

https://dspace.org/

Beyond patent expiry: development of a model for pricing generic drugs in South Africa

Keele, Mothobi Godfrey

2017

https://hdl.handle.net/10539/25605

Keele, Mothobi Godfrey, (2017) Beyond patent expiry: development of a model for pricing generic drugs in South Africa, University of the Witwatersrand, Johannesburg, https://hdl.handle.net/10539/25605

Downloaded from a DSpace repository. https://dspace.org/

BEYOND PATENT EXPIRY: DEVELOPMENT OF A MODEL FOR PRICING GENERIC DRUGS IN SOUTH AFRICA

Mothobi Godfrey Keele



A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree

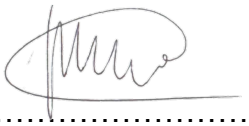
of

Doctor of Philosophy

Johannesburg, 2017

DECLARATION

I, Mothobi Godfrey Keele declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



……..

….17th.day of November 2017

DEDICATION

This study is dedicated to my first-born child Teboho Mokoena Keele who is living with autism with so much courage and zest. Paps loves you a great deal.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Publications:

Full research articles are in draft stage. An abstract based on presentation 3 as per below was published in a journal by the organisers: Keele, MG, Butkow, N, Venter, D. Beyond Patent Expiry: Development of a Model for Pricing Generic Drugs in South Africa. Value in Health. 2013 16(7): A466.

Presentations:

i. Presentation 1:

Conference: The South African Society of Clinical Pharmacy Conference

Title: Pricing of Cardiovascular Generic Drugs in South Africa.

Type of the Presentation: Podium

Date: 25 June 2012,

Place: Rhodes University, Grahamstown, South Africa

ii. Presentation 2:

Conference: Faculty Research Day

Title: Beyond Patent Expiry: Development of a Model for Pricing Generic Drugs in South Africa.

Type of the Presentation: Podium

Date: 19 September 2012,

Place: Wits University, Johannesburg, South Africa

iii. Presentation 3:

Conference: International Society of Pharmacoeconomics and Outcomes Research

Title: Investigation into the Level of Generic Penetration in the Pharmaceutical Industry and its Impact on the Affordability of Medicines in South Africa.

Type of the Presentation: Poster

Date: 04 November 2013,

Place: The Convention Centre, Dublin, Ireland

ABSTRACT

Background: Generic drugs provide a safe, effective and affordable alternative to medicines whose patent protection has expired. The affordability of generics improves access to medicines and thus improves health outcomes. The generic pharmaceutical industry is complex; profitability depends on the number of other generics on the market.

Objective: To develop a model that explains structural relationships in the off-patent market between the price of a generic drug and the characteristics of a drug, formulation market and regulatory processes in the South African pharmaceutical industry.

Sources of Data: Innovators' drugs and their generic equivalents were selected from all the molecules whose patents expired between 1999 and 2012. Data were obtained from IMS Health (Total Private Market Report) and National Department of Health (Database of Medicine Prices) for the patents' expiration dates, prices, sales, launch dates of generics, therapeutic groups, schedules, and dosage forms of drugs in the sample.

Principal Findings: Generic entry into the local pharmaceutical industry is low, slow and selective. The developed model for this study identified seven market variables that were found to have an influence on the prices of generic drugs in South Africa. The determinants of generic entry are the market size of the on-patent innovator product, and the complexity of manufacture of a dosage form. The introduction of the transparent pricing system has had a significant impact in reducing the average unit prices of generics in South Africa. However, there appears to be policy incoherencies between the public health and industrial policies of the South African government as it pertains to pharmaceuticals. The erosion of the manufacturing capacity in South Africa could potentially be attributed to the pharmaceutical pricing policy. The overreliance on pharmaceutical imports for satisfying local consumption poses a risk to the security of supply of medicines in a country that has a high burden of diseases.

Conclusion: The introduction of legislative reforms related to the pricing of medicines in South Africa has largely yielded positive results in making medicines to be more accessible. Policy-making requires monitoring and evaluation programmes and inclusivity across all the stake-holders.

ACKNOWLEDGEMENTS

First, I wish to thank God Almighty for the strength and courage to carry out this study. I also wish to thank my parents (Messr. Teboho Keele and Mrs. Elsie Keele) as well as my sisters (Asi and Ausi Ju) who all taught me the value of discipline and the fear of God. Importantly, I wish to thank them for the many sacrifices they made for me to realize my life-long dreams.

I wish to thank my wonderful supervisor, Dr. Neil Butkow, for his exceptional guidance during the course of this study. I also wish to thank my co-supervisor, Prof. Tobias Chirwa, for always explaining statistical concepts with such clarity. Furthermore, I also wish to thank the following organizations that offered me financial and material support: Aspen Pharmacare, Health and Welfare SETA and IMS Health SA. I also wish to thank the University of the Witwatersrand for the opportunity to pursue my dream.

Lastly, but not least, I wish to thank the support of my wonderful wife, Dr. Mbali Keele and my lovely kids: (Teboho Keele and Bohlokoa Keele) for their patience and encouragement especially for the many periods that I was away from them in pursuit of this study.

TABLE OF CONTENTS

1. INTRODUCTION 18
1.1. Introduction and Background 18
1.1.1. Introduction to the Healthcare System in South Africa 18
1.1.2. Brief Introduction to the Pharmaceutical Industry in South Africa 19
1.1.3. Legislative Framework for the Pricing of Pharmaceuticals in South Africa 20
1.1.4. Patent Expiry, Generic Entry and Pricing of Generic Drugs 25
1.1.5. Microeconomic Model for Pricing in the Pharmaceutical Industry 27
1.2. Purpose of the Study 28
1.2.1. Research Problem 28
1.2.2. Research Question 28
1.2.3. Research Hypothesis 28
1.2.4. Research Goals 28
1.2.5. Research Objectives 29
1.3. Significance of the Study 31
1.4. Recommendations for Further Study 31
1.5. Limitations of the Study 31
1.6. Overview of the Thesis 32
1.7. Conclusion 32
2. RESEARCH METHODOLOGY 34
2.1. Research Design 34
2.2. Sources of Data 34
2.2.1. Primary Source of Data 34
2.2.2. Secondary Source of Data 35
2.3. Selection Criteria 36

2.3.1. Inclusion Criteria 36
2.3.2. Exclusion Criteria 36
2.4. Data Processing 37
2.4.1. Data Extraction and Consolidation 37
2.4.2. Data Coding 39
2.4.3. Data Cleaning 39
2.5. Study Variables 42
2.5.1. Type of Drug Market 42
2.5.2. Type of Drug Therapy 43
2.5.3. Complexity of Manufacture of a Pharmaceutical Dosage Form 44
2.5.4. Order of Generic Entry into the Formulation Market 44
2.5.5. Impact of the Legislative Reforms 45
2.6. Data Analysis 45
2.6.1. Descriptive Data Analysis 45
2.6.2. Inferential Data Analysis 46
2.7. Data Presentation 47
2.8. Reliability 47
2.8.1. Clear Conceptualization of Constructs 47
2.8.2. Increase in the Level of Measurement 47
2.9. Validity 48
2.9.1. Internal Validity 48
2.10. Ethical Consideration 49
2.11. Conclusion 49
3. DESCRIPTION OF THE CHARACTERISTICS OF THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY 50

3.1. Application of the Selection Criteria 50
3.2. Description of the Characteristics of the South African Pharmaceutical Industry. 51
3.2.1. Number of Generic Drug Manufacturers Per Chemical Entity Following the Loss of Exclusivity (LOE) 51
3.2.2. Market Size of the Innovator Product in the Year Preceding LOE 53
3.2.3. The Impact of Generic Entry on Price Erosion 60
3.2.4. Prices of Other Generic Drugs at Entry 61
3.2.5. Frequency Distributions of Therapeutic Categories 61
3.2.6. Frequency Distributions of Dosage Forms 62
3.3. Market Segmentation of the South African Pharmaceutical Industry 64
3.3.1. Market Segmentation by Pharmaceutical Companies 64
3.3.2. Market Segmentation by Pharmaceutical Products 66
3.3.3. Shifts in the Market Segmentation of the South African Pharmaceutical Industry 68
3.4. Emerging Themes in the South African Pharmaceutical Industry 69
3.4.1. The Influence of Generic Entry on the Prices of an Off-Patent Innovator Product 69
3.4.2. The Influence of Authorized Generics on the Prices of Generic Drugs 69
3.4.3. The Influence of Authorized Generics on Price Erosion 69
3.4.4. The Influence of Close Substitutes (Me-Too Drugs) on the Price of Generic Drugs 70
3.4.5. The First-Mover Advantage and the Price of a Generic Drug 70
3.4.6. The Impact of Legislative Reforms on Pharmaceutical Sales 70
3.4.7. The Impact of Patent Expiry on the Prices of Innovator Products 71
3.5. Generic Fending Off Strategies 71

3.5.1. Introduction of Authorized Generics into a Formulation Market 71
3.5.2. Use of 'Evergreening' Tactics 72
3.6. Discussion 73
3.7. Conclusion 83
4. THE IMPACT OF THE TRANSPARENT PRICING SYSTEM ON THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY 85
4.1. Bivariate Descriptive Statistics of the Study Variables 85
4.2. Evaluation of the Impact of the Transparent Pricing System on Study Variables. 90
4.2.1. ANOVA Between the Number of Generic Manufacturers in the Formulation Market and the Transparent Pricing System 90
4.2.2. ANOVA Between the Sales of the Innovator Product Prior to LOE and Transparent Pricing System 90
4.2.3. ANOVA Between the Rate of Generic Entry and the Transparent Pricing System 90
4.2.4. ANOVA Between Price Erosion and the Transparent Pricing System 91
4.2.5. ANOVA between the Transparent Pricing System and the Average Unit Price of an Innovator Product 91
4.2.6. ANOVA between the Transparent Pricing System and the Average Unit Price of a Generic Drug 91
4.2.7. ANOVA between the Transparent Pricing System and the Prices of Other Generic Drugs at Entry 92
4.2.8. Crosstabulation Analysis Between the Type of Drug Therapy and the Transparent Pricing System 92
4.2.9. Crosstabulation Analysis Between the Type of Drug Market and Transparent Pricing System 92

4.2.10. Crosstabulation Analysis Between the Complexity of Manufacture and the Transparent Pricing 92
4.3. Transparent Pricing System and the Realignment of the Local Pharmaceutical Industry 93
4.3.1. Market Structure of the South African Pharmaceutical Industry 93
4.3.2. Market Concentration of the South African Pharmaceutical Industry 95
4.3.3. Market Segmentation of the South African Pharmaceutical Industry 95
4.4. Discussion 95
4.5. Conclusion 100
5. MODEL FOR THE PRICING OF GENERIC DRUGS IN SOUTH AFRICA 102
5.1. Univariate Descriptive Statistics of Variables 102
5.2. Structural Relationship Between the Price of a Generic Drug and Market Variables 108
5.2.1. Price of a Generic Drug and the Number of Generic Manufacturers in the Formulation Market 108
5.2.2. Price of a Generic Drug and the Market Size of the Innovator Product 109
5.2.3. Price of a Generic Drug and the Type of Drug Therapy 109
5.2.4. Price of a Generic Drug and the Order of Generic Entry 110
5.2.5. Price of a Generic Drug and the Pricing Legislative Reforms 110
5.2.6. Price of a Generic Drug and the Type of Drug Market 110
5.2.7. Price of a Generic Drug and the Complexity of the Manufacturing Process Related to a Dosage Form 111
5.2.8. Correlation Analysis Between the Price of a Generic Drug and Study Variables 111
5.3. Development of a Model for Pricing Generic Drugs in South Africa 112
5.3.1. Univariate Regression Analysis for the Type of Drug Therapy 112

