:

- *The existence and method of operation of a wholesale submarket that prevents effective control over the true sources of drugs;*
- *The re-importation of drugs that may have become sub-potent or adulterated during foreign handling and shipping;*
- *The existing system of providing samples to physicians through manufacturers' sales representatives may encourage adulteration and/or misbranding;*
- *The release of drugs by health care institutions helps fuel the diversion market; and*

- *The counterfeiting of brand names by persons in foreign countries promotes the marketing of sub-potent or impotent drugs, competes with American markets, and tarnishes the good name of legitimate products in those countries.*

Consequently, current federal law regulating the importation of pharmaceutical products – the Federal Food, Drug, and Cosmetic Act– prohibits all other parties from re-importing drugs but permits only the manufacturers to import drugs, including drugs originally produced in the United States and exported to a foreign country. The imported drugs must be produced by facilities that meet the Food and Drug Administration's Good Manufacturing Practices[56]. The FDA is a federal agency in the Department of Health and Human Services that is charged with protecting public health through approving safe products for the consumer market and preventing unsafe foreign products from entering the market.

Parallel importation or re-importation of prescription drugs from foreign countries generally violates one or more provision of the Federal Food, Drug, and Cosmetic Act (Khodeli, 2004).

- *21 USC 355* – prohibits introducing non-FDA approved medications into interstate commerce, including foreign versions of U.S. approved drugs and U.S. manufactured drugs intended for foreign markets;
- *21 USC 353 (b) (2)* – prohibits dispensing a drug without proper labeling;
- *(21 U.S.C. § 353(b)(1))*- Prescription drugs dispensed without a valid prescription
- *21 USC 331 (a), (d), (i)* – prohibits marketing misbranded, adulterated, or counterfeit drugs; and
- *21 USC 381 (d) (1)* – prohibits re-importing drugs from foreign markets except by the drug manufacturer.

- The version also may be misbranded because it may lack certain information that is required under U.S law *(21 U.S.C. §§ 352 or 353(b))* but is not required in the foreign country, or it may be labeled in a language other than English *(21 C.F.R. § 201.15(c)).*

In 2000, the United States Congress passed and then-President Clinton signed, the *Medicine Equity and Drug Safety (MEDS) Act* to allow pharmacists and wholesalers to import covered products into the United States (Medicine Equity and Drug Safety Act of 2000). However, prior to implementation, the Secretary of Health and Human Services had to demonstrate that implementation would pose no additional risk to the public's health and safety, and would result in a significant reduction in the cost of covered products to the American consumer.

In December 2000, Donna Shalala, who was then the Secretary of Health and Human Services, refused to implement the MEDS Act (Kaufman, Dec 27, 2000). She contended that the re-importation of prescription drugs *created serious health risks and expressing doubt that re-importation would result in a substantial price reduction*. As such, the MEDS Act was deregulated. Although the MEDS Act has not yet been re-implemented, Congress has considered several other bills that would permit re-importation of prescription drugs.

President Clinton vowed to send new legislation to Congress to fix the drug re-importation provisions, as did some members of Congress but their efforts failed. Senator Jeffords, for his part, promised to take up the issue with President-Elect Bush's administration. On January 31, 2001, Senator Jeffords and fifteen other Congressmen wrote to the new Secretary of Health and Human Services, Tommy Thompson, asking him to reconsider the issue. In response to Senator Jeffords and other lawmakers, Secretary Thompson had the FDA re-examine

the drug re-importation provisions and existing law to determine whether or not the MEDS Act posed *"additional risks to the public's health and safety"*. In addition, the Office of the Assistant Secretary for Planning and Evaluation (OASPE) was asked to examine whether or not consumers would realize "significant" savings should the act was implemented[57].

On July 9, 2001, Mr. Thompson sent a letter to Senator Jeffords explaining that he would not implement the MEDS Act, stating[71] *"I do not believe we should sacrifice public safety for uncertain and speculative cost savings"*[f]

A study by the National Institute for Health Care Management Foundation found that prescription drug spending in the United States increased 17% in 2001, to over $154 billion. The increase in spending has been attributed to an increase in the number of people who use prescription drugs, people switching to more expensive medications, and drug prices rising above the rate of inflation[57].

In 2002, the Senate passed legislation that would permit the importation of a ninety-day supply of prescription drugs for personal use from Canada. This legislation, however, was not passed by the House of Representatives and did not become law.

Congress continued to consider bills that push for prescription drug pricing reform, with many legislators' campaigns heavily focused on prescription drug issues. Also, in 1999, the *International Prescription Drug Parity Act* was introduced in response to the alarmingly high cost of pharmaceuticals in the U.S., as compared to Mexico, Canada and other nations. This legislation was aimed at allowing importation of FDA approved drugs from other countries. The FDA was also reluctant to implement this legislation[17].

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f See HHS.GovARCHIVE, Secretary Thompson Determines That Safety Problems Make Drug Reimportation Unfeasible

Furthermore, the *Prescription Drug Fairness for Seniors Act* was introduced in response to studies that show drug manufacturers engage in price discrimination; charging seniors and others who buy their own prescription drugs more than twice as much as they charge their most favored customers, such as the federal government and large health maintenance organizations (HMOs). Also, the *Health Care Research and Development and Taxpayer Protection Act* was introduced to prevent taxpayers from being charged twice for the same drug. *The Pharmaceutical Market Access Act of 2003* was introduced to allow the importation of drugs from twenty-five industrialized countries including Canada, Australia, Japan, South Africa, and the European Union. However, none of these introduced bills have become law (H.R.2427 -- Pharmaceutical Market Access Act of 2003 (Referred in Senate - RFS), 2003).

The Pharmaceutical Market Access and Drug Safety Act, 2005 ("PMADS Act"), was also intended to amend the *Federal Food Drug and Cosmetics Act*, allowing pharmacies and prescription drug wholesalers in the U.S. to import FDA approved drugs from other countries like Canada, Japan, and European countries and also covered regulation of importation for personal use. However, opponents of this regulation claimed that its implementation will flood the U.S market with adulterated and dangerous medications from other countries (Pharmaceutical Market Access and Drug Safety Act, 2005).

President Obama's Affordable Care Act- focuses on providing health insurance to U.S citizens who are presently not insured. It is estimated that it would reduce the health care costs by 1.5% per year (Patient Protection and Affordable Care Act, 2009). The current administration is also in the struggle to legalize drug re-importation, promote the use of generics and to lift the ban on Medicare being able to negotiate drug prices-including those for the senior Part D program.

Pharmaceutical companies in the United States invest around $1 billion on research and discovery of New Chemical Entities (NCE), $500 million to set up manufacturing facility and an additional $300 million for market launch. However, the success ratio is very low. Only *1 in 10,000 molecules* will reach the market. Out of these only *1 in 4 marketed drugs is profitable.* Therefore, all successful drugs are marketed at high prices to recover the overall investment on R&D until the patent period expires. In most cases, differential pricing system has been adopted by pharmaceutical companies based on the nation's GDP and regulatory framework[58].

Despite the continuing legal impediments to parallel imports, re-importation has been a growing source of the pharmaceutical supply in the U.S due to increased personal trafficking and the proliferation of Internet purchases. By one estimate, parallel imports of prescription drugs from Canada amounted to $1.1 billion in 2004, or about 0.5% of the U.S. market[59].

Currently, the debate on drug re-importation practice continues to escalate although its status is still illegal. The legal status of re-importation may be misinterpreted by the consumers due to the ambiguous nature of different amendments and bills. A survey by IMS Health, Inc. in 2003 revealed that 45% of the respondents perceived re-importation practices to be legal and 33% were unsure[11]. These results clearly show most consumers' lack of awareness regarding the legality of drug re-importation or parallel importation practices.

While re-importation remains a controversial issue, these concerns do not seem to affect the growing number of Americans who chose to buy their prescription medications from across the border. Currently, the estimates available indicate that 1 to 10 million of Americans purchase drugs from Canada alone and spend more than $1.1 billion on these prescription drugs in 2003[59]. Survey results from various organizations reveal some interesting results. A national survey by researchers at Stony Brook University revealed that around 58% of the consumers perceive

Canadian drugs to be safe or somewhat safe and 68% think that the practice should be legalized[13]. According to a survey by the Kaiser Family Foundation (KFF), 63% of consumers support drug re-importation and believe that the federal government should make it easier for Americans to get access to Canadian drugs[14]. The major emphasis for legalizing the practice of re-importation in the US has been the cost savings it offers. However, based on the estimates by the Congressional Budget Office (CBO), enactment of the H.R. 2427 bill that allows re-importing drugs into the U.S. would reduce total prescription drug spending by only about 1% or $40 billion in the next decade[15].

The FDA has threatened legal action against state and local governments involved in importing drugs. However, federal agencies have refrained from actually prosecuting state officials for helping their residents obtain these medications. Instead, the FDA has met with state officials who are considering the importation to warn them about safety concerns and legal liability. According to the FDA, the strategy has succeeded in mid-western states such as Iowa and Washington State[16], which had explored the option but has chosen not to pursue it.

The FDA has not aggressively enforced the ban on prescription drug importation for two primary reasons:

- First, the customs and border inspectors who are on the front line of federal law enforcement are reluctant to deny elderly and needy Americans access to cheaper medications[60]; and
- Second, top FDA officials contend that inspecting every package at the border and in the mail is impossible because of the sheer volume. The Agency is already stretched thin in meeting anti-terrorism, homeland security objectives, and enforcing the major provisions

of the Food Drug and Cosmetic Act; leaving few human and technical resources for enforcing the ban on drug importation[60].

Although the FDA has not acted against state and local officials, legal action has been brought against private storefront pharmacies in the United States that help residents fill their prescriptions from international sources. For example, a federal judge found the storefront operations of Oklahoma-based Rx Depot and Nevada-based Rx of Canada in direct violation of the Federal Food, Drug, and Cosmetic Act and barred the companies from importing prescription drugs for sale in the United States. These pharmacies had been sending the U.S. prescriptions and credit card information to a co-operating pharmacy in Canada. After a Canadian doctor rewrote the prescriptions, the pharmacy shipped the drugs directly to customers[61].

In recent years, FDA has further revealed its disapproval of re-importation/parallel trade in drugs as being a serious health risk by responding to several internet drug sales[16]. This was evident in the following enforcement statistics reported by FDA in 2003 (Hubbard, 2003)[17]:

- 372 Internet drug criminal investigations; 90 involve domestic Internet pharmacies;
- 150 Internet-related drug arrests, 60 involve Internet pharmacies, 92 convictions, 26 convictions involve Internet pharmacy cases;
- 100 open Internet drug criminal investigations; 90 sites were under active review for possible regulatory or civil action;
- Nearly 200 cyber Warning Letters had been sent to domestic and foreign online sellers;
- 5 preliminary injunctions;
- 15 product seizures;
- 11 product recalls and the voluntary destruction of 18 illegal products[g].

[g] Hubbard WK, FDA, International Prescription Drug Parity. April 3, 2003, http://www.fda.gov/NewsEvents/Testimony/ucm161404.htm (Accessed Nov 14, 2013)

3.2. EUROPEAN UNION SCENARIO

The European Court of Justice (ECJ) has held that free circulation of goods takes precedence over protection of intellectual property rights (IPR). In Merck v Stephar[72] (187/80, 1981)[h]the European Court of Justice held that a patent holder marketing its product in two different member states cannot prevent arbitrage between the two local markets, despite differences in intellectual property protection in the two countries. Thus, exhaustion applies upon first sale anywhere in the EU. Moreover, varying degrees of price control across countries do not justify prevention of parallel imports from countries with more rigorous regulations to markets with less rigorous regulations, as found in Merck v Primecrown[73] (Joined cases C-267/95 and C-268/95, 1996)[i]. Furthermore, parallel importers have limited rights to use original trademarks in marketing their products as expressed in; BMS and Others v Paranova[74] (Joined cases C-427/93, C-429/93 and C-436/93., 1996)[j]. Finally, manufacturers cannot partition the single market by introducing a new variety in member states, which could have the effect of replacing market authorization for the prior variety, where its product is subject to competition from parallel imports, as expressed in Rhône-Poulenc Rorer Ltd v MCA[75] (Case C-94/98., 1999)[k]

However, exhaustion in the European Union has important limitations. Most importantly, it does not extend to countries outside the common market[76] (EMI v CBS, case C-51/75 and Silhouette v Hartlauer[77], (case C-355/96, 1998))[l]. Thus, the ECJ has established a principle of "community exhaustion" but rejected the idea of "international exhaustion". However, the principle of community exhaustion does not extend to cases where the goods are sold in a

[h] See EUR-Lex, Access to EU Law, Merck & Co. Inc. v Stephar BV; July 14, 1981;http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61980J0187(Accessed Nov 15, 2013)

[i] EUR, 61995J0267

[j] EUR, 61993CJ0427

[k] EUR, 61998CJ0094

[l] EUR, 61996CJ0355

member state under a compulsory license, as established in Pharmon v Hoechst[78] (Case 19/84., 1985)[m] .

A member State cannot demand fees from a parallel importer of pharmaceutical products unless they are levied according to criteria identical or comparable to criteria employed in determining fees on domestic pharmaceutical products. The ECJ enunciated this rule in Officer van Justitie v. J.A.W.M.J. Kortmann[72] (Case 32/80) in which it explained that excessive fees required of a parallel importer would amount to charges equivalent to customs duties. To summarize, the EU system essentially mandates free parallel imports within its territory, despite the existence of national intellectual property regimes and price controls, as long as the manufacturer has placed the good voluntarily on the market.

In an important modification of EC policy, the European Court of First Instance ruled in 2000 that the original manufacturers could impose supply quotas for foreign wholesalers so long as those quotas did not constitute contractual agreements prohibiting export of a product (Bayer AG v Commission of the European Communities[72], Case T-41/96, October 26, 2000). A literal interpretation of this ruling would be that it permits restraints on sales from manufacturers to licensed wholesalers but does not impede the ability of parallel importers to acquire drugs and ship them abroad. It's a fine legal line, but there are plenty of "lawyers telling drug companies this is how to do it," says one European Union official[8]. However, evidence suggests that manufacturers do limit supplies available for licensees within the EU that could escape into other markets in the region[62]. As a consequence, parallel traders may encounter limits on the quantities available for their activity[9].

[m] See EUR, 61984CJ0019

Catherine Arnold, an analyst covering European drug companies for Sanford C. Bernstein in New York believes the practice of imposing quotas to wholesalers has become common, but she doesn't see this as an absolute cure, although she thinks it will reduce some of the [profit] pressure[8]. Wyeth, of Madison, N.J., is among the companies trying the approach as well. A company spokesman says it has implemented an "*inventory management system*" for one product to ensure its availability and reduce costs. The policy, he says, "*is pro-competitive*" and complies with European laws[8].

One problem feared from the implementation of the "quota approach" is that shortages may occur in the countries which have low prices if the wholesalers and distributors continue to supply parallel traders from high price countries[63]. Grounds for a pharmaceutical manufacturer or member state to prevent parallel trade can occur when:

- The manufacturer holding a patent on the drug has been required by the law of a Member State to grant a license to another party and that license contains a no-export clause[79] (Pharmon B. v. Hoechst AG, 1985)[n]
- The physician-patient relationship would be adversely affected by the customary application of the "exhaustion or rights" doctrine[80] (Regina v. Pharmaceutical Society of Great Britain, 1889)[o]
- The pharmaceutical manufacturer's trademark has been infringed when the subsequent distribution of the drug takes place, e.g., by repackaging in such a way as to obscure the trademark[81] (Centrafarm B.V. v. American Home Products Corp., 1979)[p].

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[n] See Pharmon v. Hoechst AG 1985] 3 CMLR 775

[o] See Regina v. Pharmaceutical Society of Great Britain, (1989) E.C.R, (1989)2 C.M.L.R. 751.