5.3.2. Univariate Regression Analysis for the Sales of the Innovator Product in the Year Preceding the LOE 113
5.3.3. Univariate Regression Analysis for the Order of Generic Entry into the Formulation Market 114
5.3.4. Univariate Regression Analysis of the Lagged Number of Generics in the Formulation Market 114
5.3.5. Univariate Regression Analysis of the Lagged Average Price of Other Generics at Entry 115
5.3.6. Univariate Regression Analysis of the Price of the Innovator Product in the Formulation Market 115
5.3.7. Univariate Regression Analysis of the Implementation of the Pro-Generic Policies 115
5.3.8. Univariate Regression Analysis for the Complexity of Manufacture 115
5.3.9. Multivariate Analysis of Generic Price and Predictor Variables 118
5.4. Discussion 119
5.5. Conclusion 124
6. SOUTH AFRICAN INDUSTRIAL PHARMACEUTICAL POLICY: REVIEW AND RECOMMENDATIONS 125
6.1. Optimization of the Rates of Generic Entry into the South African Pharmaceutical Industry 125
6.2. Erosion of Pharmaceutical Manufacturing Capacity: Tension between Public Health Policy and Industrial Policy 127
6.3. Pharmaceutical Pricing Policy in South Africa and the Computation of Single Exit Price Adjustments (SEPA) 129
6.4. Authorized Generics and their Impact on Access to Medicines 134
6.5. Conclusion 140
7. APPENDICES 142

7.1. Appendix A 142
7.2. Appendix B 143
8. REFERENCES 148

LIST OF FIGURES

Figure 3.1 Rates of Patent Expirations and Generic Entry 52
Figure 3.2 Sales of the Innovator Products a Year Preceding LOE,1999 - 2012 54
Figure 3.3 - Generic Entry and Price Erosion, 1999 - 2012. 60
Figure 3.4 Market Segmentation of the Local Industry, 1999 - 2012. 68
Figure 3.5 Generic Fending Off Strategy - Case Study of Loratadine 71
Figure 4.1 Prices of Other Generic Drugs at Entry, 1999 - 2012..... 87

LIST OF TABLES

Table 1.1 Legislative Framework for the South African Pharmaceutical Industry 22
Table 2.1 Original Layout of IMS Health's Data 38
Table 2.2 Summary of the Schedules of Medicines. 43
Table 2.3 Example of Anatomical Therapeutic Chemical Classification 44
Table 3.1 Overview of the Pharmaceutical Market, 1999 - 2012..... 51
Table 3.2 Authorized Generics, 1999 - 2012 53
Table 3.3 Performance of Innovator Products After Loss of Exclusivity, 1999 – 2012 56
Table 3.4 Leading Therapeutic Classes, 1999 – 2012 62
Table 3.5 Leading Dosage Forms, 1999 – 2012 63
Table 3.6 Top 20 Leading Pharmaceutical Companies, 1999 – 2012. 65
Table 3.7 Top 20 Pharmaceutical Products, 1999 – 2012 67
Table 3.8 Generic Fending Off Strategies, 1999 – 2012 72
Table 4.1 Bivariate Descriptive Statistics of the Study Variables 86
Table 4.2 Frequency Distribution of Schedules Before and After the SEP Regime 87
Table 4.3 Frequency Distribution of ATC1 Before and After the SEP Regime 88
Table 4.4 Frequency Distributions of Dosage Forms Before and After the SEP Regime ... 89
Table 4.5 Crosstabulation Analyses of the Type of the Markets 93
Table 4.6 Total Pharmaceutical Market Before and After Legislative Reforms 94
Table 5.1 Univariate Descriptive Statistics of Study Variables..... 103
Table 5.2 Frequency Distribution of ATC1 Categories 103
Table 5.3 Frequency Distribution of Scheduling Statuses 104
Table 5.4 Frequency Distribution of Dosage Forms 105
Table 5.5 Descriptive Statistics of the Sales of the Innovator Product Prior to LOE 106
Table 5.6 Descriptive Statistics of the Types of Drug Therapy and Drug Market 106
Table 5.7 Descriptive Statistics of Order of Generic Entry..... 107
Table 5.8 Descriptive Statistics - Pro-Generic Policies and Complexity of Manufacture .. 108
Table 5.9 Correlational Analyses Between Prices and Predictor Variables. 112
Table 5.10 Results of Univariate Regression Results 116
Table 5.11 Description of Variables..... 117
Table 5.12 Results of Multivariate Regression Analysis 119

NOMENCLATURE

ACE	Angiotensin Converting Enzyme
ANDA	Abbreviated New Drug Application
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ARV	Antiretroviral
ATC	Anatomical Therapeutic Chemical
BMI	Business Monitor International
BRICS	Brazil, Russia, India, and South Africa
CAGR	Compound Annual Growth Rate
CBO	Congressional Budget Office
CD4 Count	Lab test that measures the number of T-lymphocytes (CD4 cells) in a sample of blood
cGMP	Current Good Manufacturing Practice
CMS	Council for Medical Schemes
COSATU	Congress of South African Trade Unions
GDP	Gross Domestic Product
EU	European Union
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
HHI	Herfindahl-Hirschman Index
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
IMS Health	Intercontinental Medical Statistics Health
IPAP	Industrial Policy Action Plan
IPASA	Innovators Pharmaceutical Association of South Africa
IPR	Intellectual Property Rights
JSE	Johannesburg Stock Exchange
LOE	Loss of Exclusivity
MCC	Medicines Control Council
MMAP	Maximum Medical Aid Price
MRC	Medical Research Council
NAPM	National Pharmaceutical Manufacturers
NCD	Non-Communicable Diseases
NDA	New Drug Application
NDoH	National Department of Health
NDP	National Drug Policy
NEMLC	National Essential Medicines List Committee
NERSA	National Electricity Regulator of South Africa
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-Counter
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMB	Prescribed Minimum Benefits
PPI	Producer Price Index
PPPA	Preferential Procurement Policy Framework Act
PTG	Pharmaceutical Task Group

SA	South Africa
SD	Standard Deviation
SE	Standard Error
SEP	Single Exit Price
SEPA	Single Exit Price Adjustment
TPM	Total Pharmaceutical Market
Tukey HSD	Tukey Honest Significant Difference
UK	United Kingdom
UN	United Nations
US FDA	United States Food and Drug Administration
USA	United States of America
UTT	Universal Test to Treat
WEF	World Economic Forum
WHO	World Health Organization

CHAPTER ONE

1. INTRODUCTION

A favourable environment for generic medicines is likely to aid governments in sustaining the provision of healthcare and control of pharmaceutical expenditures. Generic medicines have the same quality, safety profiles and therapeutic efficacy as originator medicines, but are less expensive than originator medicines. This chapter highlights the problems of inequitable access to healthcare, particularly medicines, in South Africa.

The chapter is broadly divided into 5 sections with Section 1.1 briefly providing the basis for regulation of the prices of medicines in South Africa. This section provides a context for the research study as well as highlights gaps in the field that the study seeks to address. It is noteworthy that Section 1.1 is not a literature review section. Literature review is conducted at relevant parts throughout the thesis such as under Sections 3.6 (e.g. MCC's registration timelines and authorized generics), 4.4, 5.4 & 6.1 - 6.5. Section 1.2 presents the purpose of the study covering the research problem, question, hypothesis, research goals, and objectives. Sections 1.3 – 1.5 deal with the significance of the study, limitations and the overview of the thesis respectively. This is followed by the chapter conclusion in Section 1.6.

1.1. Introduction and Background

A review of the literature into studies that sought to understand the factors that influence the pricing of generic drugs is preceded by a brief appraisal of the healthcare system in South Africa as well as an outline of the legislative framework for pricing generic drugs in South Africa.

1.1.1. Introduction to the Healthcare System in South Africa

To put the pharmaceutical pricing policy of South Africa into perspective, it is important to provide a brief background into the structure of the healthcare system in South Africa. The country consists of two sectors of healthcare, the public and the private sectors.

The public sector is an under-resourced three-tier system (local, provincial and national government) that serves more than 85% of the South African population.[1-2] It provides the primary, secondary and tertiary healthcare organized into district, regional and tertiary

levels.[3] This sector is financed by a combination of national taxes as well as revenue contributions from local government and user fees.[2]

The public sector operates an Essential Drug List (EDL) programme, a criterion for inclusion of a medicine in the EDL is that a drug must be of high quality, cost-effective and meet the healthcare needs of the majority of the country's citizens.[3] It was estimated in 2015 that the public sector was supplied with approximately 2400 product lines by about 90 manufacturers and importers at an estimated value of $1 billion.[1] The public sector employs the use of competitive bidding, tenders system, for the procurement of its medicines and other supplies under the auspices of the Central Procurement Unit of the Department of Health.[1]

On the opposite end of the healthcare spectrum in South Africa is the well-resourced private healthcare sector that serves approximately 15% of the South African population.[1] According to Intercontinental Medical Statistics (IMS), the private pharmaceutical market in South Africa was valued at $4.1 billion in 2014.[1] There is a broad portfolio of medicines that are available in the private health sector that amount to approximately 5000 product lines by about 130 manufacturers and importers.[1]

Private healthcare in South Africa is primarily financed through medical aid schemes and to a less extent by out-of-pocket payments.[2] The pricing of medicines in the private sector was previously left to market forces.[1] As such, pharmaceutical companies engaged in a wide range of pervasive practices such as offering volumes-linked discounts and rebates to wholesalers as well as offering bonuses and samples to healthcare providers with a view to coerce them to using their products.[1] The prices of medicines in South Africa were found to be high by international standards which was attributable to the wide range of pervasive practices that were employed by pharmaceutical companies.[1-2]

1.1.2. Brief Introduction to the Pharmaceutical Industry in South Africa

Business Monitor International (BMI) Ltd, a Fitch Group Company, reported that the South African pharmaceutical industry was valued at ZAR 43.41Billion (USD 3.4 Billion) in 2015 which was 1.09% of the Gross Domestic Product (GDP).[4] The industry is regulated by

the Medicines and Related Substances Act, Act No. 101 of 1965 (as amended) under the auspices of the Medicines Control Council (MCC).[1]

The pharmaceutical landscape in South Africa comprise of the prescription and over-the-counter (OTC) pharmaceutical products supplied by both generic drug companies and research-based drug companies.[4]

Majority of leading pharmaceutical multinational companies have presence in South Africa, these companies predominantly market branded innovative drugs.[4] The local pharmaceutical industry is relatively advanced albeit its focus on the manufacture of generic drugs. Two dominant local manufacturers are Aspen Pharmacare and Adcock Ingram, both companies are generic manufacturers.[4]

1.1.3. Legislative Framework for the Pricing of Pharmaceuticals in South Africa

The advent of democracy in 1994 was amidst major health and social challenges in South Africa. In 1994, major disparities and inequalities in income, health status and access to health and other social services existed in South Africa. This was the result of previous apartheid policies that ensured racial, gender and provincial disparities. To redress this legacy of apartheid, the democratically elected South African government prioritized equity in its health policy goals.[3]

In recognition of these challenges, a new constitution was enacted in 1996; Constitution of the Republic of South Africa (No. 108 of 1996).[7] Section 27(1) of the constitution of South Africa declares that access to adequate healthcare (including medicines) is a human right. Furthermore, Section 27(2) of the constitution declares that the state is duty bound to ensure that there are sound regulations and laws that promote affordability and thus improve access to healthcare (including drugs).[7] Against this background, a White Paper on the Transformation of the Health System in South Africa was introduced in 1997.[3] A key policy objective of the White Paper was the promotion of equity, accessibility and health services. Provision of pharmaceutical care was dealt with extensively in a document called the National Drug Policy (NDP) that formed part of the addendums of the White Paper. The NDP is a blueprint that provides a policy framework on medicines

in South Africa.[5] As reported in the NDP, the government conducted a situational analysis of the pharmaceutical landscape following the advent of a democratic dispensation. The government found, *inter alia*, that the prices of medicines in South Africa were high by international standards.

Given the central role that pharmaceuticals play in the delivery of healthcare, the problem of high prices of medicines received immediate attention of the new government. This resulted in a wide range of legislative reforms aimed at ensuring equity and promotion of access to healthcare particularly pharmaceuticals across the nation. Cornerstone to the existing statutes that were targeted for reforms was the Medicines and Related Substance Act (No. 101 of 1965), henceforth Medicines Act. The first amendments to the Medicines Act were proclaimed in 1997 and in 2003 the Patents Act was also amended.[6] Except for the Medical Schemes Act (No. 131 of 1998), all other new statutes that were promulgated had broader societal benefits that transcended healthcare; notably the Competition Act (No. 89 of 1998).[8]

Table 1.1 below provides an overview of the guiding policy framework that underpins the South African legislative interventions with a view to address the challenges of inequitable healthcare delivery, particularly pharmaceutical price regulation. The government employed a broad spectrum of price regulations comprising of indirect and direct price regulations.[8] Indirect price regulations were introduced with a view to create and promote a competitive market that would result in an exertion of a downward pressure on the prices of medicines.[8] These were done with a view to increase affordability and thus increase access to medicines.[8]

As shown in Table 1.1, the Medicines Act was amended to introduce Section 15C to allow parallel importation of patented medicines. In cases where a local price for a patented essential medicine that is needed to respond to an emergency is higher than in other countries, the state is at liberty of applying this law to import such a drug into the country.

Other than parallel importation the South African legislative framework has made provision for an array of legal instruments that can be invoked to stimulate competition with a view to drive the prices down. For instance, compulsory licensing can be pursued under the Competition Act by proving to the courts that a position of dominance is being abused by a patentee to the detriment of society.[8]

Table 1.1 Legislative Framework for the South African Pharmaceutical Industry

The Constitution of the Republic of South Africa Act (No. 108 of 1996)	
Section 27(1)	Everyone has the right to have access to health care services (Bill of Rights)
Section 27(2)	The state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights (Bill of Rights)
White Paper on the Transformation of the Health System in South Africa	
Goals and Objectives	To promote equity, accessibility and utilisation of health services
	To extend the availability and ensure the appropriateness of the services
National Drug Policy of the Republic of South Africa	
Health Objectives	To ensure the availability and accessibility of essential drugs to all citizens
Economic Objectives	To lower the cost of drugs in both the private and public sectors (by developing specific strategies to increasing the use of generics in South Africa)
National Objectives	To support the development of the local pharmaceutical industry and the local production of essential drugs
Medicines and Related Substances Act (No. 101 of 1965 as Amended)	
Section 15(2)(b)	Provides for expeditious registration of medicines in the Essential Drug List within 9 months
Section 15C	Made provisions for parallel importation of medicines that are still under patent to South Africa for public sector
Section 18A	Forbids supply of medicines in terms of bonus, rebates and incentives schemes
Section 18B	Forbids the sampling of medicines
Section 22A	Control of medicines and scheduled substances
Section 22C 1(b)	Empowers the government, through the MCC, to prescribe the standard for manufacture of medicines in South Africa - PIC/S
Section 22F	Makes it mandatory for the pharmacists to inform patients of generic equivalents of the prescribed drug
Section 22G	Made a provision for the introduction of the transparent pricing system for medicines based on single exit price
Section 22G(2)	Made provisions for regulation of dispensing fees and capping of logistics fees
Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances, Medicines Act (No. 101 of 1965)	
Regulation 5(2)(e)	Made provisions for benchmarking of pharmaceutical (innovator products) prices internationally
Regulation 14(5)	Made provisions for use of pharmacoeconomic studies in support of price
Patents Act (No. 57 of 1978)	
Section 46(1)	Stipulates a duration for which a patent remains in force as 20 years
Section 69(A)	Provides for limitations to intellectual property by allowing registration of generics prior to patent expiry
Regulations in terms of the Medical Schemes Act (No. 131 of 1998)	
Regulation 8	Makes a provision for implementation of cost-containment strategies such as the use of formularies & reference price lists

Source: Hassim *et al*. [8]

In 2004, the Competition Act was used successfully in a landmark case that resulted in the issuing of compulsory licenses to local generic manufacturers to produce generic copies of antiretroviral (ARVs) drugs. The case was brought to the courts by civil society organizations in the case of *Hazel Tau and Others vs GlaxoSmithKline and Boehringer*

Ingelheim. Compulsory licensing agreements are covered by law whereby the patent holder is entitled to receive a reasonable royalty, usually (2–10) %.[8]

Further indirect price regulations were instituted by the South African government with a view to stimulate competition related to the introduction of Section 69(A) to the Patents Act, Act No. 57 of 1978 (as amended). The introduction of Section 69(A) makes a provision for a non-infringement of a valid pharmaceutical patent. This provision allows regulatory applications for generic drugs to be filed with the Medicines Control Council whilst the patent remains enforceable with a view to facilitate a timeous launch of generic drugs upon patent expiry thus improving access to medicines in line with Section 27(1) of the constitution.[6-7]

The promulgation of the Competition Act in 1998 provided an instrument for the government to act against any anticompetitive behavior in the market.[8] Such anticompetitive behavior can take a form of collusions by competitors to fix prices or agreeing to carve up the market into various segments or sectors. Collusions are aimed at keeping the competition at minimum in the market which is often to the detriment of society. [8]

On the other hand, the direct price control interventions act directly to regulate how prices are set. They are aimed at complementing the indirect price controls mechanisms where competition alone is not adequate to keep the prices of medicines down.[8] The direct price control interventions can be classified into three groups, namely, government laws that prohibit high prices, direct price controls and state guidelines for price setting. The direct price regulations were introduced with a view to improve access to medicines by directly reducing the prices of medicines in South Africa.[9] This category pertains to the rules or guidelines that are put in place by the state to assist stakeholders such as manufacturers to set their own prices. The value of this approach is that it makes it mandatory for stakeholders to justify their prices thus ensuring that there is accountability and transparency in how prices are set.[9] Prior to the institution of the legislative reforms that

deals with the pricing of medicines, the manufacturers were at liberty to set their own prices and had no legal duty to account as to how such prices were calculated. [9]

To achieve the goal of ensuring that there is transparency and accountability in how prices are set, the Medicines Act was reformed by the introduction of Section 18A, 18B and 22G. The government banned the perverse commercial activities through the operation of Section 18A and 18B.[4] Section 22G provided for the setting up of the pricing committee whose primary role is to advise the Minister of Health on transparent pricing system. Furthermore, Section 22G ensured that transparency and accountability were built into the system with the introduction of a concept of Single Exit Price (SEP).[9]

The SEP is the price that is set by the manufacturer or importer of a medicine or scheduled substance, it includes the value-added tax (VAT) and the logistics fee.[9]Prior to its implementation, the pricing regulations stipulated the methodology that the manufacturers had to follow in setting the SEP for their products.[9] On the commencement of these regulations, 02 June 2004, for any given medicine the SEP was required not to be set higher than the weighted average net selling price for the calendar year 2003.[9] In accordance with these regulations, for any given dosage form of any medicine, each unit bears the same price irrespective of the pack size. Lastly, the upward adjustment of SEP is subject to a pre-determined percentage fee that is set by the Minister of Health upon obtaining advice from the pricing committee. The price increases that are determined by the minister set the ceiling without prescribing the floor for medicines' prices.[9]

The` Medical Scheme Act makes provisions for the schemes to adopt managed healthcare principles. In this way the utilization of various healthcare services is monitored using interventions that are aimed at monitoring the appropriateness, promoting efficacy, quality and cost-effectiveness of the delivery of relevant health services.[10] Insofar as the pharmaceutical care is concerned, some of the prominent managed healthcare strategies that are used by medical aid schemes with a view to prohibit high prices of drugs are the use of formularies and reference pricing. The use of formularies is underpinned by generic

substitution in accordance with Section 22F of the Medicines Act. Mandatory generic substitution is an important instrument for reducing unnecessary drug expenditure.[11]
Reference pricing is another prominent strategy of managed healthcare that is commonly employed with a view to prohibit high prices of medicines.[12] Reference pricing consists of internal and external reference pricing. Internal reference pricing within the medical aid schemes context requires that drugs be classified into therapeutic classes with a reference drug being selected for any given class.[13] A price ceiling is then set in line with the selected reference drug, the price ceiling represents the maximum reimbursable price with a patient having to pay a difference if a more expensive drug is used.[13] This mainly encourages the use of generic drugs.[13]

1.1.4. Patent Expiry, Generic Entry and Pricing of Generic Drugs

The generic market consists of companies that are involved in the development, production, distribution, sales and marketing of usually cheaper multi-source pharmaceutical products that are interchangeable with the innovator product following an expiry of its patent protection or exclusivity rights.[14] Generic manufacturers compete 'on a knife edge' of narrow margins of profitability, and a decision to enter the generic pharmaceutical industry is risky and complex.[15] In the generic pharmaceutical industry success depends on the number of other generic drug manufacturers on the market, which affects the profit margins and volumes that each company could realize.[16] Market saturation erodes the price-cost margins due to competition that pushes the prices down.[16]

Several studies in the international arena have analyzed the dynamics of innovator's products market shares and prices following loss of patent protection and subsequent generic entry. Suh *et al.* undertook a study that sought to analyze the effect of generic entry on price competition following the loss of patent protection in the United States of America (USA)'s pharmaceutical industry. Their study enrolled 35 chemical entities that lost patent protection between 1984 and 1987. Principally, they found that the prices of innovator products continued to rise following the loss of exclusivity, while the prices of corresponding generic drugs decreased significantly over time. They defined this phenomenon as Generic Competition Paradox and concluded that pricing in the

pharmaceutical industry is influenced by how the market is classified and defined.[17] This finding is in contrast with the general theoretical pricing model proposed by Satterthwaite *et al.* to elucidate the effect of new firm entry on prices in monopolistically or oligopolistically competitive markets.[18] Satterthwaite *et al.* postulated that entry of a new company into a market results in the demand curve shifting for the originator making it less elastic.[18] Suh *et al.* concluded that since the conditions of competition in the pharmaceutical industry are complex, the general pricing theory as proposed by Satterthwaite *et al.* cannot be applied to pharmaceuticals.[17]