[p] See Centrafarm B.V. v. American Home Products Corp., (1978) E.C.R. 1823, (1979)1 C.M.L.R.326.

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), parallel trade was estimated to amount to € 5.2 Billion Euros in 2009 and € 5.0 Billion (value at ex-factory prices) in 2011[64]. A Wall Street Journal report in April, 2002, also indicated that industry estimates suggested that lost sales in the EU amounted to some $3 billion per year[12]. The shares of some EU countries' 1999 pharmaceutical sales that were imported from countries with lower wholesale prices are given in Table 2 below:

Table 2: Percentage of Pharmaceutical Sales from Parallel Imports in the EU
Source[64]: The European Federation of Pharmaceutical Industries and Associations (EFPIA)[q]

COUNTRY	SHARE OF SALES FROM PI (%), 1999	SHARE OF SALES FROM PI (%), 2011
U.K	10.1	7.8
Netherlands	10.0	13.5
Denmark	9.9	23.8
Sweden	7.6	14.8
Norway	6.6	2.6
Germany	2.3	10.1

Great Britain (UK), Netherlands, Denmark, Germany and Switzerland are mostly regarded as high-price countries for pharmaceuticals with the most importation of parallel traded drugs; while Greece, Spain, Portugal and Italy are considered low-price countries and are the main exporters for parallel traded drugs[64].

[q] European Federation of Pharmaceutical Industries and Associations (EFPIA), The Pharmaceutical Industry in Figures, 2013; http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf (Accessed Nov 12,2013)

3.3. SOUTH AFRICAN SCENARIO

In South Africa, the Department of Health headed by the Health Minister, who is appointed by the president of the Republic, is mandated by the constitution to improve health status through the prevention of illnesses and the promotion of healthy lifestyles. Also, the Department of Health is striving to consistently improve the healthcare delivery system by focusing on access, equity, efficiency, quality, and sustainability. This is an umbrella department just like the Department of Health and Human Services (HHS) in the United States with other offices or agencies under it[65].

An agency under the Department of Health, particularly involved with pharmaceuticals in South Africa, is the *Medicines Control Council (MCC).* The Medicines Control Council is a statutory body that was established in terms of the Medicines and Related Substances Control Act, 1965 (Act No. 101 Of 1965) to oversee the regulation of medicines in South Africa[66]. Its main purpose was to safeguard and protect the public by making sure that all medicines that are sold and used in South Africa were safe, therapeutically effective and consistently meet acceptable standards of quality. The responsibilities of the MCC are synonymous to those of the *Food and Drug Administration* in the United States or the *European Medicines Association* in Europe.

The MCC is mandated to do the following[66]:

- Advise the minister on any matter referred by the minister or arise from the application of the Act;
- Keep the medicines register;
- Register new medicines;
- Amend entries in the register;
- Prohibit the sale of medicines not registered;

- Transfer certificates of registration;
- Cancel the registration of medicines;
- Approve medicine labels and advertisements; and
- Authorize the sale of unregistered medicine for certain purposes.

The minister can determine and appoint members of the Council (not more than 24) as necessary. The minister designates one of the council members as chairperson and another as vice-chairperson. The Council may appoint an executive committee from among its members. The executive committee may (subject to directions of the Council) exercise all powers and perform all the functions of the Council between meetings of the Council.

The Health Minister has the authority to allow for the use of compulsory licenses and parallel importation. These are all provisions of the TRIPS agreement but many member states of the WTO, such as the U.S., have protested over implementation of these laws. The passage in December 1997 of the *Amendments to the South African Medicines and Related Substances Control Amendment Act No. 101 of 1965*[37], gave way for the use of parallel importation and use of compulsory licenses. The passage of this law was met by years of legal battles and negotiations between various pharmaceutical companies and governments. The main section of the act that was being protested was Section 15C which states as follows:

"The minister may prescribe conditions for the supply of more affordable medicines in certain circumstances so as to protect the health of the public, and in particular may-

> ***(a)*** *Not withstanding anything to the contrary contained in the Patents Act, 1978 (Act No. 57 of 1978), determine that the rights with regard to any medicine under a patent granted in the Republic shall not extend to acts in respect of such medicine which has been put onto the market by the owner of the medicine, or with his or her consent;*

(b) *Prescribe the conditions on which any medicine which is identical in composition, meets the same quality standard and is intended to have the same proprietary name as that of another medicine already registered in the Republic, but which is imported by a person other than the person who is the holder of the registration certificate of the medicine already registered and which originates from any site of manufacture of the original manufacturer as approved by the council in the prescribed manner, may be imported:*

(c) *Prescribe the registration procedure for, as well as the use of, the medicine referred to in paragraph (b).”* [37]

From the introductory part of section 15C, the authority given to the Minister (of Health) is expressly stated to prescribe conditions for the supply of more affordable medicines in certain circumstances, to protect the health of the public. The provisions of section 15C were interpreted by the pharmaceutical industry as empowering the Minister to be in a position to override patent and trademark rights at any time by mere administrative action[27]. Those opposed to the law viewed it as being contrary to South Africa's international obligations in terms of the TRIPS Agreement, namely that patented inventions in all fields of technology are to be given full patent protection, subject only to the limitations as set out in TRIPS itself[20].

The TRIPS agreement provided limitations or the so called *Flexibilities* under which the exclusive rights of a patent could be waived. These were outlined mainly in Article 31 as follows[50]:

- Use by third parties must be considered on individual merit;
- Efforts must first be made to obtain authorization from the patentee on reasonable commercial terms;

- The authorized use will be to supply predominantly the domestic market;
- Adequate remuneration is to be paid to the patentee; and
- The legal validity of the decision must be subject to judicial review

In terms of parallel importation, the TRIPS agreement leaves the decision in the hands of individual governments but insist that it be done in a way consistent with other provisions of the TRIPS agreement.

Many pharmaceutical companies and western governments have shown high opposition to how developing countries handle parallel importation and compulsory licensing. They believe that this will give the room for patent infringement or parallel traders and generic manufacturers free-riding on their research and development efforts, as well as their investment in marketing the drug[7]. Such strong opposition in the global market could directly or indirectly affect the way countries trade with each other. It would be more likely to see situations in which countries that do not implement parallel trade or, do not want to do business with countries which do parallel trading. *Fix The Patent Laws* is a non-profit organization involved with access to essential medicines and patents in South Africa. They reported in January 2012 that the US and the EU were already vigorously pushing countries not to use their TRIPS flexibilities through trade agreements, IP conferences, and even by providing training for judges that are ruling on patent challenges in developing countries. They said that this was not surprising, given that, in 2008, of 2,442 patents granted in South Africa, 1,988 patents were from American and European companies, whereas only 16 were from South African companies[22].

The high number of patents being issued can be attributed to the less stringent and highly flexible patent laws in the country. Many companies have abused the patent system by applying for more than one patent for a single product in a process called "*Ever Greening*". By doing so,

their monopolistic exclusivity for the sale and distribution of brand name drugs is being unfairly extended making it difficult for generic competitors to start manufacturing generics for such drugs.

Even with the global trading difficulties at stake, the South African government passed the *Medicines and Related Substance Control Amendment Act (MRSCA) of 1997*, which provided for parallel importation and compulsory licenses[50]. The premise of the law was that imported drugs were very expensive and were not affordable to the local population who had the need for some essential medicines. Available data at the time of passage of the law showed that the prices set by pharmaceutical companies for imported drugs sold in South Africa were extremely high compared to the prices in other markets like India or the UK. Enforcing the new regulations will have given consumers more price options to choose from. The passage of the new regulation caused uproar of anger among major pharmaceutical companies who filed lawsuits against the South African Government. About 39 multinational pharmaceutical companies and the *Pharmaceutical Manufacturers' Association* of South Africa (PMA) together filed the lawsuit against the South African government[19].

The Pharmaceutical Research and Manufacturers of America (PhRMA), a trade group representing the U.S. pharmaceutical industry, managed to convince the U.S. government that the issue was sufficiently important to warrant putting pressure on South Africa to repeal the contested legislative measures[35]. As a result, Section 15C was put on the agenda for high-level bilateral trade talks between the United States and South Africa.

James Joseph, at that time the U.S. Ambassador to South Africa, wrote a letter to representatives of the South African government, strongly urging South Africa to alter Section 15C and stating, *"My Government opposes the notion of parallel imports of patented products*

anywhere in the world"[23]. Upon a determination by the U.S. Trade Representative (USTR) that South Africa lacked adequate intellectual property protection to the extent that merited bilateral attention, South Africa was put on the Special 301 "watch list" both in 1998 and 1999[26]. By being on the U.S Watch List the Republic of South Africa was one step closer to the imposition of unilateral trade sanctions by the United States[24]. In February 1998, forty-seven members of Congress sent a letter to the USTR calling for a response to the MRSCA, stating that Section 15C permitted parallel importation and allowed for the *"administrative expropriation of patented technology,"* both of which would violate the TRIPS Agreement. In July 1998, pending sufficient progress on intellectual property rights protection in South Africa, the USTR used its discretion to withhold trade benefits for a range of South African products that had previously been approved under the Generalized System of Preferences (GSP) program[24].

A provision inserted into an omnibus appropriations act in October 1998 conditioned U.S. development assistance to South Africa based on the Secretary of State's written report on the steps being taken by the U.S. government to work with South Africa implementation of Section 15C[25]. The Department of State submitted this report in February 1999, stating that all relevant agencies of the U.S. government *"have been engaged in an assiduous, concerted campaign"* to persuade South Africa to withdraw or modify Section 15C, which the State Department believed was "*inconsistent*" with South Africa's obligations and commitments under TRIPS[26]. Despite this assessment, which mirrored statements made by PhRMA[27], the U.S. did not bring a WTO case against South Africa.

During 1999, the high stakes of the controversy between the United States and South Africa attracted a great deal of attention in the media, which ultimately led to a shift in the U.S. Administration's policy towards South Africa. Vice President Al Gore, as co-chairman of the

United States/South Africa Binational Commission (established to improve communication and cooperation between the two countries), had been actively involved in pressuring South Africa to give in to the demands of the pharmaceutical industry. This seems to have been particularly important, as he became one of the main targets of AIDS activists who had long urged the U.S. government to change its policy towards South Africa. AIDS activists – realizing that the 2000 Presidential campaign made Vice President Gore particularly vulnerable to negative publicity – disrupted a number of his campaign events to shouting "*Gore's greed kills*", including the event where he announced that he would be running for President[67].

Gore was openly attacked for engaging in an astonishing array of bullying tactics to prevent South Africa from implementing policies, legally under international trade rules that are designed to expand access to HIV/AIDS drugs. These actions further increased public awareness of the conflict between the pharmaceutical industry and developing countries. Meanwhile, Rep. Jesse Jackson, Jr., (D-Ill.) had introduced the *HOPE for Africa Bill* that contained a provision drafted by AIDS activists that called upon the U.S. government not to "*seek, through negotiation or otherwise, the revocation or revisions of any sub-Saharan African intellectual property or competition law or policy that is designed to promote access to pharmaceuticals or other medical technologies*" and that complies with TRIPS[28].

In June 1999, Gore replied to a letter sent to him by the Chairman of the Congressional Black Caucus, James E. Clyburn, inquiring into the issue of affordable medicines for South Africa. In his letter, Gore indicated that U.S. policy may change by saying that he supported South Africa in its efforts to provide AIDS drugs at reduced prices through compulsory licensing and parallel importing, as long as they were carried out in a manner consistent with international agreements.

In July 1999, the House Committee on Government Reform, Sub-committee on Criminal Justice, Human Resources and Drug Policy, held hearings on the role of the United States in combating the global HIV/AIDS epidemic. For the first time, consumer advocates were invited to express their views on U.S. foreign trade policy regarding patent protection and public health.

In September 1999, the USTR and the South African government announced that the controversy was resolved and that the U.S. government would no longer pressure South Africa. In return, South Africa promised to adhere to its obligations under TRIPS[29]. Consequently, South Africa was taken off the *Special 301 Watch List*. In a speech given at the 1999 WTO Ministerial Conference in Seattle, President Clinton made it clear that the United States would adjust its trade policies to enable poor countries, such as South Africa, to gain access to essential medicines. On May 10, 2000, he formally ordered thus "*the United States shall not seek, through negotiation or otherwise, the revocation or revision of any intellectual property law or policy of a beneficiary sub-Saharan African country, that regulates HIV/AIDS pharmaceuticals or medical technologies*" and prohibited the U.S. Government from taking action pursuant to Section 301 with respect to laws or policies that promote access to HIV/AIDS pharmaceuticals or medical technologies and that provide adequate and effective intellectual property protection consistent with TRIPS[30]. In February 2001, the Bush Administration re-affirmed that the United States would not raise any objection if WTO Members take steps to address major health crises *"availed themselves of the flexibility"* afforded by TRIPS[31].

In April 2001, the pharmaceutical companies under tremendous international pressure and negative publicity, dropped their law suit and hence enabled the government to fully enforce its legislation and allow for the importation of Discounted Pharmaceuticals through Parallel Importation. They also agreed to cover the South African government's legal expenses in the face

of what had been described as a public relations nightmare[32]. Advocates for the use of parallel importation and compulsory licenses praised this move as one which puts treatment before profits[33].

The talks behind the scenes leading to the withdrawal involved Kofi Annan, the then Secretary General of the United Nations, who was contacted by Jean-Pierre Garnier, the CEO of GlaxoSmithKline, on behalf of the largest pharmaceutical companies to broker a deal with Thabo Mbeki, the then President of South Africa. Both the European Union and the WHO supported South Africa's position. As part of the deal, South Africa reiterated its pledge to comply with TRIPS when implementing the amendments to the MRSCA and invited the pharmaceutical industry to help draft future regulations[68]. The withdrawal of the lawsuit was welcomed by most commentators, including Mike Moore, the Director General of the WTO, who said that the "settlement" was a "*win-win situation*" for all stakeholders[r]. With respect to price reductions, however, the new South African Minister of Health, Manto Tshabalala-Msimang, cautioned that the withdrawal of the lawsuit would not mean that South Africa would provide low-cost drugs immediately, because "*the country's medical infrastructure is insufficient*"[33]. However, in any event, the controversial provisions of the amended MRSCA could finally take effect.

In October 2004, the CEO of Novartis, Dr. Daniel Vasella, became the new president of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), replacing the CEO of Merck, Ray Gilmartin. On this occasion, Dr. Vasella gave an interview to a Swiss newspaper, discussing the question of how the pharmaceutical industry could improve its declining reputation[34]. When asked what went wrong in the industry over the past twenty-five years, Vasella responded, "*The conflict was about who would get access to the first effective*

[r] WTO, Moore welcomes news of settlement of South Africa drug lawsuit[82], April 19, 2001; http://www.wto.org/english/news_e/spmm_e/spmm58_e.htm

anti-AIDS-drug and how much the company would be allowed to charge for life-saving treatment. In this discussion, the pharmaceutical companies took a very traditional position. This was a mistake." However, Vasella rejected the idea that it was patent protection that was at the core of the issue by saying, "*The debate about patents emerged under the impression that patents would prevent access to life-saving medicines for poor patients. People forgot that patents are a fundamental condition for obtaining the financial means to pay for research and development. But again – instead of developing timely alternatives with partners, the industry behaved defensively."*

Due to South Africa's pledge to ensure that the MRSCA was in full compliance with the TRIPS agreement, they provided guidelines to the public on how to obtain a parallel import permit. As such, the government of South Africa could be held liable should they fail in their responsibility to prevent patent infringement[68].

The objectives of the 1997 MRSCA Amendment Act, were to amend the Principal Act (*MRSCA 101 of 1965)*, to make further provision for the prohibition of the sale of medicines which are subject to registration and are not registered:

- To provide procedures that will expedite the registration of essential medicines;
- To provide for the re-evaluation of all medicines after five years;
- To provide for measures for the supply of more affordable medicines in certain circumstances;
- To provide for the licensing of certain persons to compound, dispense or manufacture medicines; and
- To provide for generic substitution of prescribed medications.