In another study undertaken in the USA, Saha *et al.* conducted a study focusing on the interaction between generic entry, generic share and generic-to-brand price ratio. They examined 40 drugs from 9 therapeutic classes that experienced generic competition between July 1992 and January 1998.[19] They developed an econometric model that describes the interaction between various key variables. They found that generic share and price are inextricably linked while the number of generics in the formulation market is a key driver of the market share and price erosion. Lastly, they found that generic competition is more intense for blockbuster drugs than the innovator products that had moderate sales whilst under patent protection.[19]

In 2000, Hudson investigated generic uptake in Japan, United Kingdom (UK), Germany and the United States of America (USA) following the loss of patent protection. Using IMS Health data, the study enrolled 50 molecules that came off patent between 1985 and 1996. Only the oral products, oral retard products, liquid products and topical products were included in the study. Hudson concluded that the market size of the innovator product before loss of exclusivity (LOE) was a key determinant of generic entry.[20] Elsewhere, Magazzini *et al.* also employed the use of IMS Health data that enrolled 269 active ingredients across multiple countries (USA, UK, Germany and France). They also held that the commercial success (relative market size) of the innovator product facilitates generic entry. [21]

In Belgium, Adriaen *et al.* investigated the pricing strategies of innovator and generics in the off-patent market. Their study enrolled 91 innovator products that lost patent protection between 2001 and 2005.[22] They found that pricing strategies are influenced by regulatory processes, market incentives and the level of competition between the innovator product and multi-source products. They concluded that the complexity of the industry is such that there is no single strategy that spurs the pricing behavior for both the innovators and manufacturers of generic drugs.[22]

1.1.5. Microeconomic Model for Pricing in the Pharmaceutical Industry

Supply and demand represents an economic model of price determination in a market.[23] In a competitive market, an economic equilibrium for both the price and the quantity is reached when the unit price for a particular good varies until it settles at a point where, at current prices, the quantity demanded by consumers equals the quantity supplied by producers.[23] Supply and demand conforms to the following four basic laws:

a) If demand rises and supply remains constant, a deficit occurs, resulting in a higher equilibrium price
b) If demand declines and supply remains constant, a surplus occurs, resulting in a lower equilibrium price
c) If demand remains constant and supply increases, a surplus occurs, resulting in a lower equilibrium price
d) If demand remains constant and supply decreases, a shortage occurs, resulting in a higher equilibrium price.[23]

Simply stated, it means that the lower the price of a good the greater the quantity that consumers are willing and able to buy.[23] The economic theory dictates that both production costs and demand are integral parts of determining the price for a commodity.[24] The demand curve slopes downward as the price of a commodity continues falling.[24]

As seen in the foregoing literature review, there are many empirical studies in the international arena that have focused on the effect of price competition in the generic pharmaceutical industry. These studies gave rise to various models that accounts for interaction of various key market variables that explain the competitive dynamics of

pricing generic drugs in the pharmaceutical industry. A literature search and review indicated that there are no studies that were conducted in South Africa to understand how structural relationships in the market influence the pricing of generic drugs. This is despite having several landmark legislative reforms thus a gap in knowledge was identified.

1.2. Purpose of the Study

The purpose of this study is articulated below following the presentation of the research problem, question, and hypothesis.

1.2.1. Research Problem

According to the National Drug Policy, generic drugs underpin the government's plan to improving access to safe, efficacious and affordable quality drugs. However, the influence of the structural relationships (characteristics of the drug, formulation market, and the impact of legislative reforms) on the prices of generic drugs has not being explicitly accounted for. The extent to which South Africa is reliant on imported medicines can be attributed to, *inter alia*, the poor understanding of the dynamics of the local pharmaceutical industry such that it serves as barrier to attracting investment into the local generic pharmaceutical industry.

1.2.2. Research Question

What are the factors that influence the pricing of generic drugs in South Africa? Insofar as such factors are concerned, is there an association between a price of a generic drug and the characteristics of a drug, market and the regulatory changes?

1.2.3. Research Hypothesis

The legislative reforms related to the transparent pricing system have resulted in changes in the prices of generic drugs in South Africa.

1.2.4. Research Goals

To understand the effect of generic entry on price competition after loss of exclusivity in the South African pharmaceutical industry by developing a model that explains the structural relationships that underpins the pricing of generic drugs.

1.2.5. Research Objectives

- To understand and describe (using descriptive statistics) the characteristics of the pharmaceutical market in South Africa as it pertains to the following:
    - Number of generic drug manufacturers per chemical entity that has lost its patent protection
    - Market size at first generic entry with respect to the sales of the innovator product prior to patent expiry
    - The rate of generic entry (months since expiry of patent) and how it results in price erosion as it relates to generic-to-innovator-price ratio
    - Prices of other generic drugs at entry
    - Therapeutic class
    - Scheduling status
    - Dosage form
- To conduct a trend analysis of the pharmaceutical market with a view to establish whether or not the introduction of the transparent pricing system in South Africa had any influence on the following:
    - Number of generic drug manufacturers per chemical entity that has lost its patent protection
    - Market size at first generic entry with respect to the sales of the innovator product prior to patent expiry
    - The rate of generic entry (months since expiry of patent) and how it results in price erosion as it relates to generic-to-innovator-price ratio
    - Prices of other generic drugs at entry
    - Therapeutic class
    - Scheduling status
    - Dosage form
- To perform a univariate analysis with a view to establish whether or not there is an association between a price of a generic drug and the following factors:
    - Number of generic drug manufacturers per chemical entity that has lost its patent protection

    - Market size at first generic entry with respect to the sales of the innovator product prior to patent expiry
    - The rate of generic entry (months since expiry of patent) and how it results in price erosion as it relates to generic-to-innovator-price ratio
    - Prices of other generic drugs at entry
    - Therapeutic class
    - Scheduling status
    - Dosage form
- Develop a multiple linear regression model to describe the correlation between the price of a generic drug in South Africa and the following factors:
    - Number of generic drug manufacturers per chemical entity that has lost its patent protection
    - Market size at first generic entry with respect to the sales of the innovator product prior to patent expiry
    - The rate of generic entry (months since expiry of patent) and how it results in price erosion as it relates to generic-to-innovator-price ratio
    - Prices of other generic drugs at entry
    - Therapeutic class
    - Scheduling status
    - Dosage form
- Having identified and understood the factors that influence the pricing of generic drugs in South Africa, generate a detailed account of such factors with a view to:
    - Influence policy making of the Pharmaceutical Economic Evaluation Unit within the Department of Health
    - Support the goal of the National Drug Policy of ensuring the increased supply of cost-effective drugs (generics) by helping aspiring generic drug manufacturers to better understand the dynamics of the generic drugs sector and thus give them enough confidence to enter the market

1.3. Significance of the Study

This study builds on prior work done in several studies conducted abroad but contributes to the body of knowledge in several dimensions. According to an extensive literature search in Nexus database system, this is the first study within the South African context that explicitly accounts for the structural relationships that underpin the pricing of generics. This study examines a relatively large sample of panel data, 204 molecules, over a fairly long period, 1999-2012.

Secondly, the choice of the study period is instructive in appraising policy responsiveness following the legislative reforms. Furthermore, this study consists of the most comprehensive inclusion criteria and thus higher generalizability of the results. Lastly, the study makes a fundamental contribution to the body of knowledge in the pharmaceutical industry by revealing the structural relationships that spur the pricing behaviour of generic manufacturers in South Africa. This could potentially encourage more generic entrants which will stimulate competition resulting in affordable medicines and thus increased access.

1.4. Recommendations for Further Study

It is recommended that a study be undertaken that will develop a model for pricing generic drugs in South Africa by accounting for both the external and the internal variables. Furthermore, it is recommended that a study be done that will investigate the impact of pricing in the transparent pricing system wherein the consumer price index (CPI) is replaced by the producer price index (PPI) with a view to establish whether a PPI will be a fair criterion to use that accounts for the cost pressures of the pharmaceutical companies. Lastly, it is recommended that a study be conducted that will use the latest pricing data to demonstrate that the model replicates reality in terms of pricing of generic drugs.

1.5. Limitations of the Study

The study only accounts for the external factors that influence the pricing of generic drugs. This is evident in the low adjusted R^2 (35.0%) as discussed in Section 5.3. Furthermore,

the study employs the use of historical data such data it does not offer predictive properties of the generic prices in the South African market.

1.6. Overview of the Thesis

The thesis comprises of six chapters. The first chapter dealt with the introduction and background focusing on pertinent literature with a view to identify research gaps in the field. More detailed literature review was done throughout as the thesis developed. This was followed by the purpose of the study which covered a research problem, question, presentation of a hypothesis as well as the research objectives in Sections 1.2.1 – 1.2.5. Furthermore, the chapter dealt with the significance of the study, limitations of the study and the overview of the thesis, Sections 1.3 – 1.5 respectively. This was followed by a conclusion.

Chapter 2 expounds on the research methodology that underpins the study. The chapter consists of ten sections that dealt with the research processes that were undertaken in executing the study. Chapter 3 is comprised of six sections. The results provide an overview of the key features of the South African pharmaceutical industry. Chapter 4 consists of five sections that deal with the impact of the transparent pricing system in South Africa. This is followed by Chapter 5 which is also comprised of five sections that covers the inferential statistics related to the development of a model for pricing generic drugs in South Africa. Finally, Chapter 6 presents an integrated discussion on the findings of the study and makes policy recommendations. The chapter is comprised of five sections.

1.7. Conclusion

Generic drugs are an important expenditure optimization tool that facilitates access to healthcare. The pharmaceutical landscape in South Africa has undergone major legislative reforms aimed at making medicines more affordable and by extension accessible. Whereas generic drugs are central to the government's plans of ensuring the availability of good quality, safe, efficacious and affordable medicines; there has never been a study that has accounted for the intricacies of pricing generic drugs in South Africa.

The purpose of this study is to set up a model that explains generic competition and prices in South Africa by considering the influence of the structural relationships in the market. Whereas several studies of this nature have been conducted in the international arena, this is the first study that considers the South African perspective and is therefore poised to fill a research gap and make recommendations for pharmaceutical policy formulation.

CHAPTER TWO

2. RESEARCH METHODOLOGY

Chapter 2 provides a detailed account of the research process that underpins the study. The chapter is broadly divided into ten sections. The first three sections deal with the research design, sources of data and the selection criteria for the study. This is followed by the second three sections of the chapter that deals with the processing of the data, an outline of the study variables as well as the analysis of data. Finally, the remaining four sections of the chapter focuses on the presentation of data, reliability, validity and ethical considerations.

2.1. Research Design

The orientation of this study is the positivist research paradigm that employs the quantitative research method using a non-experimental retrospective longitudinal design. WHO argues that conducting non-experimental retrospective longitudinal studies such as document reviews is a cost-effective way of doing research.[25] Furthermore, WHO argues that insofar as document reviews are concerned "sales statistics provide useful information and can be obtained from Intercontinental Medical Statistics (IMS) Health affiliates in each country".[125] Accordingly, the current research study employed the use of panel data emanating from IMS Health South Africa.

2.2. Sources of Data

Two sources of data were employed in this study comprising both of a primary and secondary source of data.

2.2.1. Primary Source of Data

The primary source of data for this study was IMS Health comprising of two of their 'off-the shelf' commercially available reports: Sales Audits and Market Segmentation Reports. The Sales Audits report presents national sales of products by pack and manufacturer. The prices are reported at ex-factory level. Additionally, the Sales Audit report keeps track of the number of units sold, revenue generated and market shares of the products. On the other hand, the IMS Market Segmentation report provides comprehensive information

on the products with respect to the dates of patent expiry for innovator products and the launch dates for both the innovator and generic products.

For the purposes of this study, IMS Health was requested to provide a report that incorporated both reports (IMS Market Segmentation and Sales Audits) into an integrated annual series based report. This report served as a primary source of data and included the following variables: proprietary names, dosage forms, strengths, pack sizes, launch dates and patent expiry dates and monthly sales data (price, sales and market share).

The prices were based on ex-factory prices less discounts in pre-2004 data and SEP (exclusive of value-added tax, VAT) post-2004. This distinction is to account for the differences before and after the implementation of the transparent pricing system. The ex-factory prices less discounts in the period preceding the introduction of the transparent pricing system is an equivalent of the SEP in the period following the implementation of the reforms.[9]

Prior to analysis of data, VAT at 14.0% was applied to all the prices to comply with the legal definition of SEP. These are the prices that the pharmacies and other licensed dispensers in terms of section 22G of the Medicines Act obtain their medicines at. Additionally, the sales and prices were deflated to constant rands using 1999 as a base year.

2.2.2. Secondary Source of Data

Pharmaceutical Economic Evaluation (PEE) Unit within the NDoH served as a secondary source of data. The PEE Unit is required to maintain a comprehensive database of all medicines that are registered in South Africa. This database is a public record that is hosted on the website of the PEE Unit within the NDoH (http://www.mpr.gov.za/PublishedDocuments.aspx#DocCatId=21).

The database is updated on a regular basis and keeps track of, *inter alia*, the following pertinent details of medicines: product name by proprietary and API, dosage forms, pack sizes, SEP, ATC codes, scheduling status, the 9-digit product nappi code, and the product

MCC registration number. The database was used to extract the ATC codes, scheduling statuses, and active ingredients with a view to supplement the primary data.

2.3. Selection Criteria

The eligibility of each case (pharmaceutical product) for inclusion or exclusion was assessed based on a pre-determined selection criterion.[26] The study period, 1999-2012, was chosen to represent a period wherein major legislative reforms were enacted as discussed in Section 1.1. This was done with a view to establish their impact by drawing comparisons of the period prior to their introduction and the period following their introduction.

2.3.1. Inclusion Criteria

The inclusion criteria were based on both the patent expiry dates in the case of non-generic drugs and product launch dates in the case of generic drugs. The criterion was inclusive insofar as the various dosage forms, scheduling status and therapeutic categories were concerned.

All the innovator (non-generic) products whose patents expired between 01 January 1999 and 31 December 2012 were included in the study. Furthermore, all the generic equivalents of the innovator drugs that had patent expirations during this window period and were launched between 01 January 1999 and 31 December 2012 were included in the study. Information on the registered generic drugs was based on launch dates. Given that every strength and dosage form of a product represents a formulation, every product that was launched on a different date based on a different strength and/or dosage form was treated as a separate case.

2.3.2. Exclusion Criteria

As described above, the original IMS Health data listed the expiry dates for each product. A Microsoft Excel custom sort function was used to sort the data based on market segmentation (generic or non-generic markets), followed by product expiry information in the case of innovator products and launch dates in the case of generic drugs. If a patent protection of an innovator product expired either prior to the 1st of January 1999 or after 31st of December 2012 it was automatically excluded from the sample. Exclusion of an

innovator product triggered an exclusion of its associated generic drugs. However, a provision was made not to exclude authorized generics that entered the market prior to patent protection of their corresponding innovator product.

In the case of generic drugs, the product launch dates were used to exclude products if a generic drug was registered before the 1st of January 1999, the data set did not contain any data post 2012. Exclusions were also applied in cases where an innovator product had a patent expiry date that was outside the window period but had a generic equivalent being registered and launched between the 1st of January 1999 and the 31st of December 2012.

Lastly, to avoid distorting the dynamics of the industry based on technical grounds insofar as the intellectual property rights (IPR) are concerned, the antiretroviral drugs (ARVs) were also excluded from the study. As seen in Section 1.1.1, this class of drugs was a subject of a long-protracted court battle that resulted in the ARVs being 'genericized prematurely' because of a court order that led to the issuing of compulsory licenses to local generic manufacturers.[8]

2.4. Data Processing

Data processing was carried out in three stages that involved data extraction, coding and data cleaning. These functions were achieved by making an extensive use of Microsoft Excel 2007 logical functions without using any macros.

2.4.1. Data Extraction and Consolidation

The data processing started with extracting data from all the separate workbooks, eight from IMS Health, and one from the NDoH (PEE Unit). All these data were consolidated into a master workbook whilst keeping them in separate worksheets. Insofar as the data from IMS Health was concerned, the data was organized into horizontal and vertical configurations. The horizontal configuration was organized into fixed columns each dealing with sales data on monthly basis. Each month provided an account of sales data as it pertains to the product's average price per pack, monthly sales and market share

data per product. The vertical configuration was organized into six data layers based on the level of detail as shown in Table 2.1.

Table 2.1 Original Layout of IMS Health's Data

Data Layer No.	Level of Detail on the Vertical Plane	Level of Detail on the Horizontal Plane
1	Total Selected	Provided total monthly sales for the Total Pharmaceutical Market
2	Market Segmentation (Non generic and Generic)	Provided total monthly sales for each sector of the Market (Innovators & Generics' sectors)
3	Manufacturer	Provided total monthly sales for each Manufacturer
4	Patent Expiry Data	In addition to the sales data, it Provided aggregated data on patent expiry dates at Manufacturer level
5	Product Launch Dates	Cumulative data including the product launch dates at proprietary level
6	Full Product Description	Cumulative data including the product launch dates at full product level (dosage forms, strengths & pack sizes)

Data from various worksheets was extracted and consolidated into a master worksheet of a master workbook. This was done in a manner that maintained the annual organization and various data layers as it had been from the original workbooks. The consolidated worksheet and workbook served as master worksheet and master workbook respectively. To optimize data processing and analysis the vertical organization of the data was reorganized into a data matrix consisting of records in rows and variables in columns. The variables in columns individually described the level of data at disaggregated level as shown in layer six of Table 2.1 above.

Each pharmaceutical product in the data matrix constituted a record. Each record consisted of the following variables organized into columns: product name, market segmentation (generic or innovator), name of the manufacturer, dosage form, strength, pack size, product launch date, patent expiry date, and sales data including the year in which such sale was made.

As discussed in Section 2.2, to facilitate data analysis, it was necessary to supplement the primary data with pertinent variables such as active ingredients, scheduling status, and ATC codes from the secondary data. The original organization of the NDoH data was such that the products that consisted of more than one API were organized into rows. Prior to the extraction of the NDoH data into a master worksheet, the products with

multiple active ingredients were converted from a vertical listing in rows to horizontal listing in columns. Microsoft Excel's IF function was used to extract the multiple ingredients listed in rows into columns. Another column was created where all such ingredients were all combined into one field with a view to optimize data processing and analysis. Standardization was maintained by using sequential order of active ingredients based on the highest strength first to the lowest strength last.

The specific variables of the secondary data were extracted from their sheets in the master workbook into a master worksheet by making use of look up tables (match and index functions as well as V-look Up function). In the case of a match function, both the exact match and approximate match functions were used. Follow ups were made to resolve cases where no matches were found.

2.4.2. Data Coding

Codification was employed in this study with a view to optimize data processing and to maintain consistency.[26]

A separate sheet was created for codification of pertinent variables. This was done by sorting all the data alphabetically and arranging it on an annual basis in accordance with the year in which the sales took place. Microsoft Excel was employed to assign unique numerical codes to manufacturers, market sectors, ATC, active ingredients and products.

2.4.3. Data Cleaning

Neuman contends that "a researcher who has a perfect sample, perfect measures, and no errors in gathering data, but who makes errors in the coding process or in entering data into a computer, can ruin a whole research project".[26] It is for this reason that a carefully planned data cleaning process was undertaken. The process consisted of three stages starting with standardizing the codes for dosage forms, doing the dosage split and resolving data conflicts.

The dosage forms from the primary data were standardized by application of the guidelines for describing and presenting dosage forms as stipulated by the PEE Unit. This required converting the initial dosage forms into consistent and abbreviated form with a view to conform to convention and to optimize dissemination of results. This task was

performed by copying a column with the dosage forms onto a separate worksheet where the standardization of codes was completed. To avoid repetition of tasks for products with similar dosage forms, a Microsoft Excel function of ‘remove duplicates was used. All the remaining dosage forms were converted into abbreviated dosage form codes by matching the dosage form to its corresponding code in the PEE Unit’s guidelines. Upon conclusion of this task, a Microsoft Excel Look Up function was applied back in the master worksheet with a view to standardize the codes.

In accordance with Table 2.1, at layer six the original IMS Health product information with respect to strength, dosage form and pack size were presented as a single field. Furthermore, the order of these variables was not organized in a consistent manner. To resolve this problem, a dosage split was done in which the dosage form which had incorporated the strength, and the pack size was broken up into individual components.

The dosage split was accomplished by transferring the data into a new sheet followed by application of the Microsoft Excel function of text to column. This resulted in the separation of variables that were originally in a single field into various columns. The columns that emanated from a dosage split consisted of the strength, pack size and dosage form. The data was transferred back to the master sheet.

As discussed in Section 2.5, a generic drug must match the originator product based on a common API, dosage form, strength and by extension: ATC, and scheduling status. Formulation markets were created in conformance with this criterion of a generic drug. As such, the products were mapped by linking the generic drugs to their corresponding innovator products in a formulation market. This was achieved by sorting all the data based on a report year, API, strength, schedule, ATC category, and market segmentation.

Two keys were used in the process of mapping the products. Key 1 used a less strict criterion whereby the link was established based on common active ingredients. On the other hand, key 2 was a lot more stringent in establishing the generic (s)-to-innovator mappings. In addition to the active pharmaceutical ingredient, it used the following as a criterion: dosage forms, strengths, ATC 4 codes, launch date, market segmentation and

scheduling status. These two keys were used as a basis of the data cleaning process. Where no link was found, a filter and sort function was used to deselect all the products whose generic (s)-to-innovator mapping was established. The remaining products were scrutinized for possible errors or differences based on any valid explanations.

The products were transferred onto a new sheet using a copy and paste special function followed by a remove duplicates function. The duplicates were removed with a view to avoid repetition of tasks in cases where common problems existed. The remaining products were scrutinized for errors such as missing data, spelling mistakes and typos.

There were instances where the generic (s)-to-innovator mapping could not be established because of mismatches based on active ingredient (s), manufacturers, market segmentation, and ATC codes. The mismatches were found to emanate from errors (e.g. spelling mistakes and typos), lack of consistency (e.g. representation of film coated tablets as F/C Tablets *vis-a-vis* Tabs FC) other reasons were related to use of various salts for the API etc.

Where such mismatches were identified, they were resolved by standardizing the variants of the same variable such as all F/Cs being converted to FC followed by the application of a find and replace function in the master worksheet. Upon conclusion of this step the Microsoft Index function based on the formulas of key 1 and key 2 were repeated. This was done with a view to identifying cases that remained unresolved.

Where there were cases that remained unresolved, a further investigation was undertaken to establish the reasons. In most instances, it was found that the unresolved cases were based on valid reasons such as a use of active ingredients by generic manufacturers that had salt bases that differed from the innovator products. Such a practice is provided for under Section 22A of the Medicines Act. Those cases were resolved by converting their base salts to a base exclusive of the salt.