These objectives are accepted to be legitimate and necessary in providing the needed machinery to implement government policy, such as to ensure that the entire population has access to affordable health care and fairly priced medicinal products. However, in creating a legislative and regulatory framework to achieve these objectives, it is important that certain principles be adhered to, namely those principles contained in, recognized and enforced by, national and international intellectual property laws and treaties. It is in this context that serious questions have been raised regarding the Medicines Amendment Act.

Furthermore, Regulation 7 of the MRSCA sets out the requirements and conditions to be met in order to obtain a parallel importation permit[36]. Under the Act, a medicine under patent in the Republic (South Africa) could be imported into and disposed of in the Republic if such medicine had been put onto the market outside the Republic by or with the consent of the patent holder of the medicine in the Republic subject to the provisions of the Act and other established Regulations. The holder of a *certificate of registration* for a medicine in the Republic was not entitled, on account of such registration, to prevent the parallel importation of such medicine into the Republic and the disposal thereof within the Republic. A person desiring to parallel import a medicine into the Republic had to apply to the Minister of Health for a license to parallel import such a medicine.

In the application to the Minister, the potential parallel importer had to include the price at which the medicine was being sold in the Republic by the patentee. They also had to include the price at which they intend to sell the medicine. Furthermore, they needed to include a declaration that the medicine to be parallel imported is a medicine under patent in the Republic. More information could be requested by the Minister on an individual basis[36].

After a license to parallel import a medicine is issued to the parallel importer, they could now apply to the Medicine Control Council (MCC) to register the medicine. The parallel importer had to provide sufficient information to the MCC so the agency could determine the safety and effectiveness of the parallel imported drug. The MCC also ensured that the parallel importer had a domestic storage area with pre-established quality measures in place. The Council was to determine the fee for every application and determine a reasonable timeframe for a complete review. The parallel importer of a drug into the Republic was entitled to use the South African name and trademark of such medicine, even though the medicine was marketed outside the Republic under a different name or trademark. The new name and trademark had to be approved by the Council[36].

After a complete review of an application by the Council, they could either approve the registration of such medicine as a parallel imported medicine or deny such registration. A person issued a license to parallel import a medicine in terms of the Act had within 14 days after such medicine had been registered, to inform the holder of a certificate of registration in the Republic of such fact. The registrar keeps a separate register of medicines registered in terms of the ACT. Such registration is published in the Gazette (Online Government Registry), with the contact details of the parallel importer, and any other information as the Council may determine. A license issued in terms of the parallel import regulation was valid for a period not exceeding one year and could be renewed if an application for renewal was approved by the Minister.

The parallel importer was not allowed to sell or dispose any other drugs unless they were registered in the country. They were also prohibited from purchasing drugs from unauthorized wholesalers or distributors in the exporting countries. In case of any changes in the initial conditions under which the registration was approved, parallel importer had to inform the council

within 30 days. Quality and emergency action plans had to be pre-specified and all employees well trained. There were designated ports of entry for all imported drugs. These ports included: Cape Town Airport or harbour; Port Elizabeth Airport or harbour; Durban Airport or harbour; and Johannesburg international airport.

The Minister of Health may, on good cause shown, revoke the license to parallel import a medicine. The Medicine Control Council may, on good cause shown, revoke the registration of a parallel imported medicine.

With the terms of parallel importation of drugs being clearly stated, parallel traders of pharmaceuticals would be expected to take advantage of global market segmentation and supply essential medicines to the South African population. Also, given the high prices of pharmaceuticals in South Africa, more than most other countries and the high demand for essential drugs like Anti-Retro-Virals (ARV) for HIV; one will expect that parallel trade of pharmaceuticals should be a booming business.

CHAPTER 4

METHODOLOGY

The objective of this study was to determine the regulatory impact, socio-economic impact, and the effect on drug quality due to parallel importation of drugs into South Africa. This research was prompted by the high prices of pharmaceuticals in developing countries and the debate over South Africa's passage of its Medicines and Related Substance Control Amendment Act of 1997, which gave way for the use of parallel importation and the use of compulsory licenses.

This study did not begin until Institutional Review Board (IRB) approval was received from the university to conduct this research. The approval was granted on June 27, 2013, and the IRB ID under which this approval was granted is *STUDY00000017*.

This retrospective study involved researching existing data and documents publicly available regarding parallel importation of human drugs. The goal was to look at data before and after implementation of parallel importation regulations and see what significant changes exist. Since the parallel importation regulations were passed in 1997, indicators from at least 5 years before passage of the law and at least 5 years after the passage of the law were used for our analysis. The five year period was adequate to provide a sample size that could be used to test for significant differences of the various indicators using the statistical analysis of choice. Nine indicators were used in the statistical analysis: Gross National Income (GNI) per Capital, Import and Export of Goods and Services, Import Prices, Education, Vaccination, etc. These indicators gave real time data which could be analyzed to supplement responses from the study

questionnaire. Data for the indicators were obtained from reliable sources like The World Bank Database, The World Health Organization, United Nations Educational Scientific and Cultural Organization (UNESCO).

A *PROC STEPDISC in SAS v 9.2* was used for the technique stepwise Discriminant Analysis. It is a method that selects the most significant dependent variables, in ranking order, that explain differences between the two periods (before 1997 and after 1997). The procedure stepwise Discriminant Analysis (DA) searches step by step which dependent variable had a significant change from 1st period (before the law passed) to 2nd period (after the law passed). It selects the first most correlated variable with a period, removes that variance in the grouping variable period. It then adds the next most correlated and continues until the change in canonical correlation is not significant. The correlation is measured by the *Partial Rsquare*. The Partial Rsquare decreases from step 1 to step 2. In other words, it looks for which variable had the most power to discriminate (differentiate), had the largest difference between the 2 periods. The p-value related to *Average Squared Canonical Correlation (ASCC)* gives the significance of the correlation. The analysis here will provide the indicator with the highest effect due to the passage of the parallel import regulations.

Further comparison was conducted between the 1st period (1990 – 1995) before the law was passed, and the 2nd period (2000-2005) after the law was passed. Two-sample t-test was performed for each dependent variable (Degree of Freedom, D.F= 4). This is an appropriate test because the two samples for the two periods are independent of each other (separate samples, not related). The data can be grouped into independent categories which reference data collected before and after 1997. The independent variable, here identified as Passage of Parallel Import Regulations can be represented as a categorical variable with two levels: before and after passage

of the law. Further analysis of the distribution of scores showed that the data was approximately normally distributed. Finally the Levene's test of homogeneity of variances was used to show that there was homogeneity of variances for each of the indicators under study. However, when many tests are performed simultaneously on a single data set, the printed P-values (Raw P-values) can be misleading. To control for this misleading effect in the 2-sample t-test, the Bonferroni Method and the Bootstrap method was used[46]. The probability of a false alarm for one test is 0.05 (the level of significance, α). To run nine tests, the probability that one of these nine tests is a false alarm is $1- (1-.05)^9 = 0 .37$. The type-I error rate here is inflated. To keep the family-wise alpha at 0.05 level, the following two methods of adjusting the p-values were selected:

I. BONFERRONI METHOD: Here the new cutoff level would be 0.05/9 =0.006 (raw P-value). A result is significant if it is less than or equal to this new cutoff. If the observed p-value is greater than 0.006 then there is no significant effect. As the number of tests increase, it becomes a very conservative method (more likely to miss a difference that is actually there). This characteristic, in turn, increases the risk of generating false negatives (type II errors) but controls type I errors.

II. BOOTSTRAP METHOD: Here the data are resampled with replacement n =100 times. The adjusted p-value is calculated from the p-value computed for each sample. It is the proportion of p-values from the n samples that were smaller than the raw p-value based on the original data. It incorporates all sources of correlation and distributional characteristics. This test is most often used in deriving robust estimates of standard errors and confidence intervals of a population parameter like a mean, median, proportion, odds ratio, correlation coefficient or regression coefficient.

Note that both methods can be used for any type of variables regardless of its dependency or conditions. In practice, the cut-off level of 0.05 would be applied to the adjusted p-value. The procedure PROC *MULTTEST in SAS v 9.2* was used to adjust the p-values for multiple comparisons.

Furthermore, *Creative Research Systems*[42], which specializes in survey software solutions, was used in designing the study questionnaire. Creative Research Systems have been providing questionnaire validation services for more than 30 years. The main approach here was to keep the questionnaire short and simple. Participants also had the option not to answer a question (e.g. Not Applicable). The first question of the questionnaire was a screening question which asked for the respondent's background and experience as related to parallel import regulations. Any respondent who did not have a regulatory background related to parallel importation was disqualified from taking part in the study. Two basic types of questions were used: Multiple Choice and Text Open End. After the questionnaire had been designed, it was pre-tested by sending it to some respondents in our target population. When the questionnaire was completed, the questions were further adjusted to get the right interpretation needed to answer the study questions. Also, tools in *Survey Monkey*, an online survey validation system were used to ensure further that the questionnaire design was up to standard.

Potential participants for this study were searched from Internet sources including LinkedIn, South African Department of Health website, published literature, and referrals from some potential respondents who had been contacted to take part in this study. In order for someone to participate in this study, they had to be knowledgeable about parallel importation or have regulatory experience either with government, industry, private sector or academia. They also had to be at least 18 years and older. The knowledge and background for most of the

respondents were readily available on LinkedIn. Three years or higher of regulatory experience was required. In cases where potential respondents were identified through a company website, their position had to be related to regulatory affairs, and they indicated that they understood the parallel import regulations in South Africa. After the backgrounds of these respondents were deemed to be compatible with the purpose of this research, emails were sent to invite them to be a part of the study. Those who wanted to be part of the study voluntarily completed the questionnaire after reading the subject informed consent and other study materials.

According to the Regulatory Affairs professional society (RAPS), there are about 10,000 active regulatory affairs professionals worldwide who come from various sectors including government, industry, and academia. Brazil, which is about 4 times the population of South Africa, has about 574 regulatory affairs members while Mexico, which has a population double the size of South Africa, has 239 members. Both Brazil and Mexico are emerging markets just like South Africa. The number of members in the Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA), which is an equivalence of RAPS in South Africa, had an estimated 176 members in fiscal year 2012. The average of these three numbers provided an estimated regulatory affairs professional population in South Africa of about 146. Using the Creative Research System's Sample Size and Confidence Interval calculation[42], the sample size of 10 at the 95% Confidence Level was determined. The 10 respondents chosen for this study were representative of the target population (146) and did supplement more detailed data from the background data analysis. More than 150 potential candidates were contacted, and 10 valid responses were obtained. The main reason for the low response rate was that most of the invitations to enroll in the study were unsolicited. Most people also are reluctant to complete questionnaires compared to say a 10 minutes face-to-face interview. The response rate might

have been greater with a face-to-face interview but because this study had limited resources, and the respondents were in South Africa, the use of a questionnaire was the best other option.

The questions in the questionnaire were focused on three areas: *Regulatory implications, Socio-economic impact, and Quality of human drugs***.** After it became apparent from the study questionnaire responses that parallel importations had not been put into practice in South Africa, the underlying reason for this became of interest in this research. Questions were then re-phrased, and participants contacted again. *The World Bank database (World DataBank)* was a rich source of specific data of indicators associated with socio-economic impact, which could be related to the use of parallel imports. The *World Bank* has been collecting such data for years for different countries and from their database, trends that occur over the years could be determined.

Socio-economic impact was evaluated by looking at the general trends regarding the South African population, not just for the respondents. This involved evaluating the impact on indicators such as: education, income, life expectancy, HIV prevalence, etc., prior to and after the passage of parallel importation regulations. An increase in socio-economic status comes with increased literacy rates, increased income levels and better standards of living. Furthermore, regarding the quality of human drugs, importation or manufacturing of counterfeit or low quality drugs as a result of the passage of parallel importation regulations, which could have provided safety and efficacy concerns to the public, was evaluated. Finally, regarding regulatory implications, the ease of importing and exporting drugs into the Republic was evaluated. Also, of importance was how industry and other private organizations used the parallel import regulation.

CHAPTER 5

RESEARCH DATA

Part of the research data was obtained from the World DataBank. This is a reliable source of data that provides specific information about the socio-economic conditions of various nations as well as some of their peculiar indicators over the years. In this chapter data used in the statistical analysis to test significance of the passage of parallel import regulations will be presented. Some of the available data are given below:

5.1. THE GROSS NATIONAL INCOME (GNI) PER CAPITA

The Gross National Income (GNI) per capita is the dollar value of a country's final income in a year, divided by its population. It reflects the average income of a country's citizens. Knowing a country's GNI per capita is a good first step toward understanding the country's economic strengths and needs, as well as the general standard of living enjoyed by the average citizen. A country's GNI per capita tends to be closely linked with other indicators that measure the social, economic, and environmental well-being of the country and its people. For example, generally people living in countries with higher GNI per capita tend to have longer life expectancies, higher literacy rates, better access to safe water, and lower infant mortality rates.

Table 3: Gross National Income (GNI) per Capita for South Africa
Source[21]: World DataBank[§]

YEAR	1990	1993	1995	1997	2000	2003	2005	2006
GNI per Capita, PPP (Current International $)	5540	5610	5980	6330	6620	7320	8420	9080

[§] World DataBank, World Development Indicators, 1990-2006, http://databank.worldbank.org/data/views/reports/tableview.aspx (Accessed Nov 13, 2013)[21]

5.2. LIFE EXPECTANCY AT BIRTH

This is the average number of years to be lived by a group of people born in the same year, if mortality at each age remains constant in the future. Life expectancy at birth is also a measure of overall quality of life in a country and summarizes the mortality at all ages. It can also be thought of as indicating the potential return on investment in human capital and is necessary for the calculation of various actuarial measures[21]. According to the Central Intelligence Agency (CIA), the life expectancy at birth for the United States is 78.62 while that for South Africa is 48.48 as estimated for 2013[45].

Table 4: Life Expectancy, South Africa
Source[21]: World DataBank[t]

YEAR	1990	1993	1995	1997	2000	2003	2005	2006
LIFE EXPECTANCY AT BIRTH, TOTAL (YEARS)	62	61	60	58	55	52	51	51

5.3. SCHOOL ENROLLMENT, SECONDARY (% GROSS)

The data here represents the percentage of people that enrolled into secondary school relative to the total population. Secondary school in South Africa is almost equivalent to high school (Grades 9-12) in the United States. Secondary school enrollment increases with high socio-economic status and will decrease if socio-economic status decreases[21]. Table 5 below shows secondary school enrollment between 1990 and 2004.

[t] World DataBank,1990-2006

Table 5: Secondary School Enrollment, South Africa
Source[21]: World DataBank[u]

YEAR	1990	1991	1994	1998	2000	2001	2004
SECONDARY SCHOOL ENROLLMENT AS % THE GROSS POPULATION	66	70	80	90	85	86	91

5.4. IMMUNIZATION TO MEASLES

Here the administration of vaccines to fortify an individual's immune system against a disease-causing agent or immunogen was the main focus. Such data is a good indicator for the availability of vaccines. This data was obtained from the World DataBank.

Table 6: Immunization to Measles, South Africa
Source[21]: World Databank[v]

YEAR	1990	1993	1995	1997	2000	2003	2005
IMMUNIZATION, MEASLES (% CHILDREN AGES 12-23 MONTHS)	79.0	85.0	76.0	82.0	72.0	62.0	63.0

[u] World DataBank, 1990-1994
[v] World DataBank, 1990-1995

5.5. PREVALENCE OF HIV

This is related to the percentage of people living with HIV, the virus which causes AIDS. The high prevalence of HIV was one of the reasons why the South African government passed the 1997 MRSCA. It will be important to see how the availability of ARVs has changed relative to the HIV prevalence rate and the mechanisms used to distribute new supplies to consumers. It will be important to determine if there is a significant difference in data before 1997 and after 1997.