As a way of an example, the product Norvasc by Pfizer Laboratories contains the active ingredient Amlodipine. Upon the expiration of its patent protection in April 2007, several generic manufacturers launched generic equivalents of Norvasc. Amongst these companies were companies such as Austell, Aurobindo and Dezzo Trading who all made use of Amlodipine Besylate. On the other hand, companies such as Dr Reddy's Labs, Pharma Dynamics etc made use of yet another salt, Amlodipine Maleate. In such cases Key 1 (and consequently Key 2) was unable to establish a linkage between an active ingredient of the generic manufacturer and that of the originator product. These cases were resolved by converting the salts to the base and re-running the index function again.

2.5. Study Variables

Section 22A of the Medicines Act stipulates that for a drug to be deemed as an interchangeable multi source agent (generic drug), it needs to compare favorably with the corresponding innovator product insofar as the following attributes are concerned: active pharmaceutical ingredient (s), strength, dosage form, route of administration and therapeutic equivalence.[27]

Three types of binary variables representing the characteristics of the drug were constructed to investigate their influence on the price of a generic drug. In addition to the characteristics of the drug, the study enrolled four variables that represented the dynamics of the market that potentially had a bearing on the price of a generic drug. Finally, a binary variable representing the impact of the implementation of the legislative reforms was also enrolled into the study.

2.5.1. Type of Drug Market

In accordance with Section 22A of the Medicines Act[27], active pharmaceutical ingredients are assigned into different schedules based on their risk-benefit relationship, Table 2.2. In terms of the type of the drug market, Schedules 0 – 2 are classified as the over-the-counter medicines. On the other hand, Schedule 3 – 6 medicines form part of the prescription drug market. As discussed in Section 2.5.2, the prescription only drugs can be further subdivided into those that treat acute diseases and those that are used to treat chronic diseases.

Finally, the type of drug market has a bearing on the length of treatment which potentially influences the price of a generic drug.[28] Scheduling statuses formed part of the variables that the study collected for every medicinal product that met the selection criteria. The inclusion of scheduling statuses sought to establish whether the type of drug market had an influence on generic entry, the number of generic competitors and the price of a generic drug.

Table 2.2 Summary of the Schedules of Medicines.

Scheduling Status	Condition of Sale
Schedule 0	Sold in any retail outlet
Schedule 1 - 2	Sold by a pharmacist
Schedule 3 - 4	Prescription is required, repeatable for 6 months
Schedule 5	Prescription is required, no repeats allowed
Schedule 6	Prescription is required, no repeats allowed
Schedule 7	Controlled Substances
Schedule 8	Strictly Controlled Substances

Adapted from: Business Monitor International (BMI), Q3 2012

2.5.2. Type of Drug Therapy

The international classification of diseases in terms of the anatomical therapeutic chemical (ATC) system[29] was employed in this research study with a view to establish the influence of the type of drug therapy on the price of a generic drug. All the medicines that met the selection criteria were grouped according to their 1–digit ATC (ATC1) classification with a view to understand general trends by therapeutic category.

Furthermore, the 3-digit ATC (ATC3) classification in terms of acute or chronic as published by the WHO[30] was employed with a view to establish if the type of drug therapy influences the price of a generic drug. Finally, the study included a variable that conveys information about the 4-digit ATC (ATC4) classification of all the medicines that met the inclusion criteria. Based on the ATC4 data the study investigated whether having closely related chemical entities (me-too drugs)[31] in the same therapeutic category had any

bearing on the prices of generic drugs. Table 2.3 below provides an example of the ATC system for the drugs that act on the alimentary canal.

Table 2.3 Example of Anatomical Therapeutic Chemical Classification

Levels	**ATC Code**	**Level of Detail**	**Criterion of Classification**
Level 1	A	Alimentary Tract and Metabolism	Main Anatomical Group
Level 2	A10	Drugs Used in Diabetes	Main Therapeutic Group
Level 3	A10B	Oral Blood-Glucose Lowering Drugs	Therapeutic/Pharmacological Subgroup
Level 4	A10BA	Sulphonamides, Urea Derivatives	Chemical/Therapeutic/ Pharmacological Subgroup
Level 5	A10BA02	Glibenclamide	Subgroup for Chemical Substance

Adopted from: South African Medicines Formulary (SAMF), 12th Edition

2.5.3. Complexity of Manufacture of a Pharmaceutical Dosage Form

The study included information about a dosage form of all the products that met the selection criteria. The influence of pharmaceutical dosage forms on the price of a generic drug was investigated. Aulton argues that the design of a pharmaceutical dosage form must account for such factors as biopharmaceutical properties, physicochemical properties, and its therapeutic properties.[32] Inherent in the choice of the dosage form are the challenges that are associated with the technical aspects (skills, technology, capital etc) of manufacture that has a bearing on the price of a drug.[33] The study investigated the influence of the complexity of manufacture of a dosage form on generic entry and on the price of a generic drug.

2.5.4. Order of Generic Entry into the Formulation Market

The difference (months) between the expiration date of a patent of an innovator product and the date of entry of a corresponding generic drug was computed. The rate of generic entry was used to establish the order of generic entry into a formulation market and how it influences the prices of generic drugs.

2.5.5. Impact of the Legislative Reforms

As discussed in Section 1.1.1, the South African government was obliged by Section 27(2) of the constitution to reform the healthcare sector to progressively move towards the realization of the right to healthcare as espoused under Section 27(1) of the constitution. Accordingly, a wide range of policy interventions with a view to facilitate affordability of medicines and thus improve access were undertaken. Government Gazette No. 24279 assented to in January 2003 introduced such instruments as mandatory generic substitution, provisions for the introduction of the marketing code, and the transparent pricing system to the Medicines Act. On the other hand, Government Gazette No. 24256 which was also assented to in January 2003 introduced Section 69(A) to the Patents Act, No. 57 of 1978. As discussed in Section 1.1.1, this reform (also known as the Bolar amendment) was introduced with a view to facilitate a timeous entry of generics following the loss of patent protection.

Collectively the various instruments that were introduced by the government over time begun working in tandem in 2005 following the judgement by the constitutional court on the implementation of the transparent pricing system.[8] A cumulative impact of the legislative reforms was investigated by dividing the market into the period before and after the 31st of December 2004. Specifically, the study investigated the impact of the legislative reforms on generic entry, rate of generic entry, price erosion, average unit price of a medicine, type of drug therapy, type of drug market and the complexity of manufacture of a pharmaceutical dosage form.

2.6. Data Analysis

Both the descriptive and inferential statistical procedures were employed to subject the data to analysis using Statistica 13.2.

2.6.1. Descriptive Data Analysis

The use of descriptive statistics techniques reduced numerous observations into a descriptive summary (presented as frequency tabulations for categorical variables; and either means with standard deviation or median with inter-quartile range for continuous variables) that revealed the parameters of interest about the South African

pharmaceutical industry.[26] Univariate descriptive statistics is a technique that describes variables of interest by focusing on one variable at the time.[26] Univariate descriptive statistics were conducted for the number of generic drug manufacturers per chemical entity following loss of patent protection, market size of the innovator product prior to loss of exclusivity, price erosion, therapeutic categories, and dosage forms. Bivariate descriptive statistics were employed to draw a comparative analysis (association) between the above-mentioned variables before and after the implementation of the pricing reforms.

An overall picture of these research variables provided an insight into the preferences of generic drug manufacturers in South Africa. Disproportionate distribution in the market with respect to market variables could suggest that certain markets would be less competitive than others. This has significant policy implications, as less competitive markets result in high prices which raise questions about affordability and access to drugs.[34] Being able to account for these factors is instructive in policy-making.

2.6.2. Inferential Data Analysis

Inferential statistics were employed in this study with a view to explain the influence of the characteristics of the drug, market and legislative reforms on the price of a generic drug. This involved the use of techniques such as analysis of variance (ANOVA), correlational analysis, crosstabulation analyses, and regression analysis.

ANOVA was used extensively to establish whether there is a statistically significant difference between the study variables before and after the implementation of the transparent pricing system. If the ANOVA results were significant, the post-hoc pairwise comparisons using the Tukey HSD was used to investigate where the differences lie. Where the study variables were categorical measures, cross-tabulations were used to establish the impact of the transparent pricing system on study variables. On the other hand, correlational analysis was employed to study the strength and the nature of the linear relationship between the price of a generic drug and the study variables with continuous measures. Finally, linear regression analysis comprising of both univariate regression and multivariate regression was employed to establish the influence of the

study variables (independent variables) on the price of a generic drug, dependent variable. Variables that were significant on the univariate analysis were considered in the multivariate regression where they were adjusted for each other. Significance was considered at 5% level.

2.7. Data Presentation

The results of the data analysis for this study were presented by means of graphs, tables (ordinary tables and cross-tabulations) and by means of statistical summaries such as correlation coefficients, means with standard deviations, medians with range etc.

2.8. Reliability

To ensure the reliability of the study results, several measures were put in place comprising of the clear conceptualization of constructs, increasing the level of measurement and use of multiple indicators of a variable.[26]

2.8.1. Clear Conceptualization of Constructs

Constructs should be specified with a view to remove noise from other constructs. This requires a single construct or sub-dimension of a construct to be measured in such a way that each measure indicates one and only concept.[26] In this study scheduling status as it relates to the level of restriction on access to a drug was examined to establish its impact on the price of a generic drug. However, given the fact that a schedule can cater for drugs with a wide range of therapeutic applications with different disease incidences and thus different dynamics, an ATC group was introduced to the regression model to accentuate this effect.

2.8.2. Increase in the Level of Measurement

It is critical that specific information is measured so that it becomes less likely that anything other than the construct will be captured.[26] The ease of manufacture as it relates to dosage design has an influence on generic entry and thus the price competition.[33] To establish the impact of a dosage design on the price of a generic drug, a dosage form instead of a route of administration was employed with a view to increasing the level of measurement.

2.9. Validity

Every research design is susceptible to bias and design threats which can adversely affect the internal validity (i.e., accuracy) and external validity (i.e., generalizability) of the study results from the population where the sample was derived.[26] Furthermore, research design must also make provisions for construct validity, and statistical validity.[26]

2.9.1. Internal Validity

Longitudinal studies have been described as most likely to be susceptible to the following internal validity threats: maturity, history, testing, instrumentation, statistical regression, selection, and attrition. In this study, these specific internal validity threats were mitigated as outlined below.

a) Maturation

The collection of 13 years' pharmaceutical sales data allows for robust examination of trends and dynamics. Neumann argues that it is not uncommon for variables obtained from document reviews to undergo definitional and standardization changes over a period.[26] The researcher addressed the internal validity of the data by holding meetings with the provider of the primary data (IMS Health) with a view to circumvent possible challenges related to changes in data definitions, reporting practices, technical aspects of the report, and consistency of measurements.

b) History

History entails the events that affect the dependent variable that occurs between the measurements.[26] Innovator companies for ARVs were compelled by a court order in 2003 to issue compulsory licenses to local generic manufacturers to produce generic equivalents of their products.[8] This 'premature' generic entry of ARVs to the market was deemed as likely to confound the 'natural' trends of the industry as it relates to price erosion. To mitigate this, the ARVs were excluded from the sample.

c) Instrumentation

Any changes to a data collection device may result in changes in the measurement of the dependent variable.[26] The accuracy of data collection was safeguarded by making use of IMS Health which is a reputable international organization with validated and highly sophisticated data collection tools and systems. IMS Health data is recognized by the WHO as a mainstay in conducting health research on use of pharmaceuticals.[25]

d) Selection Bias

Selection bias arises when the sample has components that are not equivalent to each other.[26] The selection of the study period, 1999-2012, represents two different eras in the pricing of pharmaceutical products in South Africa, i.e., the before and after implementation. To mitigate against selection bias, a study objective that seeks to probe the actual differences that are associated with these two eras was installed by performance of an ANOVA. Additionally, an inclusive criterion with respect to dosage forms, schedules and therapeutic classes was employed.

2.10. Ethical Consideration

The study did not involve human subjects and as such a waiver for ethical clearance was obtained, Appendix A.

2.11. Conclusion

This chapter provided the scientific rationale behind the research methodology that underpinned the study. The chapter also dealt with the ethical considerations related to executing. Since the study did not involve human subjects a waiver for ethics' clearance was sought and granted.

CHAPTER THREE

3. DESCRIPTION OF THE CHARACTERISTICS OF THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY

This chapter provides a comprehensive description of the structural characteristics of the South African pharmaceutical industry. The chapter comprises of five sections. Section 3.1 deals with the application of the selection criteria for the study and provides a summary of the key statistics. Section 3.2 provides descriptive statistics of the study variables. Section 3.3 expounds on the shifts in market segmentation of the local pharmaceutical industry. This is followed by an appraisal of the emerging themes in the local pharmaceutical industry in Section 3.4. Generic fending off strategies are presented in Section 3.5 followed by a discussion and conclusion in Section 3.6 and Section 3.7 respectively.

3.1. Application of the Selection Criteria

The primary data from IMS Health covering private sector sales for the period 01/01/1999-31/12/2012 had a total of 63763 products. Upon application of the selection criteria, 53477 products were excluded from the study based on falling outside the window period for this study with respect to the expiry dates of the patents and launch dates of the generic drugs. Table 3.1 provides an overview of the main study's variables. A total of 549 innovator products whose patent protection expired between 1999 and 2012 were enrolled into the study. In addition to the innovator products, there were 970 generic drugs that were also enrolled in the study resulting in a total of 1519 products. The prices of these 1519 products were appraised on an annual basis resulting in a grand total of 10286 (n = 5660 for innovators and n = 4626 for generics) cases being included for the duration of the study, 1999 to 2012.

Table 3.1 Overview of the Pharmaceutical Market, 1999 - 2012

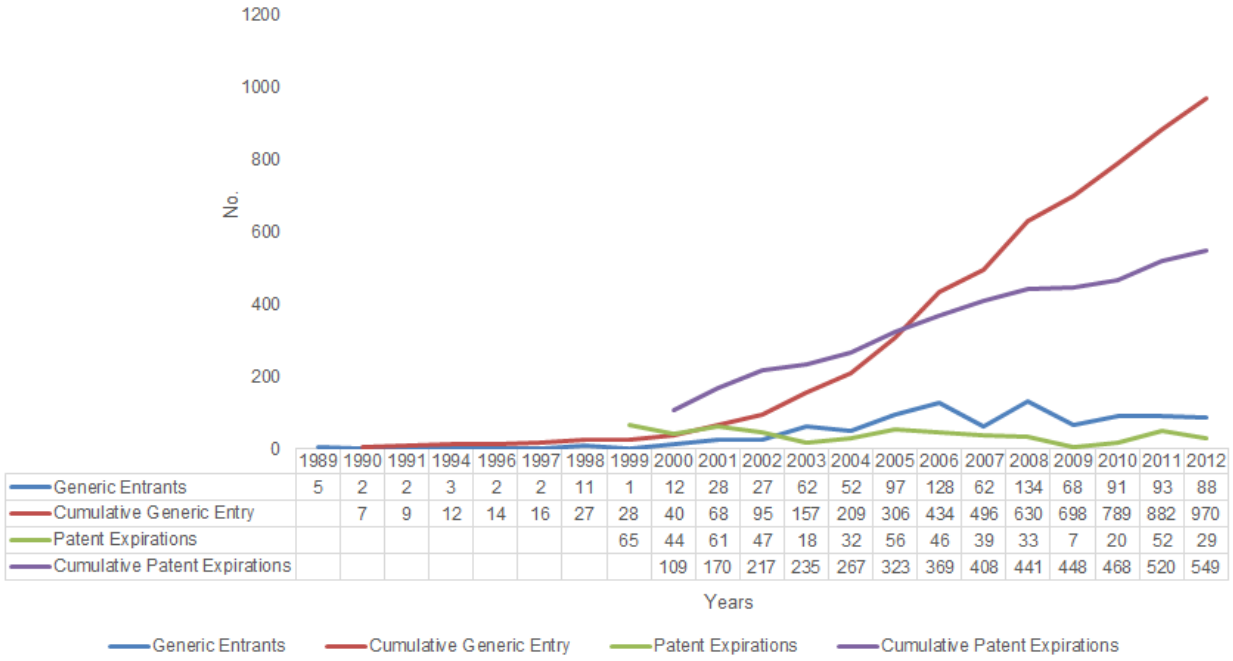
Overview of the Pharmaceutical Market	Generics Sector	Innovators Sector
Number of Chemical Entities (at molecular level)	97	204
Number of Innovator Products that Lost Patent Protection (formulation level)	-	549
Number of Pharmaceutical Products (formulation level)	970	549
Number of Pharmaceutical Companies	48	38
Number of Dosage Forms	21	44
Number of Schedules	5	6
Number of ATC 4	58	111

3.2. Description of the Characteristics of the South African Pharmaceutical Industry

The features of the pharmaceutical industry that have a bearing on the pricing of generic drugs in South Africa are appraised in the forthcoming sections.

3.2.1. Number of Generic Drug Manufacturers Per Chemical Entity Following the Loss of Exclusivity (LOE)

Figure 3.1 shows the rates of patent expirations and generic entry; sub-optimal levels of generic entry are evident in that less than half of all chemical entities that lost patent protection attracted generic entry; Table 3.1. The annual rate of patent expirations was an average of 39.2 patents (SD = 4.7 patents) for the period spanning 1999 to 2012. The patents had varying rates of expirations, ranging from 7 patent expirations in 2009 to 65 patent expirations in 1999. The launch dates ranged from May 1982 to March 2012. The earliest expiry date was Jan 1999 and the latest expiry date was Nov 2012. The average effective patent life was 9.24 years (SD = 3.95 years) with a minimum of 2 months for Perdix® (Moexipril) and a maximum of 19.6 years for Clexane® (Enoxaparin).



	1989	1990	1991	1994	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Generic Entrants	5	2	2	3	2	2	11	1	12	28	27	62	52	97	128	62	134	68	91	93	88
Cumulative Generic Entry		7	9	12	14	16	27	28	40	68	95	157	209	306	434	496	630	698	789	882	970
Patent Expirations								65	44	61	47	18	32	56	46	39	33	7	20	52	29
Cumulative Patent Expirations									109	170	217	235	267	323	369	408	441	448	468	520	549

Figure 3.1 Rates of Patent Expirations and Generic Entry

As outlined in Table 3.1, there were 970 generic equivalents for the 549 innovator products that were previously covered by patents. On average, there were 4.39 generic drug versions (SD = 3.69 generic drug versions) for every chemical entity that lost patent protection and resulted in generic entry for the period spanning 1999 to 2012.

There was a high degree of variability in terms of the annual entry rate of generics, on average 46 generics (SD = 45 generics) entered the pharmaceutical market per annum ranging from 1 generic drug in 1999 to 134 generics in 2008. As shown in Table 3.2, there were 25 generics that entered the market prior to loss of patent protection. The earliest generic entrants ranged from -180 months for Ramace® (Ramipril) to -1 month for Foxair® (Fluticasone) before patent expiry.

Table 3.2 Authorized Generics, 1999 - 2012

Chemical Entity	Company of the Generic	Innovator Company	Months to Patent Expiry	Expiry Date	Launch Date	Type
Lisinopril	MSD	Astrazeneca	-121	Dec-99	Nov-89	Own Generic
Ceftazidime	Elli Lilly	Elli Lilly	-113	May-99	Dec-89	Own Generic
Ramipril	Astrazeneca	Sanofi-Aventis	-180	Apr-05	Apr-90	Multinationals: Sanofi-Aventis
Loratadine	MSD	MSD	-116	Jun-01	Oct-91	Own Generic
Loratadine	MSD	MSD	-41	Jun-01	Jan-98	Own Generic
Loratadine	MSD	MSD	-2	Jun-01	Apr-01	Own Generic
LoratadinePseudoephedrine	MSD	Msd	-56	Jun-01	Oct-96	Own Generic
Pantoprazole	Nycomed	Nycomed	-128	Jun-05	Oct-94	Own Generic
Lomefloxacin	Aspen Pharmacare	Glaxosmithkline	-99	Sep-04	Jun-96	Own Generic
IbuprofenPseudoephedrine	Sandoz	Novartis	-96	Apr-05	Apr-97	Subidiary of Norvatis
Norfloxacin	Cipla Medro	Astrazeneca	-43	Jul-01	Dec-97	Licensee
Mometasone	MSD	MSD	-116	Sep-07	Jan-98	Own Generic
Etoposide	Pfizer Laboratories	Pfizer Laboratories	-110	Jul-08	May-99	Own Generic
Diclofenac	Adcock Ingram	Norvatis	-70	Apr-07	Jun-01	Licensee
Perindopril	Biogaran	Servier Laboratories	-53	Apr-08	Nov-03	Subsidiary of Servier
Amlodipine	Pharma Dynamics	Pfizer Laboratories	-29	Apr-07	Nov-04	Licensee
Clarithromycin	Aspen Pharmacare	Abbott Laboratories	-2	Mar-05	Jan-05	Licensee
PerindoprilIndapamide	Servier Laboratories	Servier Laboratories	-30	Apr-08	Oct-05	Self and Subsidiary (Biogran)
Valsartan	Novartis	Novartis	-59	Feb-11	Mar-06	Self and Subsidiary (Sandoz)
Atorvastatin	Pharmacia Corporat	Pfizer Laboratories	-39	Jul-10	Apr-07	Subidiary of Pfizer
Irbesartan	Sanofi-Aventis	Sanofi-Aventis	-21	Mar-11	Jun-09	Own Generic
IrbesartanHydrochlorothiazide	Sanofi-Aventis	Sanofi-Aventis	-21	Mar-11	Jun-09	Own Generic
Telmisartan	Boehringer Ingelheim	Boehringer Ingelheim	-22	Feb-12	Apr-10	Own Generic
TelmisartanHydrochlorothiazide	Boehringer Ingelheim	Boehringer Ingelheim	-22	Feb-12	Apr-10	Own Generic
Estradiol	Novartis	Glaxosmithkline	-3	Oct-10	Jul-10	Another Innovator

3.2.2. Market Size of the Innovator Product in the Year Preceding LOE

Figure 3.2 depicts a relationship between the sales of innovator products a year preceding patent expiration and the average number of generic entrants. Save for the range R29.0M to R 32.1M the higher the sales of innovator products in the year preceding loss of exclusivity the higher the number of generic entrants. The sales of the innovator products in the category R29.0M to R 32.1M were found to comprise of technologically advanced dosage forms such as accuhalers, inhalers, transdermal patches, slow release tablets and capsules.