Table 7: Prevalence of HIV, South Africa
Source[21]: World DataBank[w]

YEAR	1990	1993	1995	1997	2000	2003	2005	2009
PREVALENCE OF HIV, TOTAL (% OF POPULATION AGES 15-49)	1	2	5	9	15	17	17	17

5.6. EXPORT AND IMPORT OF GOODS AND SERVICES

This data would be used to evaluate the significant differences of what quantity of goods and services entered and left the country. All mechanisms of import and export are included in this summary. This could be a good indicator of bilateral trade relations with other countries. A decrease in values could be expected if trade relations were strained due to intellectual property violation concerns together with other factors. Furthermore, if domestic production continued to increase, then an increase in exports would be expected. Table 8 below gives us import and export values between 1990 and 2006. Analysis of import and export data will be used to determine the effect on regulation of pharmaceuticals before and after 1997.

[w] World DataBank, 1990-2009 (Accessed October 22,2013)

Table 8: Export and Import of Goods and Services, South Africa
Source[21]: World DataBank[x]

YEAR	1990	1993	1995	1997	2000	2003	2005	2006
IMPORT OF GOODS AND SERVICES(% OF GDP)	19	18	22	23	25	26	28	32
EXPORTS OF GOODS AND SERVICES(% OF GDP)	24	22	23	25	28	28	27	30

5.7. HIGH TECHNOLOGY EXPORTS

High technology trade is defined as exports and imports of products of the Standard International Trade Classification (SITC – Rev. 3). This list, based on the Organization for Economic Co-operation and Development's (OECD) definition, contains technical products of which the manufacturing involved a high intensity of R&D. For pharmaceuticals this includes:

- 5413 = Antibiotics
- 5415 = Hormones and their derivatives
- 5416 = Glycosides, glands, antisera, vaccines
- 5421 = Medicaments containing antibiotics or derivatives thereof
- 5422 = Medicaments containing hormones or other products of heading 5415

[x] World DataBank, 1990-2006 (Accessed October 22,2013)

Scientific Instrumentation (Medical Devices), chemicals and other raw materials also makeup part of high tech products.

Advocates for parallel importation in developing countries supported its provision in the TRIPS agreement because, they believed that cash flow of high tech products was greater from the developing nations when compared to developed nations[22]. According to one study, the amount of high tech exports has increased in the developing countries from 8% in 1988 to about 23% in 1997[38]. This increase has been country specific and not generalized. Developing countries like Singapore, Malaysia or Korea, have seen an increase in their high tech exports. Table 9 below gives us data of high-tech exports between 1992 and 2009.

Table 9: High Tech Exports, South Africa
Source[21]: World DataBank[y]

YEAR	1992	1994	1995	1997	2002	2004	2006	2009
HIGH TECH EXPORTS (% MANUFACTURED EXPORTS)	7	5	6	8	5	6	6	5

5.8 IMPORT PRICES

Import prices in South Africa are reported by the South African Reserve Bank. In South Africa, import prices correspond to the rate of change in the prices of goods and services purchased by residents of that country from, and supplied by, foreign sellers. It would be important to determine the effect of the passage of parallel import regulations on import prices. Table 10 provides import prices from 1990 to 2005.

[y] World DataBank, 1990-2009

Table 10: Import Prices, South Africa
SOURCE[83]: WWW.TRADINGECONOMICS.COM[z]

YEAR	1990	1993	1995	1997	2000	2003	2005
IMPORT PRICE INDEX POINTS	32.2	39.3	45.8	53.6	81.7	91.9	102.2

5.9. QUESTIONNAIRE RESPONSES

In total, 10 participants completed and returned the questionnaire sent to among more than 150 potential candidates contacted. The response rate was low mainly due to the medium of conducting this survey and also because invitations sent to potential respondents were unsolicited. However, using Creative Research Systems' sample size calculator, the 10 study participants could still produce significant results at a 95% confidence level and confidence interval of 30. Creative Research Systems' sample size calculator automatically generates the sample size when you insert the estimated target population of 146, and a confidence interval of 30. With a wide confidence interval, the more certain one could be that the responses of the whole population, would be within that range[42]. The results of the questionnaire were also used to supplement a more robust statistical analysis from the background research. These two results would increase the overall accuracy of this study. Thirty nine percent (39%) of the respondents were from industry, 31% from private/non-profit sector, 15% from the government, and 15% from academia. The questions on the questionnaire were focused on the impact of parallel importation regulations on 3 main factors: Quality, socio-economic, and regulatory.

However, because our study showed that parallel importation had not been practically implemented, the questions were based on the effects of the passage of this law. Information was

[z] Trading Economics, South African Import Prices, 2013, http://www.tradingeconomics.com/south-africa/import-prices.(Accessed October 22,2013)

also obtained regarding challenges involved with the practical implementation of parallel importations. The respondents were represented as Q1 through Q10, based on the order their responses were received. Respondents had 4 answer choices for the main research questions: **Positive impact (P)** OR a **Negative impact (NI)** or **No significant impact (N)** or **Did Not Answer the Question (NA)**. The responses are presented in the tables below:

- **QUESTION A: WHAT IS THE OVERALL IMPACT ON DRUG QUALITY DUE TO PASSAGE OF PARALLEL IMPORT REGULATIONS?**

Table 11: Questionnaire Response on Drug Quality

Respondent	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Response	N	N	NA	N	N	N	N	N	NA	N

In total, 80% (8 out of 10) of the respondents said parallel import regulations had NO SIGNIFICANT IMPACT on drug quality. Every respondent from government and the private sector said passage of the parallel import regulations has had no effect on drug quality. Drug quality referred to the concern about import or manufacturing of counterfeit or sub-potent drugs with poor safety and efficacy rates. Figure 3 shows the responses from the different groups in this study.

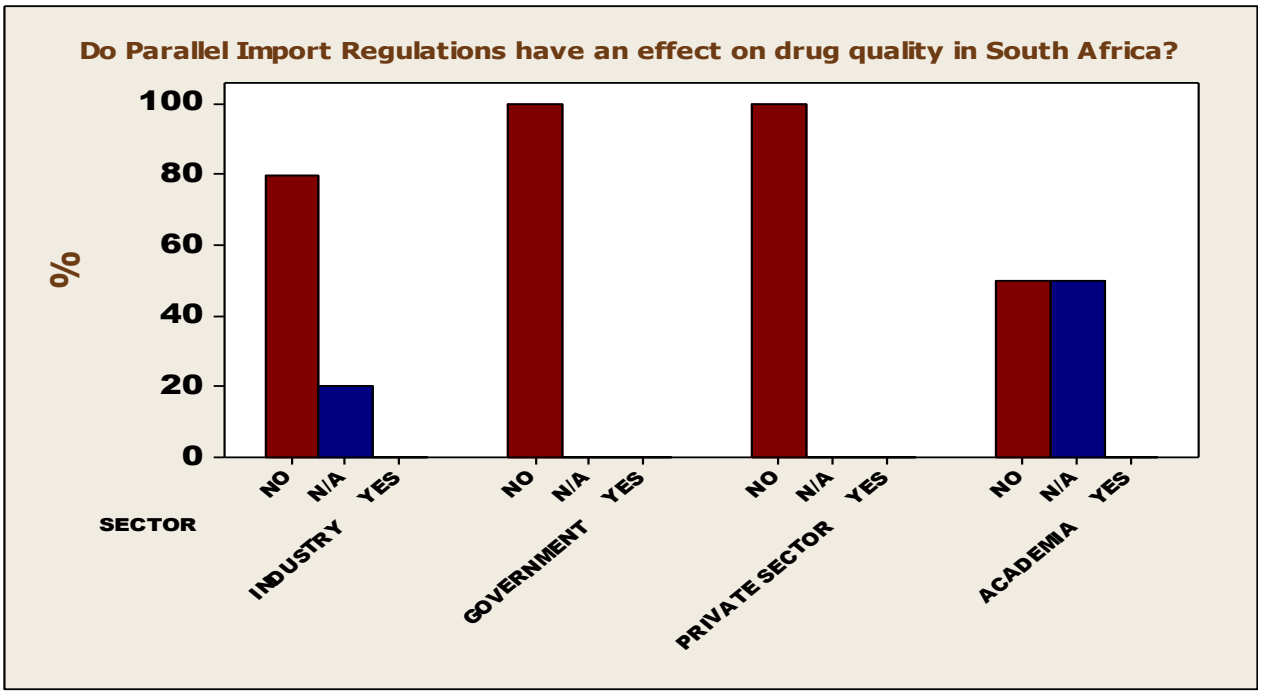


Figure 3: Impact of Parallel Import Regulations on Drug Quality

- **QUESTION B: WHAT HAS BEEN THE EFFECT ON THE REGULATION OF PHARMACEUTICALS DUE TO THE PASSAGE OF PARALLEL IMPORT REGULATIONS?**

Table 12: Questionnaire response on Pharmaceutical Regulation

Respondent	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Response	N	N	N	N	N	N	N	N	N/A	N

Eighty percent (8 out of 10) of the respondents said that the parallel import regulations had No Significant Impact on the regulation of pharmaceuticals in South Africa. No respondent said parallel import regulations had an effect on the regulation of pharmaceuticals. Some respondents said parallel import regulations will affect intellectual property laws if fully implemented and that the government was drafting new regulations that will be compliant with both international and national laws. Figure 4 shows how the different sectors answered our questionnaire:

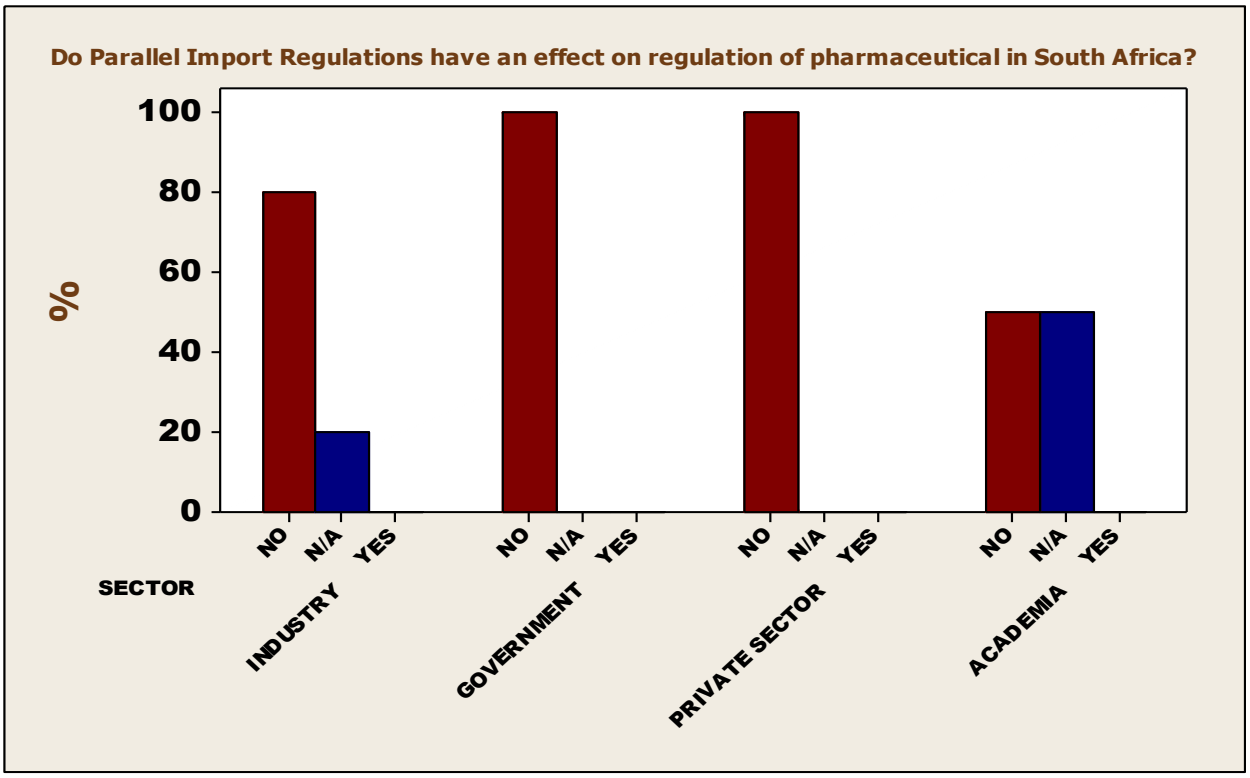


Figure 4: Impact of Parallel Import Regulations on the Regulation of Pharmaceuticals

- **QUESTION C: WHAT HAS BEEN THE IMPACT ON THE SOCIO-ECONOMIC STATUS DUE TO PARALLEL IMPORT REGULATIONS IN SOUTH AFRICA?**

Table 13: Questionnaire Response on Socio-Economic Status

Respondent	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Response	N	N	N/A	N	NA	N	NA	N	NA	N

Here 60% (6 out of 10) of the respondents said parallel import regulations had NO SIGNIFICANT IMPACT on the socio-economic in South Africa. Forty percent did not answer this question or could not relate its effect on parallel importation. No respondent said parallel import regulations had an effect on the socio-economic status of the Republic. As a side note, most of the respondents indicated that more people have had access to essential medicines like Anti Retro Viral (ARV) drugs, primarily due to the issuance of voluntary licenses to local drug

manufacturers, and also the importation of generic drugs from countries like India at a cheaper price. Some respondents also indicated that drug prices have decreased over the years due to use of voluntary licenses and the government's tender price system. Figure 5 shows how the different groups responded:

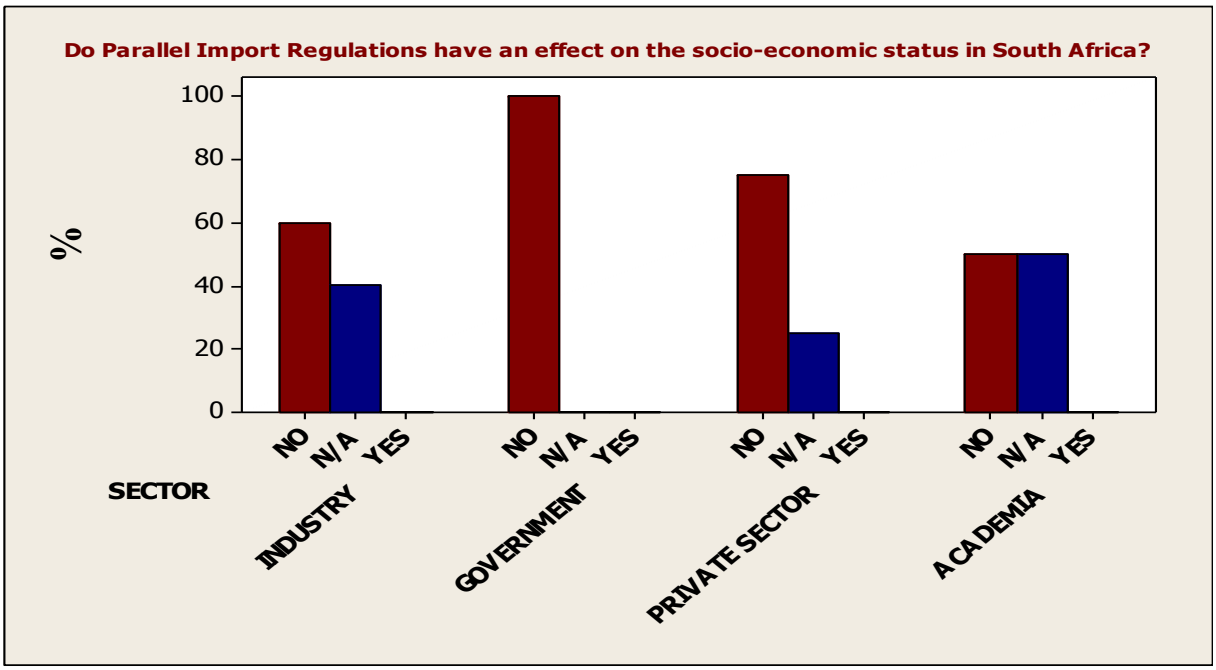


Figure 5: Impact of Parallel Import Regulations on Socio-Economics in South Africa

CHAPTER 6

STUDY ANALYSIS AND DISCUSSION

After consultation with various statisticians[85-88], it became more feasible that, instead of only using a 2-sample T-test which could produce misleading p-values, two other tests should be used; the Bonferroni method and the Bootstrap method. These tests had adjusted p-values and increased the overall effectiveness of the results. These two tests could determine the significance in a complex data set regardless of its underlying conditions such as dependency, multivariate or continuity[46]. The adjusted p-values from these two tests were used to determine the significance of the results in this study. The rules for both tests were as follows:

- If the adjusted p-value is ≤ 0.05, the laws had an impact;
- A positive test statistic (t) indicates a decrease;
- A negative test statistic indicates an increase;
- An adjusted p-value > 0 .05 indicates no impact.

The procedure PROC *MULTTEST in SAS v 9.2* was used to adjust the p-values for both tests.

First of all, the socio-economic status of South Africa before and after the passage of the 1997 law that allowed for parallel importation was evaluated. Socio-economic impact refers to the combination of social and economic factors such as education, income, occupation, and healthcare. Data from the World DataBank on the GNI per capita for South Africa was plotted as shown in Figure 6. We used the Bonferroni method and the Bootstrap method to determine if there was a significant difference in the GNI per capita values before and after 1997.

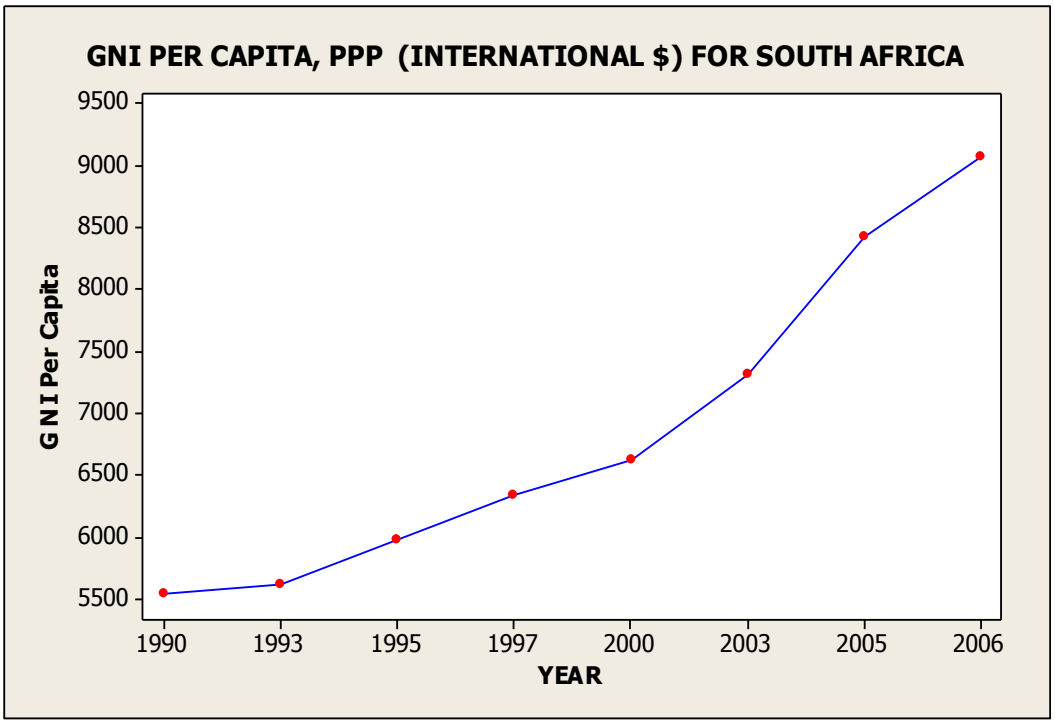


Figure 6: Gross National Income per Capita, South Africa

The Null Hypothesis was that passage of parallel import regulations as well as other factors in the country had no significant impact on the GNI per Capita. The Alternate hypothesis was that passage of parallel import regulations together with other factors had a significant impact on GNI per Capita. Analysis of data presented in Table 3 on GNI per capital before and after the passage of parallel importation regulations showed that the passage of the parallel import regulations had no significant effect on the GNI per Capita (t=-3.22, Bonferroni adj. p-value=0.29, Bootstrap Adj. p-value=0.12, d.f. = 4). This further suggests that the increasing trend in the GNI per capita was approximately the same before and after passage of the law. A significant increase in the GNI per capita is very vital for an effect to be on the socio-economic status of a country.

As shown in Figure 7, the South African (SA) government spends more on R&D followed by local businesses. This implies that the government is investing in all areas of innovation, not just in public health. This will also imply that, by the passage and implementation of parallel

import regulations, it will be of high interest to the government to protect intellectual property rights even more than foreign investors. This theory will support the fact that the passage of the 1997 law allowing parallel importation (PI) and compulsory licenses (CL) was not necessarily creating a path for patent infringement.

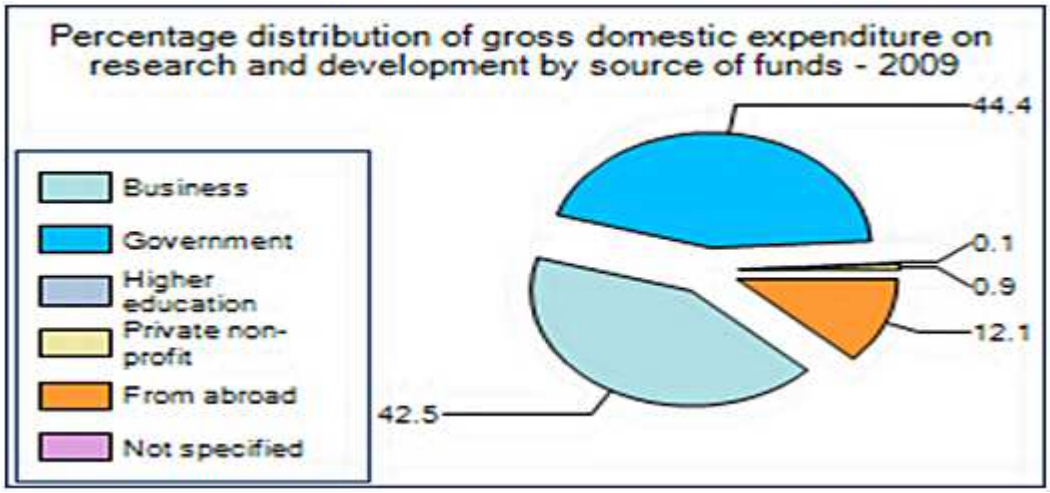


Figure 7: Percent Distribution of Gross Domestic Expenditure on R&D by source of funds (2009)
Source[47]: UNESCO[aa]

Another factor which is important in determining the socio-economic status of a country is life-expectancy. Life expectancy at birth is also a measure of overall quality of life (QoL) in a country and summarizes the mortality at all ages. It can also be thought of as indicating the potential return on investment in human capital and is necessary for the calculation of various actuarial measures[84]. The data reported by the CIA are different from estimates by the World DataBank. This could be due to differences in the methods both agencies use to collect data. However because the CIA had very limited data for other indicators used in this analysis, just data from the World DataBank was used. Differences in data sources could have increased the chances of error in the analysis.

[aa] UNESCO, General Profile-South Africa, 2011. http://stats.uis.unesco.org/unesco/TableViewer/document.aspx?ReportId=121&IF_Language=eng&BR_Country=7100&BR_Region=40540. (Accessed Nov 13, 2013)

Life expectancy in South Africa had been falling since the 1990's; this was one of the reasons why the government passed the 1997 law allowing for parallel importation and access to cheap essential medicines. Even with the passage of the regulations to give access to medicines, life-expectancy was not immediate impacted as shown in Figure 8.

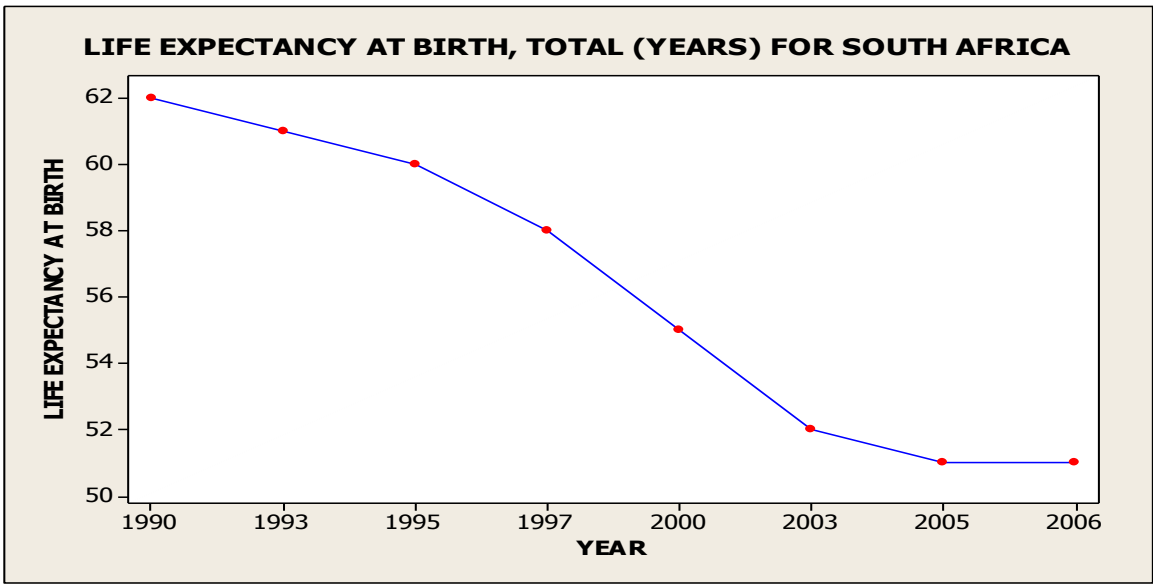


Figure 8: Life Expectancy at Birth, South Africa

After analysis of the life expectancy data from 1990 to 2005 using a 2 Sample t-Test, it was found that there was a significant impact on life expectancy after passage of parallel import regulations (MRSCA) in 1997 (t=6.25, Bonferroni adj. p-value=0.03, Bootstrap Adj. p-value=0.05, d.f. = 4). Life expectancy decreased by an estimated 8.33 years (95% CI: 4.6, 12.0) compared to life expectancy before 1997. It was expected that the passage of parallel import regulations will increase access to pharmaceuticals and hence, increase life expectancy. This did not happen before 2005. However, from 2005 to 2007, life expectancy stayed constant at 52 years and then continued to increase after that to about 55years by 2011 according to World Bank Database. The stabilization followed by an increase in the life expectancy can be partially attributed to the issuance of voluntary licenses and the influx of off-patented generic drugs coupled with healthcare infrastructure improvement in the country[22].

Furthermore, analysis of secondary school enrollment data given in Table 5, showed that passage of parallel import regulations together with other factors did not result in a significant increase in secondary school enrollment (t=-3.36, Bonferroni adj. p-value=0.25, Bootstrap Adj. p-value=0.12, d.f. = 4). However, there was an estimated increase in secondary school enrollment by 15.3% (95% CI: -28.0, -2.7) when compared to the years before, but this increase was not significant. A significant increase in school enrollment could have implied partly that families now have enough for their healthcare needs and can afford school expenses and also that people are healthy enough to go to school. Figure 9 shows the trend in school enrollment; - Figure 10 also shows the 2011 literacy percentage in South Africa with 93.0% of adults and 98.8% of youth being literate according to the United Nations Educational Scientific and Cultural Organization (UNESCO)[47].

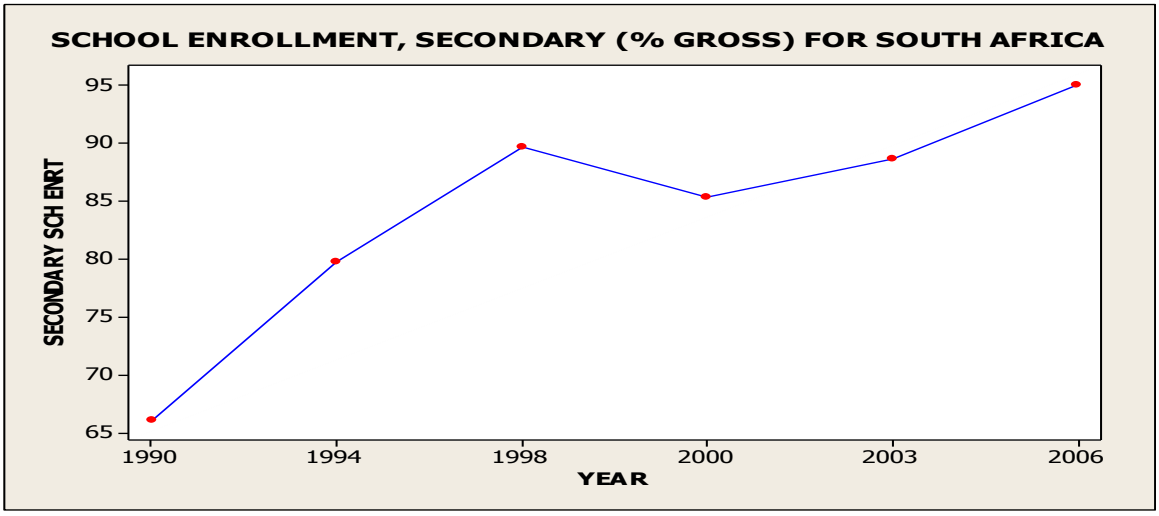


Figure 9: Secondary School Enrollment, South Africa

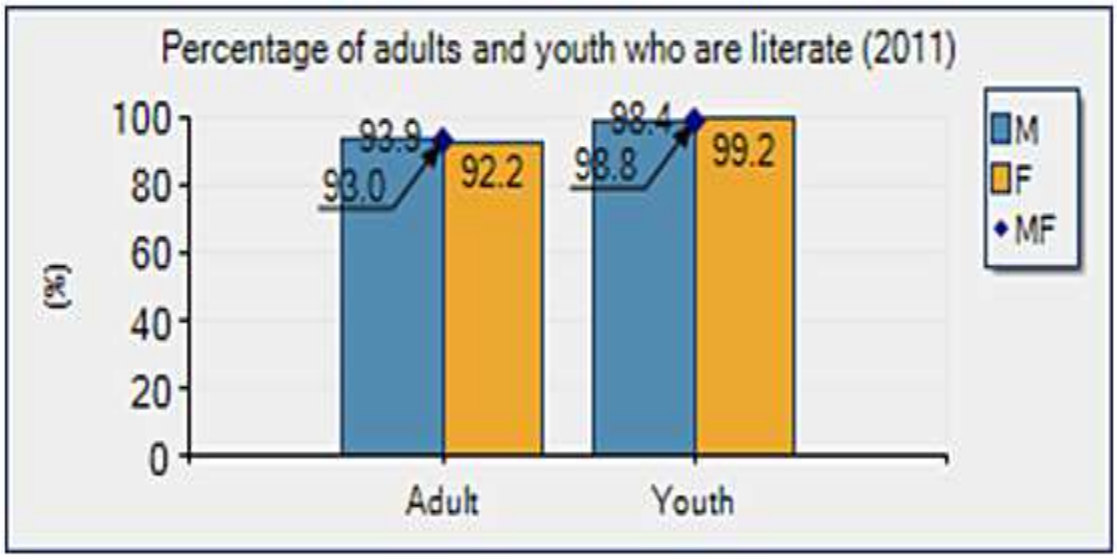


Figure 10: Literacy Rate, South Africa (2011)
Source[47]: UNESCO[bb]

Another health related aspect examined was immunization and more specifically immunization to measles to determine the trend with importation and use of vaccines. Immunization to measles has been falling over the years (Figure 11). Analysis showed that there has been a reduction in the immunization to measles but this reduction was not significant (t=3.47, Bonferroni adj. p-value=0.23, Bootstrap Adj. p-value=0.11, D.F. = 4). An estimated 14.3% (95% CI: 2.8, 25.8) decrease was observed after the passage of the law. This could have been due to shortage of vaccines or vaccines available at high prices and people being unable to afford them. This could also have been due to a drop in the number of reported cases of measles as shown in Figure 12 as a result of eradication of the disease.

[bb] UNESCO, Education profile-South Africa, 2011. http://stats.uis.unesco.org/unesco/TableViewer/document.aspx?ReportId=121&IF_Language=eng&BR_Country=7100&BR_Region=40540. (Accessed Nov 13, 2013)

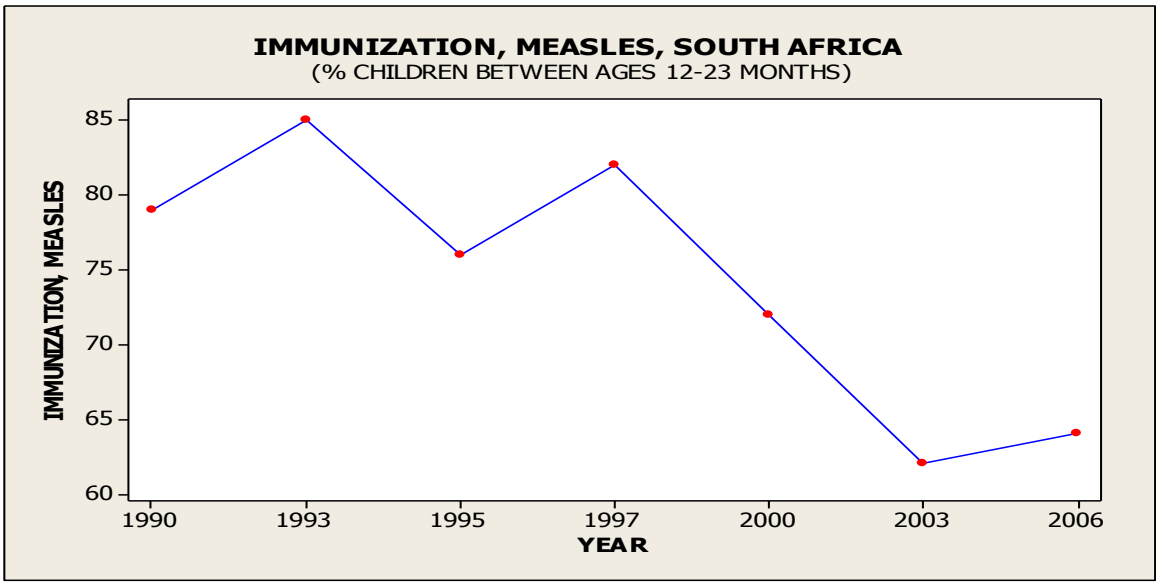


Figure 11: Immunization to Measles, South Africa

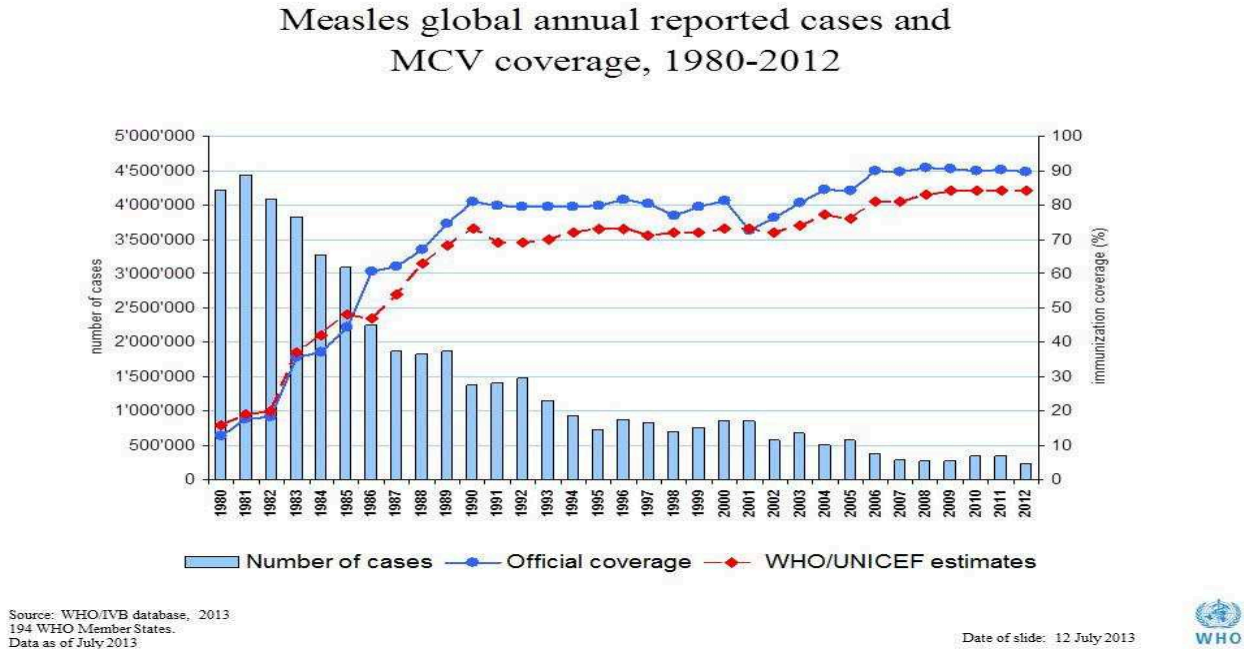


Figure 12: Global Annual Reported Cases for Measles

Another indicator examined was the prevalence of HIV (As % of population ages 15-49). The prevalence of HIV/AIDS had continued to increase between 1990 to about 2003 where it stabilized at about 17% (Figure 13). The passage of parallel import regulations together with other conditions could not immediately slow down the prevalence rate of HIV (t=9.94

Bonferroni adj. p-value=0.005, Bootstrap Adj. p-value=0.03, D.F. = 4). This increase in the prevalence of HIV was very significant especially before 2003. Since HIV does not have a cure, it can be expected that the prevalence rate will be more likely to stay constant or increase rather than decrease in the presence of ARVs. Access to ARVs has been on the rise after the passage of MRSCA in 1997. The steady HIV prevalence rate after 2003 is a good indication that people infected with HIV are living longer lives due to availability of ARVs. By passage of the parallel import regulations, companies have been more flexible in approving voluntary licenses and more off-patented ARVs have also flooded the SA market leading to a drop in prices for these drugs. This has also led to an increase in the number of people receiving ARV drugs (Figure 14). The WHO estimates that, on average, about 66% of people infected with advanced HIV in SA had coverage as of 2011. The WHO also estimates that more than 95% of women infected with HIV in 2011, in SA, received ARVs to prevent mother-to-child transmission[48].

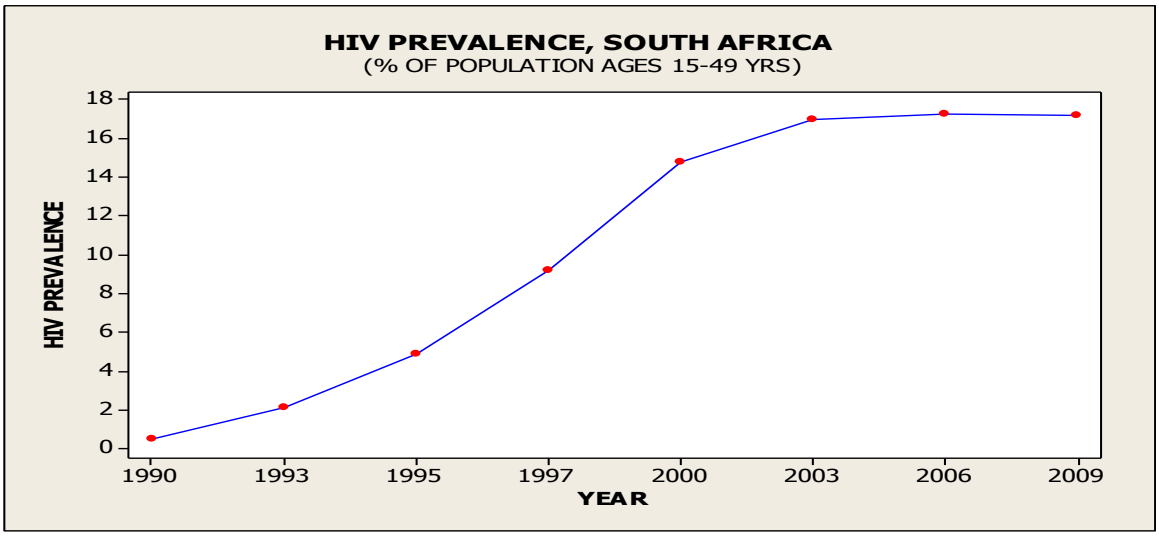
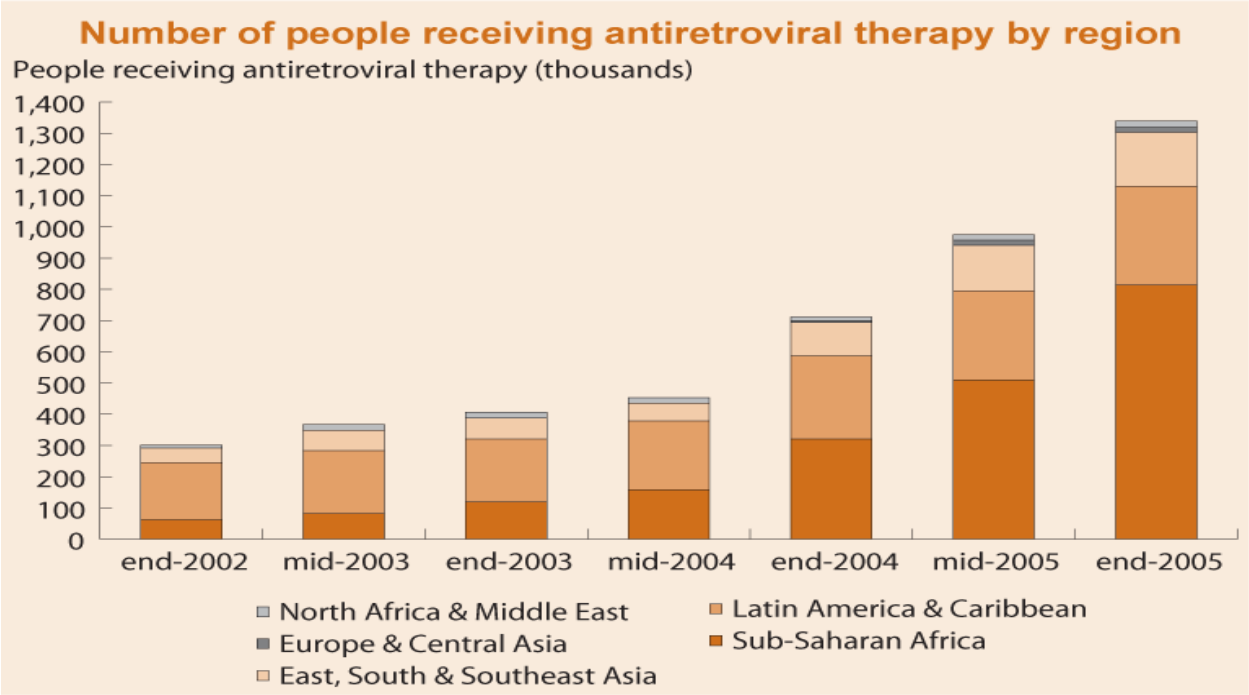


Figure 13: Prevalence of HIV, South Africa



Source: WHO and UNAIDS report, 2006.

Figure 14: Global ARV Coverage

The general availability of generic medicines in 2004 was *71.7%* in South Africa according to data from WHO. For the whole sub-Saharan Africa, the most affected region, ARV coverage rose 20% between 2009 and 2010, reaching 49% (WHO) compared to 66 % coverage in SA, in 2011[5].

Furthermore, the PROC STEPDISC in SAS v 9.2 was used for the technique stepwise Discriminant Analysis. It is a method that selects the most significant dependent variables, in order, that explain differences between the two periods (before 1997 and after 1997). The results showed that the dependent variable prevalence of HIV, (total % of population ages 15-49) had the most significant discriminatory power (Partial Rsquare = 0 .9611, F= 98.88, p =0.0006, P>ASCC *= 0.0006) followed by secondary school enrollment as % of the gross population (Partial Rsquare = .6869, F=6.58, p = .0828, P >ASCC* = .0013). These results suggest that the indicator most widely affected by the passage of the law was prevalence of HIV.

In summary, given the above socio-economic indicators of South Africa before and after the passage of the Medicines and Related Substance Control Amendment act of 1997; there is evidence that there has been a significant change in some socio-economic indicators such as the HIV prevalence, and no significant change in others, such as the GNI per capita. However, a change in the socio-economic status cannot be solely attributed to the passage of the parallel import law; other sectors of the economy and government policy might have influenced this change. On the other hand, it cannot be denied that the passage of the MRSCA of 1997 has acted like a "Big Stick" to soften pharmaceutical patent holders to issue voluntary licenses and increased the influx of generic products into the market. Furthermore, 60% of respondents (6 out of 10), said the passage of the law had no significant impact on the socio-economic status of the people in South Africa while 40% (4 out of 6), could not make a distinction of whether the passage of MRSCA of 1997 was solely responsible for the increase in socio-economic status or not. Given the analysis and discussion on the indicators related to socio-economic status, it became more apparent that passage of the law had no significant effect on the socio-economic status of South Africans.

Furthermore, the regulatory impact due to the passage of the parallel import regulations within the MRSCA was analyzed by looking at indicators that could show if the country had good relations with other countries as well as the domestic industry when it comes to the pharmaceutical trade. Less trade would be expected if regulations are not good but if they were good, an increase in international trade and domestic manufacturing could be expected. The main indicator used was the import and export data for the nation before and after the passage of the parallel import laws. If domestic manufacturing were high, more exports of pharmaceutical products and other products would be expected, but if domestic manufacturing were low, it

would only serve domestic needs and not give room for increasing exports. Also, if importation of pharmaceuticals and other products increased that would imply that companies were satisfied with the regulatory framework in place. Figure 12 shows the trend in the nation's import and export activities as reported by the World DataBank.

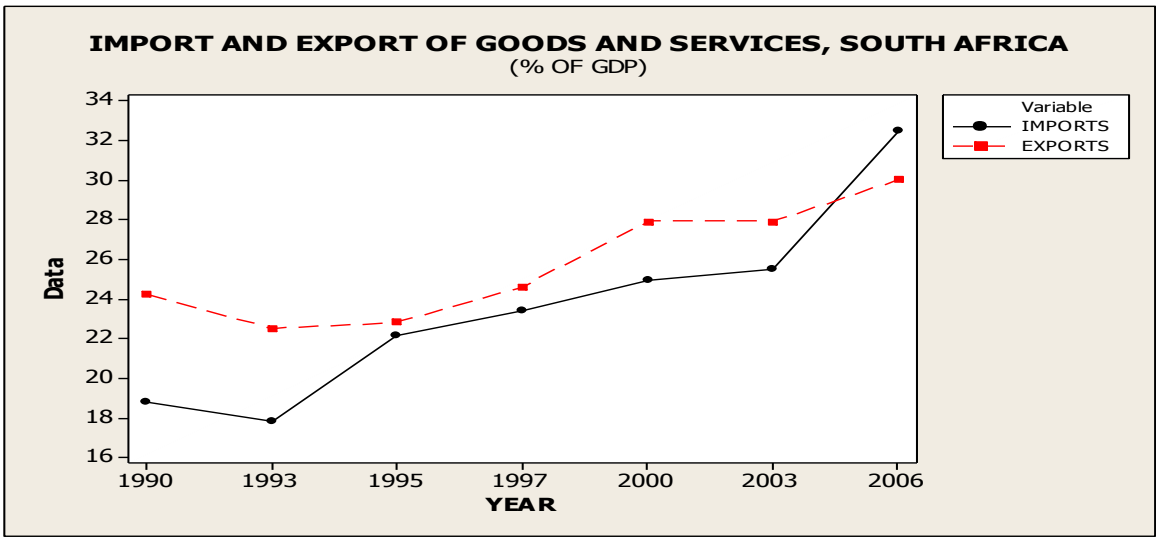


Figure 15: Import and Export of Goods and Services

Statistical analysis gave further evidence about the variation of import and export values before and after 1997 when the MRSCA was passed. It was determined that there was no significant change in the amount of imports due to the passage of the MRSCA (t=-4.47, Bonferroni adj. p-value=0.0995, Bootstrap Adj. p-value=0.08, D.F. = 4). The estimated increase in imports of 6.67 % of gross domestic manufactured product (95% CI: -10.8, -2.5) after the passage of the law showed that international trade was increasing, and the parallel import laws did not scare potential importers away for fear of patent infringement or abuse of intellectual property rights. This increase also meant that companies could make a profit from importing products through regular channels without the fear of competition from parallel imported products.

Analysis on export of goods and services showed no significant reduction in the number of exported products (t=7.0, DF=3, P=0.997) due to the passage of the MRSCA. On the other hand, there was a significant increase in the number of exports after passage of the law (t=-7.0, Bonferroni adj. p-value=0.0197, Bootstrap Adj. p-value=0.05, D.F. = 4). An increase in the quantity of exports of about 4.7 % of gross domestic manufactured products (95% CI: -6.5, -2.8) was observed after passage of the law. The export of high-tech products, which includes some groups of pharmaceuticals as discussed in chapter 5 above, did not significantly change due to the passage of the MRSCA(t=0.50, Bonferroni adj. p-value=1.0, Bootstrap Adj. p-value=0.99, D.F. = 4). There was a reduction in the export of high tech exports by an estimated 0.3% (95% CI: -1.5, 2.2). The export figures show that domestic manufacturing continued to increase over the years and that there was enough product to supply the domestic market and export to the international market. This is further evidence that the regulation of pharmaceuticals was not affected due to the passage of the law.

It is important to recall that, after the passage of the parallel import laws in South Africa, 39 pharmaceutical companies filed a lawsuit against the South African government and other countries were concerned about doing business with South Africa including the U.S. which had put South Africa on its "Watch-List" and implemented some trade sanctions[27]. It is apparent that the South African government had somehow come to some type of agreement with these opposing governments and companies because the amount of import and exports of both goods and services continued to increase between 1990 to present. By 2006, the country was now importing more goods and services than it was exporting in the previous years (Figure 15). This is a good indication that trade relations had continued to improve between South Africa and other countries and that companies were comfortable with the regulatory framework in place.

Some of the respondents to the questionnaire agree that more generic drugs are now being imported into the country than before.

Domestically, the effect of the parallel import regulations based on the incentive of both government and the private sector to invest in research and development and the number of high technology goods being exported was examined. According to UNESCO, the amount invested in research and development has continued to increase with the government spending the most in R&D followed by industry. This valued increased from about $1.6 Billion in 1997 to about $4.5Billion in 2009[47]. Figure 16 shows this trend:

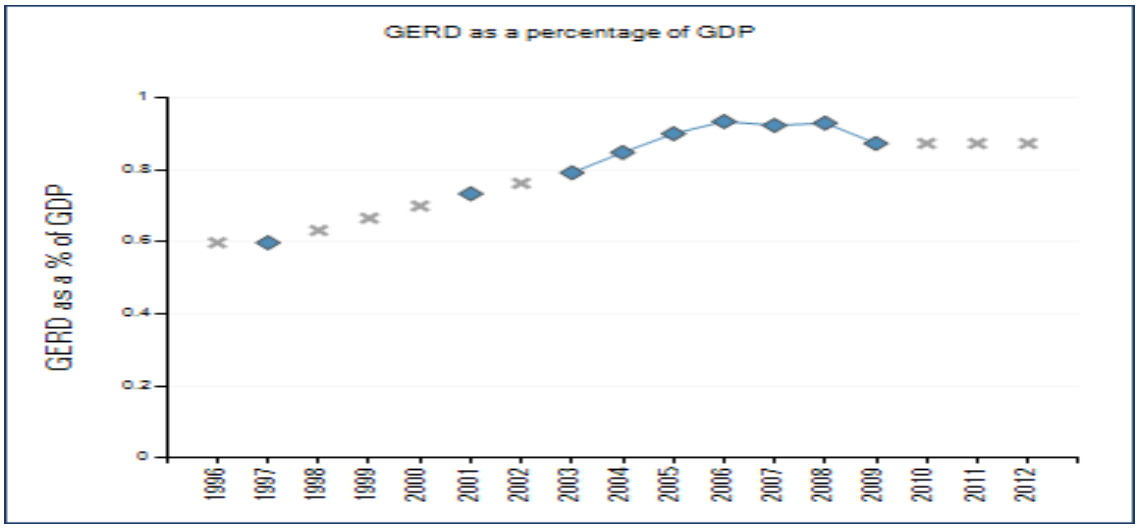


Figure 16: Gross Domestic Expenditure on Research and Development (GERD)
Source: UNESCO[47]

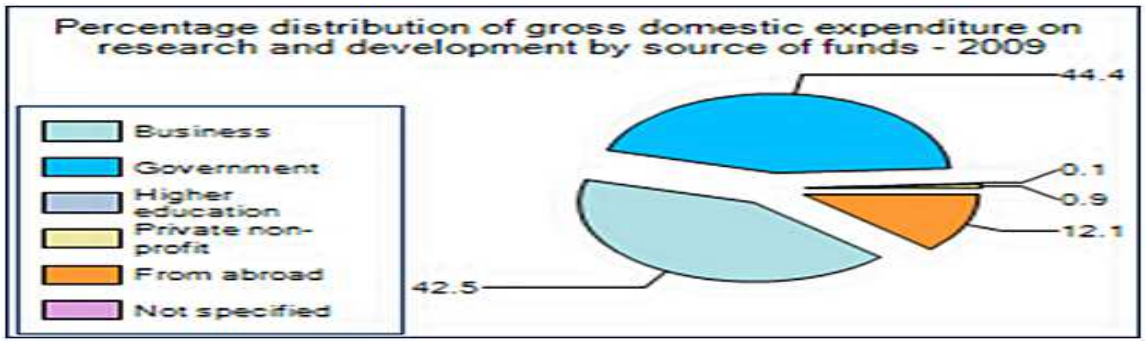


Figure 7: Percent Distribution of Gross Domestic Expenditure on R&D by source of funds (2009)
Source: UNESCO
(Used earlier under GNI PER CAPITAL analysis in this chapter)

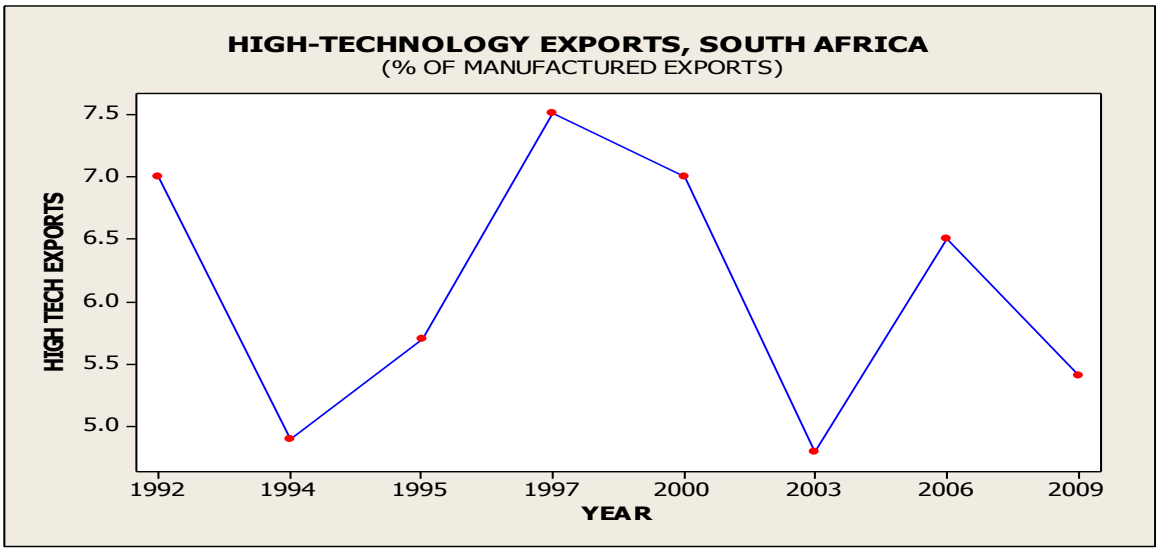


Figure 17: High-Technology Exports as % of Manufactured Exports

Figure 7 shows the percentage distribution of gross domestic expenditure in 2009. By having government and other entities investing more in R&D, it is expected that the government will not be negligent in its duty to protect intellectual property rights. If this nation were a safe haven for the abuse of patents, trademarks and other intellectual properties, a reduction in the investment in R&D from both the private and public sector would be expected. Local business was investing more in R&D followed by foreign investments. This is an indication that both local business and foreign investors are comfortable with the regulatory framework and believe they will make good returns on their investment.

Figure 17 shows that the export of high-tech products has constantly changed over the years. Statistical analysis using Bonferroni and Bootstrap method further showed a minor decrease in the quantity of export of high-tech products over the years by an estimated 0.3% (95% CI: -1.5, 2.2). The amount of high tech goods generally produced in developing countries is very low compared to that in developing countries[38], the use of parallel imports to import high tech goods would be of financial benefit in most developing countries. Furthermore, patent holders have been more open to issue Voluntary Licenses (VLs) in order to avoid the use of

parallel importation or compulsory licenses. In a 2007 study of voluntary license practices in the pharmaceutical sector[39], it was observed that 13 ARV voluntary licenses were issued from 1997 to 2006 in South Africa. Among these VLs, GlaxoSmithKline (GSK) issued 6 (mainly in 2004 and 2006); Boehringer Ingleheim issued 2 (2003/2004); Bristol Myers Squibb issued 1 (February 2006); Merck Sharpe Dhome issued 2 (2004/2005); Gilead Sciences issued 1(2005) and Roche issued 1 (2006). Aspen Pharmaceuticals was the main generic manufacturer who received these licenses. Royalties for most of these licenses were 5% and some companies chose not to ask any royalties and also provided technology transfer and assistance. There is no indication that any voluntary licenses for ARV were issued before 1997.

Even though prices for some essential medicines fell due to voluntary licenses and importation of off-patented generics, general import prices continued to increase across the board (t=-7.44, Bonferroni adj. p-value=0.016, Bootstrap Adj. p-value=0.05, D.F. = 4) by an estimated 52.83 Import Price Index (95% CI: -72.6, -33.1) after 1997. Figure 18 shows this increasing trend while Figure 19 shows the increasing trend in general Consumer Price Index, CPI for all other goods and services.

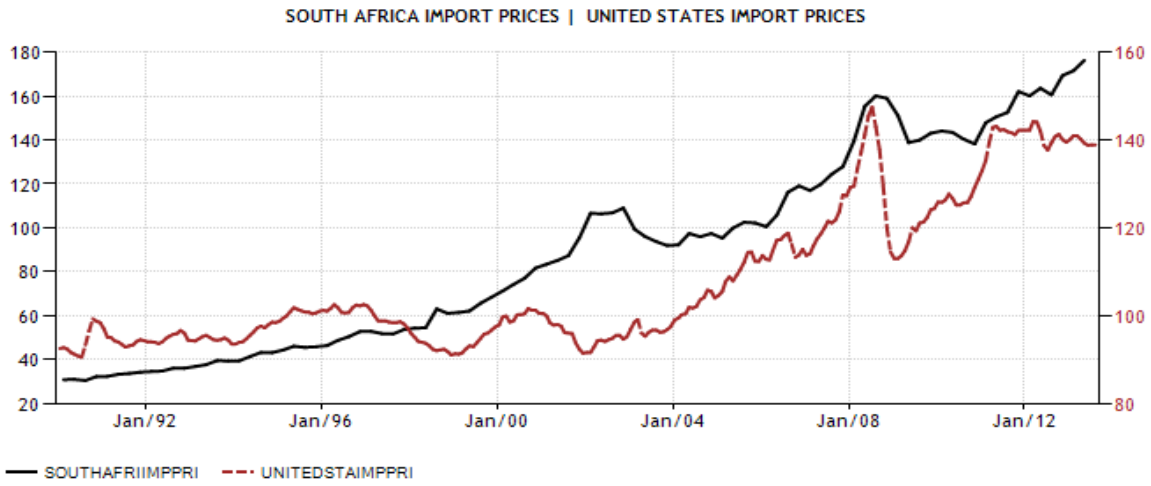


Figure 18: Import Prices For South Africa Vs the U.S
SOURCE: TRADINGECONOMICS.COM[84]

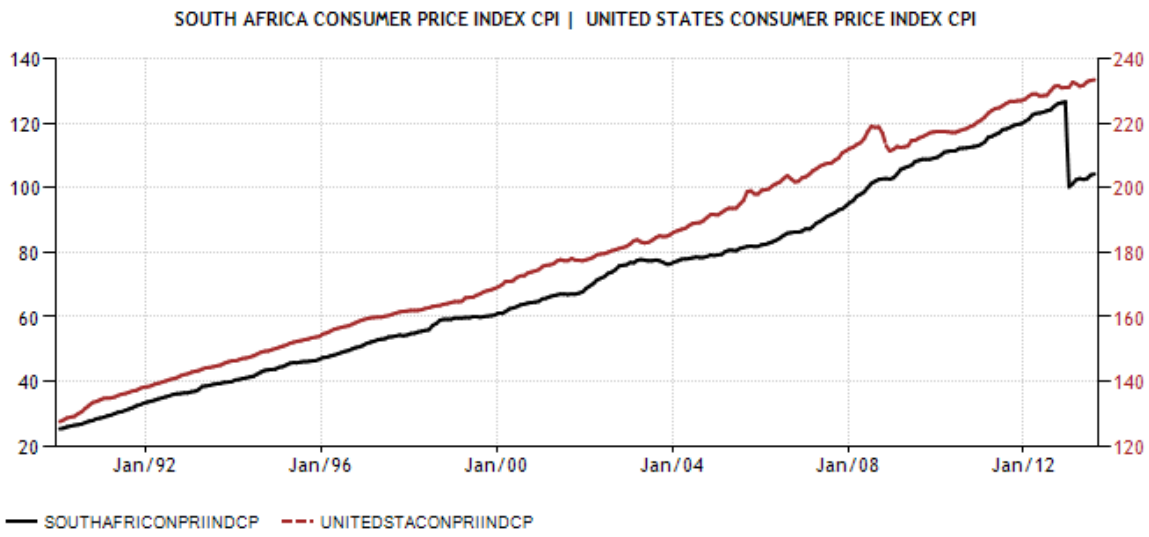


FIGURE 19: Consumer Price Index for S.A Vs the U.S
SOURCE: TRADINGECONOMICS.COM[84]

From the analysis of the indicators, it became apparent that there has not been any significant impact on the pharmaceutical regulatory framework in South Africa based on the parallel import provisions of the law. Eighty percent (8 out of 10) of the respondents to the questionnaire also confirmed this finding. Most people had viewed the provisions of the MRSCA allowing parallel importation to be unworkable, time consuming and complex. To date no individual has made an official application to parallel import pharmaceuticals. Even though parallel importation had not been used, it had an indirect effect on patent holders who became open to issuing more voluntary licenses in order to prevent the government and local business from taking advantage of the parallel import provision in the law.

Finally, looking at the quality of drugs before and after passage of the parallel import regulations, 80% (8 out of 10) of the respondents to the questionnaire said the regulations had no significant effect on drug quality. Since no single application for parallel importation had been received or permits granted, it was clear that no parallel import drugs were sold in the country. On the other hand, there was a significant increase in generics, in the country, as well as an

increase in locally manufactured drugs as part of the voluntary license program and other agreements. With regards to importation of pharmaceuticals, South Africa had designated sea ports and airports where such products could get into the country. Such imports will not be allowed entry if they were not inspected and the Medicines Control Council must have received proper documentation to show that the drugs were safe and efficacious for human consumption. Furthermore, importers of drug had to have a local agent and storage area (e.g. Pharmacy or warehouse)[36]. This could ease communication between the regulatory authority and the importer in case of a recall or any enforcement action.

Some counterfeit drugs have also been found in the market mostly from neighboring countries, but this situation has been rare in South Africa but is common in most other developing nations such as Cameroon or Kenya (30% of the market). According to a WHO estimate, many countries in Africa and parts of Asia and Latin America have areas where more than 30% of the medicines on sale can be counterfeit, while other developing markets have less than 10%. Overall, they estimated a reasonable range to be between 10% and 30%[40]. The *Pharmaceutical Research and Manufacturers of America (PhRMA)* list countries where counterfeit drugs are a problem[41], but do not include South Africa[cc].

[cc] PhRMA, LEARN ABOUT COUNTERFEIT DRUGS AROUND THE WORLD; http://www.phrma.org/issues/counterfeit-drugs

CHAPTER 7

CHALLENGES PHASED IN IMPLEMENTING PARALLEL IMPORTATION REGULATIONS

When it became apparent that the people in South Africa had not taken advantage of the benefits involved with parallel importation, respondents in this study were asked to give their opinion regarding the challenges involved with practical implementation of the parallel import regulations.

One of the research participants was a pharmacist and senior lecturer within the discipline of pharmaceutical sciences. His research interests included policy analysis (in particular, the development and implementation of National Medicines Policies), rational medicines use, and the application of antiretroviral therapy in resource-constrained settings. He has worked as a senior executive with many agencies involved with pharmaceutical regulations and policy including the South African Medicines Control Council, Board of Pharmaceutical Practice of the International Pharmaceutical Federation (FIP), and the World Health Organization (WHO). He had commented on and presented to parliamentary committees regarding the legislative changes that resulted in the legalization of parallel importation of medicines. His comments regarding challenges to implementing parallel import regulations were:

"My own sense is that, perhaps, the process of obtaining permission for parallel trade has appeared too onerous to be worthwhile. In particular, sub-regulation 7(2) requires the submission of extensive documentation to the Minister of Health. There is no existing administrative infrastructure to handle such submissions, so applicants might anticipate considerable delays. Then, sub-regulation 7(3) limits the permit to 2 years, which is a short time to gain from such activity. Most importantly, sub-regulation 7(5) then requires the applicant to

seek registration of the parallel traded medicine with the Medicines Control Council. Currently, there is a significant backlog in respect of ordinary applications for registration (marketing authorization) for all medicines, whether new chemical entities or generics. The average time to complete such a process is around 3 years. It is possible that the permit from the Minister would expire before permission to market the medicine was granted. Another very important inflexibility is the requirement, in 7(2)(e)(iv) for the applicant to reveal the price at which the parallel traded medicine will be sold. There are two pricing schemes in South Africa – the Single Exit Price, SEP (or factory gate price) at which medicines are sold in the private sector (where no volume discounts or any form of bonusing or incentives are allowed) and the state tender price (set every 2 years after a sealed competitive bidding process). The seller of the patented medicine on the market already would be able to lower the disclosed SEP to match or under-cut the parallel trader, thus negating any arbitrage advantage and retaining market share. As state tenders are only issued every 2 years, on a fairly predictable schedule, but are predominantly for off-patent medicines, the chances of a parallel trader being able to navigate the permit and registration steps in time to make a sealed (and hence undisclosed) bid for the tender business, under-cutting the patent holder, are slim. Although there is some evidence that SA private sector SEPs are higher, in some cases, than in other markets, no one it seems has identified a large volume market from which to draw sufficient stocks to generate a margin in SA, to such an extent that it could not be matched or even exceeded by the patent holder.

So, a good idea in theory, and an important flexibility to enshrine in law, but perhaps made impractical by the overly complex and time-consuming permit and registration requirements. The contrast with the European situation, where parallel trade is perhaps best established, is clear – we lack a regional centralized medicines regulatory authority with coverage over the areas from which we might seek to procure parallel traded medicines"

Another respondent, a Director at the South African Medicines Control Council had this to say about why parallel importation has not been put to practice:

"The Medicines Act makes provision for Parallel importation. The Regulatory Authority is able to accommodate the matter. The Pharma Industry need to embrace and use the tool if needed.

Therefore my view is that due to other measures in place in RSA to make sure that affordable medicine is made available to the public, the tool is not needed."

Another respondent, a professor of Public Law in South Africa, had this to say about challenges to use of the parallel import regulations:

"My guess is that shortly after these provisions were written into the law, there was sustained generic competition from Indian suppliers in the ARV market, resulting in massive reductions in the prices of those drugs. Once generics could be sourced so cheaply, the advantages of parallel importation were not so significant.

Parallel importation will still be useful in situations where there are no generic alternatives available, and the branded products are available at a premium. Then it would be worthwhile for a consumer or distributor to comparison-shop around the world for the cheapest prices."

Another response to the challenges phased in implementing parallel import regulations came from the Chief Executive Officer (CEO) of *The National Association of Pharmaceutical Manufacturers (NAPM)* in South Africa. This organization was established since 1977. This is what he had to say regarding the use of parallel importation:

"The main reason for the clause was to get access to anti retroviral drugs. However many of the multinational originators have given voluntary licenses to local manufacturers to market and /or manufacture their drugs."

"South Africa is a signatory to the WTO TRIPs agreement, which recognizes patents.

Only in emergency cases, (such as a pandemic), when a drug is unobtainable or when the Department of Health and the registered owner of the drug cannot reach an agreement with price, will the Minister invoke the clause for parallel importing.

The major obstacle is the question of who will take responsibility for an unpredicted side effect of the drug. In our law the importer would be open to litigation."

Another respondent who is the Executive Director of *Innovative Pharmaceutical Association of South Africa (IPASA)* had a straight forward answer as to why parallel importation was not being used. He said:

"Perhaps there is no price advantage to incentivize a third party to invest in the significant effort in getting regulatory approval."

Another respondent was a Marketing Head for *Aspen Pharmacare,* a multinational pharmaceutical company, which is the number one pharmaceutical company in South Africa. She had more than 10 years of experience in the regulatory affairs environment and being a Regulatory Affairs Manager during the period when the MRSCA was passed. Her comments about the practical implementation of the parallel import regulation provision were:

"The main reason the clause was included in the legislation was to allow government to reduce medicine prices. It was meant to allow mainly the government to by-pass the multinational manufacturers and be able to purchase the patented drugs from other countries where they are available. With the compromises reached during that time on the patents particularly on ARVs and the promulgation of the pricing of medicines in general, there hasn't been a real need to parallel import any medicines from other countries. Many Multinationals like GSK, MSD, etc. allowed local companies to produce generics of their patented HIV/AIDS drugs and the price controls on medicines were implemented in 2006 and the process has been running "smoothly" since then with the government determining what percentage increase all medicines will take per annum."

Another respondent, a Group Corporate Affairs and Investor Relations Manager at *Adcock Ingram Healthcare* and Chief Operating Officer (COO) for the *Innovative Pharmaceutical Association of South Africa (IPASA)* representing both local and multinational companies. She

has worked with intellectual property matters and policy issues for more than 15 years. This is what she had to say about the parallel import provisions of the Act:

"I think the easiest answer is that it has not been necessary.
Secondly there is no regulatory framework in which to do this and it has never been done in pharmaceuticals in SA before;"
"It is generally regarded as a 'big stick' to control industry/pricing"
" I think our Medicines Regulatory authority has to set a regulatory framework but have never had detail on this – in other words the new source would probably have to be registered and the importer? Don't know just guessing. This is besides the IP issues.
SA is currently working on an IP policy. This is intended to facilitate the TRIPS flexibilities – Compulsory Licenses and Parallel Imports are both included in the policy. The other major thrust is Examination of patents.
South Africa is a major manufacturer of pharmaceuticals (top local manufacturers constitute 25% of the market) – thus with local manufacturing capacity our needs are not really lack of supply of any product but rather a price issue.
Our government tendering system if highly efficient will result into competitive prices to the state. SA also has a local manufacturing policy (PPPFA)"

Finally, another respondent to our questionnaire, the Head of Regulatory Affairs for Dr. Reddy's Laboratories (Pty) Ltd, said parallel importation had not been used *"Probably because medicines are quite accessible and available in South Africa and at cost competitive prices."*

With all these diverse views on the challenges to implementing parallel importation of pharmaceuticals in South Africa, they were summarized into the following points:

- The regulatory review and filing process is cumbersome and back-logged leading to unwarranted delays in the approval process.
- The regulatory framework does not give the parallel importer of a drug sufficient incentive to be able to import pharmaceuticals and sell them at a reasonable profit margin.
- The 2 year duration of an issued permit from the Health Minister is short and is not guaranteed to still be valid before registration approval from the Medicines Control Council.

• Patent holders have welcomed the idea of issuing Voluntary Licenses to the local drug manufacturers as opposed to Parallel Importation and Compulsory Licenses. This has lead to a surge in the number of Voluntary licenses in South Africa.

• Off-patented generic drugs have also flooded the market leading to a significant drop in essential drug prices especially for ARVs. Most generics have come from India, who has produced and sold these generics at low prices.

• The government has put into place price control schemes that determine how much a drug will be sold in the market. This process takes place every two years, and it leads to a bidding war where potential distributors and manufacturers try to get a fair price comparable to the price in other markets.

• The parallel importer will be liable to legal enforcement actions should the drugs being sold produce significant side effects in subjects. The fear of potential litigation scares away potential parallel importers.

• Parallel importers have not found a rich source of low price pharmaceuticals that they can invest the time and money involved in getting regulatory clearance to make enough profit.

• The difficulty in merging TRIPS agreement with domestic patent laws. Failure to properly merge both laws leaves the government vulnerable to international sanctions.

CHAPTER 8

CONCLUSION AND RECOMMENDATIONS

8.1 CONCLUSION

In conclusion even though parallel importation was made part of the law in the Republic of South Africa in 1997 by passage of the Medicines and Related Substance Control Amendment Act, it has not been used in practice. The passage of the law was met with tremendous industry and foreign government opposition but with these opposing parties backing down, it appears that the law is still impractical and does not give potential parallel importers any significant financial benefit to involve in such trade. As a result, there has not been any significant impact on the quality of drugs, socio-economic status or pharmaceutical regulatory changes. Alternatively, the parallel import regulations stand as a "Big Stick Diplomacy" to give the government a bidding advantage in its pricing scheme. The drop in the price of most pharmaceutical in South Africa is now evident. This price drop in some essential medicines like ARVs can also be attributed to pharmaceutical patent holders issuing voluntary licenses to local manufacturers who produce brand name drugs at a cheaper price and also the influx of off-patented pharmaceuticals from other countries like India.

8.2 RECOMMENDATIONS

The South African pharmaceutical regulatory scenario is a good example of a developing country to try to implement the flexibilities in the TRIPS agreement. Although the TRIPS agreement has made it possible to import pharmaceuticals through parallel importation or

manufacture them through compulsory licensing, many developing nations have shied away from using these flexibilities. When comparing South Africa with other developing countries like Cameroon, S. Africa has made a lot of adjustments and research over the years since the passage of the 1997 MRSCA. They have better resources than many other developing countries to accommodate a change in their national laws to embrace the TRIPS flexibilities. It is evident from the review of data and information that there are potential benefits if they work on both their current patent laws as well as the MRSCA to align with the provisions of the TRIPS agreement. Even though such a policy has been in the works for years, it has not been passed. Further pressure is needed by advocacy groups and associations to get this into law.

Patent granting measures should be re-enforced, and the practice of "Ever Greening" or granting secondary patents to current patent holders must be examined and loop holes closed. This practice has been known to extend exclusivity rights and prevent generics from entering the market keeping prices high for longer durations.

South Africa must avoid signing bilateral trade agreements with other countries with clauses that prevent the use of parallel trade. Many developing countries have used this technique to prevent their allies in developing countries to participate in parallel trade in the hopes that they will gain from the trade agreements, as well as other forms of aid.

Where high domestic prices in low volume products are caused by exclusive distributorship regulations, such requirements should be eliminated in order to complement the effects of parallel imports. Such distributorship policies have monopolistic effects that can warrant an unnecessary increase in price by such distributors or wholesalers.

Since one major barrier to parallel importation might be the lack of sources, the government should consider entering into bilateral trade agreements with countries that have a high supply of

low price medications like India or Brazil or even another African country. Such trade agreements should include provisions that will not allow pharmaceutical companies to excessively limit the supply in the source country so as to prevent parallel trade. Limitation of supply has been noted in some European countries where supply is done by using estimated supply quotas to meet only local supply. Such quotas will lead to a shortage in the source country. The governments in these source nations can pass legislation that allows for parallel importation and prevents use of supply quotas.

If the parallel import regulations are to be workable, the reviewing authority should have a centralized submission and reviewing system where applications could be submitted. Traditional paper applications could be the cause for the backlog in reviewing of applications. A simplified electronic system like the FDA's eCTD system would help speed up the license granting process at the Department of Health and registration of medicines at the Medicines Control Council.

The country must educate and train personnel on the pharmaceutical regulatory framework from the start to finish. People should know how to use the electronic data system. Reviewers should be trained on how to review applications efficiently, border officers should know how to inspect imports in a timely manner, and quality auditors should know how to audit a storage site or manufacturing facility. Both the Department of Health and Medicines Control Council must be adequately staffed to handle the volume of applications that are received. If applicants need to be charged more in order to speed up the applications process, this should be done. Such extra funds can help to better staff the agencies involved and get the necessary software programs.

Finally, the response rate for this study could have been higher if a face-to-face interview was used rather than a questionnaire. Potential study respondents were contacted through unsolicited emails which could be considered as spam or junk email. With more respondents in

this study, the analysis will have further minimized any chances of error. However, because of the difference in the location of the researcher and the respondents, and also lack of resources, the questionnaire option was the best option.

It was also difficult to obtain data for indicators in the years before 1997. Data for most of the years before 1997 are not readily available. It could be that they were not reported or were not determined at all at that time. If a study could source more data for indicators in the years before 1997, it would reduce possible chances of error. The use of data for many years after passage of the law could also help in reducing error.

This research had limited resources and could not exploit a very wide range of indicators, so there could be chances of error. If more indicators with a significant relationship to parallel importation are used in future studies, this could reduce possible chances of error.

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