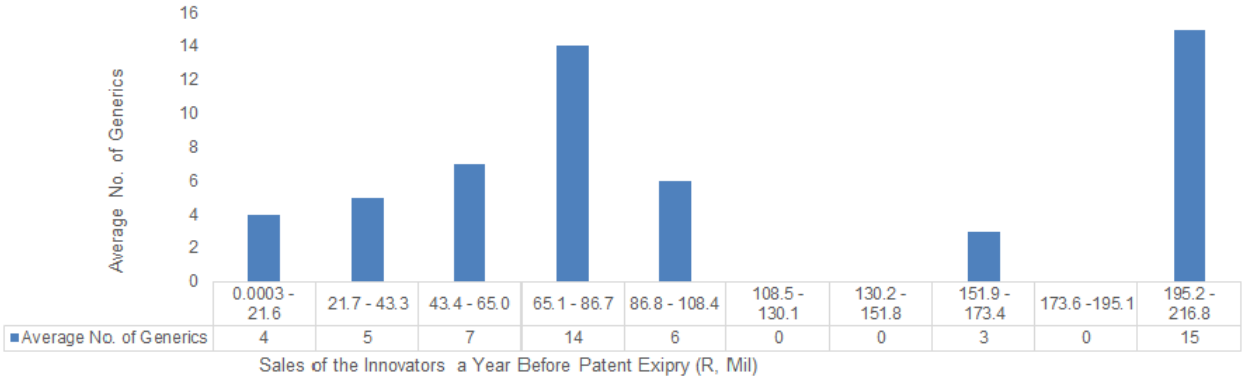


Figure 3.2 Sales of the Innovator Products a Year Preceding LOE,1999 - 2012

Table 3.3 shows the Top 40 sales of the innovator products over a 5-year period following the loss of patent protection, the remainder of the 184 innovator products are shown in Appendix B. The passage of time results in decline in sales due to competition from either generic drugs and/or close-substitutes. Innovator products with annual sales of less than a million rands tIn describing the local pharmaceutical market the author also focused end to exit the market within 3 years of loss of exclusivity.

Within the first 3 years following the loss of patent protection, a quarter of all innovator products (26.5%, n = 54) left the market. Eleven innovator products (20.4%) left the market in the first year following the loss of their patent protection. Three (27.3%) and 9 (81.8%, n = 11) of these products experienced competition from generic drugs and close-substitutes respectively. The innovator products that left the market within a year of patent expiry had average sales of R 2.31M (SD = R 4.86M) and R 0.05M (SD = R 0.003M) in the year preceding their loss of patent expiry and at patent expiry respectively.

Overall sales of the innovator products plummeted by 11.8% (n = R 481.4M) at the end of the first year following the loss of patent protection. Despite not experiencing competition from neither generics nor other chemical entities in the same therapeutic group, Halofantrine (ATC 4, P01BX), Atovaquone (ATC 4, P01BX) and Zanamivir (ATC 4, J05AH) left the market in the first year following the loss of patent protection. Products that act on the cardiovascular system had the highest exit rate (36.4%, n = 11); only one of these products experienced a self-induced generic competition. Abbott replaced

Gopten® (Trandolapril, ATC 4 C09AA) with its own generic product, Mavik®. The remainder of the other innovator products that act on the cardiovascular system had no generic competition.

Table 3.3 Performance of Innovator Products After Loss of Exclusivity, 1999 – 2012

					Year 1 After Patent Expiry			Year 2 After Patent Expiry			Year 3 After Patent Expiry			Year 4 After Patent Expiry			Year 5 After Patent Expiry			
Trade Name	Generic Name	ATC 4	Date of Patent Expiry	Sales 12 Months Preceding Expiry	Sales at Patent Expiry	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Max No. of Generics
FLIXOTIDE	Fluticasone	R03BA	Feb-01	R215.90M	R188.5M	151.7		-20%	R118.6M		-37%	R124.3M		-34%	R48.3M		-74%	R46.3M		-75%	0
CIPROBAY	Ciprofloxacin	J01MA	Sep-01	R205.63M	R269.7M	240.1	4	-11%	R254.2M	9	-6%	R204.5M	11	-24%	R152.5M	13	-43%	R155.3M	13	-42%	15
CLEXANE	Enoxaparin	B01AB	Jun-11	R167.91M	R179.9M	145.7		-19%	R113.1M		-37%	R114.6M		-36%							
EFEXOR	Venlafaxine	N06AX	Dec-03	R164.97M	R146.7M	128.2		-13%	R107.8M		-26%	R89.4M	1	-39%	R56.7M	1	-61%	R45.1M	2	-69%	3
TAVANIC	Levofloxacin	J01MA	Jun-06	R96.89M	R107.2M	95.0	1	-11%	R92.7M	3	-13%	R78.2M	3	-27%	R86.6M	4	-19%	R42.9M	5	-60%	7
SINGULAIR	Montelukast	R03DC	Oct-11	R86.80M	R78.2M	72.8	5	-7%	R61.8M	5	-21%	R59.0M	5	-25%		5			5		5
ZYRTEC	Cetirizine	R06AE	Feb-02	R86.34M	R67.4M	67.8	2	1%	R57.0M	3	-15%	R45.1M	9	-33%	R10.8M	10	-84%	R8.6M	11	-87%	13
ZOCOR	Simvastatin	C10AA	Feb-01	R69.06M	R78.6M	87.2		11%	R82.1M	1	4%	R71.0M	2	-10%	R11.4M	5	-85%	R8.4M	8	-89%	16
CLARITYNE	Loratadine	R06AX	Jun-01	R67.60M	R59.8M	54.4	4	-9%	R41.6M	10	-30%	R33.5M	11	-44%	R2.2M	12	-96%	R2.2M	15	-96%	20
LANZOR	Lansoprazole	A02BC	Aug-05	R65.75M	R44.3M	42.8	4	-3%	R31.3M	6	-29%	R26.8M	7	-40%	R6.7M	7	-85%	R4.8M	8	-89%	8
TRITACE	Ramipril	C09AA	Apr-05	R61.57M	R42.2M	38.1	4	-10%	R30.5M	4	-28%	R24.4M	5	-42%	R12.2M	6	-71%	R9.8M	6	-77%	6
KLACID	Clarithromycin	J01FA	Mar-05	R57.95M	R37.4M	33.1	6	-12%	R27.1M	7	-28%	R22.9M	8	-39%	R17.1M	8	-54%	R20.2M	8	-46%	8
TARGOCID	Teicoplanin	J01XA	May-03	R56.16M	R60.0M	55.7	3	-7%	R44.0M	3	-27%	R34.2M	3	-43%	R55.0M	3	-8%	R59.0M	3	-2%	1
ZYPREXA	Olanzapine	N05AH	Apr-11	R54.57M	R40.0M	37.5	3	-6%	R29.8M	3	-26%	R24.1M	3	-40%		3			3		3
MAXIPIME	Cefepime	J01DE	Jan-09	R62.91M	R59.8M	59.8		-5%	R48.1M		-23%	R39.9M		-36%							
LAMICTIN	Lamotrigine	N03AX	May-00	R50.88M	R67.7M	69.7		3%	R60.0M		-11%	R47.8M		-29%	R156.0M		131%	R168.0M	2	148%	9
RENITEC	Enalapril	C09AA	Dec-99	R49.29M	R202.1M	172.4	4	-15%	R176.1M	7	-13%	R126.0M	7	-38%	R23.6M	7	-88%	R16.8M	7	-92%	8
ROCEPHIN	Ceftriaxone	J01DD	May-99	R49.16M	R214.1M	180.0		-16%	R184.3M	2	-14%	R173.1M	2	-19%	R220.4M	6	3%	R106.9M	6	-50%	10
TOPAMAX	Topiramate	N03AX	Sep-04	R48.64M	R65.2M	67.1		3%	R56.2M		-14%	R44.6M	3	-32%	R49.1M	5	-25%	R47.1M	5	-28%	6
RISPERDAL	Risperidone	N05AX	Mar-06	R47.64M	R60.4M	56.2		-7%	R44.7M		-26%	R39.7M	6	-34%	R32.7M	9	-46%	R30.2M	10	-50%	11
MERONEM	Meropenem	J01DH	Jul-07	R46.95M	R64.5M	62.2		-4%	R51.8M		-20%	R43.2M	1	-33%	R85.6M	2	33%	R56.2M	2	-13%	2
CIPRALEX	Escitalopram	N06AB	Apr-08	R45.57M	R44.6M	46.4	2	4%	R31.8M	3	-29%	R27.3M	5	-39%	R21.1M	5	-53%		5		5
DIFLUCAN	Fluconazole	J02AC	Jun-02	R44.69M	R63.4M	61.5	1	-3%	R49.4M	5	-22%	R40.9M	6	-36%	R14.9M	7	-77%	R12.0M	7	-81%	9
PREPULSID	Cisapride	A03FA	Sep-02	R43.35M	R18.8M	13.7		-27%	R11.0M		-42%	R9.0M		-52%	R.2M		-99%	R.0M			
LOSEC	Omeprazole	A02BC	Apr-99	R39.59M	R20.3M	14.6		-28%	R12.3M		-39%	R10.0M		-51%	R10.1M		-50%	R7.8M	3	-62%	7
SERETIDE	FluticasoneSaln	R03AK	Sep-10	R37.95M	R27.1M	24.2		-11%	R17.6M		-35%	R14.0M		-48%							
ZOFRAN	Ondansetron	A04AA	Jan-05	R34.95M	R25.7M	20.0	4	-22%	R16.3M	5	-36%	R13.4M	5	-48%	R8.3M	6	-68%	R7.4M	7	-71%	7
ACCUPRIL	Quinapril	C09AA	Sep-01	R33.02M	R33.5M	31.1		-7%	R24.5M		-27%	R20.8M		-38%	R13.9M	1	-59%	R7.5M	1	-78%	4
SEROQUEL	Quetiapine	N05AH	Mar-07	R32.61M	R38.0M	33.4		-12%	R27.3M		-28%	R23.3M		-39%	R51.9M	1	37%	R19.4M	5	-49%	5
FLIXONASE	Fluticasone	R03BA	Feb-01	R30.09M	R32.5M	30.0		-8%	R22.5M		-31%	R19.2M		-41%	R22.7M		-30%	R46.3M		42%	0
PRAVA	Pravastatin	C10AA	Nov-02	R28.60M	R38.2M	34.0		-11%	R28.5M		-25%	R23.7M	2	-38%	R12.4M	3	-68%	R8.1M	3	-79%	6
DESELEX	Desloratadine	R06AX	May-06	R44.00M	R28.15M	41.0		-7%	R31.1M	1	-29%	R26.2M	1	-40%	R18.7M	3	-58%	R15.9M	4	-64%	4
TRAMACET	Tramadol	N02AX	Sep-12	R27.16M	R33.3M	30.7		-8%	R23.7M		-29%	R19.8M		-40%							
GEMZAR	Gemcitabine	L01BC	Mar-04	R27.00M	R28.4M	26.0		-8%	R20.3M		-29%	R16.2M		-43%	R33.5M		18%	R34.8M		23%	4
KYTRIL	Granisetron	A04AA	Apr-06	R26.31M	R30.8M	27.8		-10%	R21.6M		-30%	R18.4M	1	-40%	R18.7M	3	-39%	R11.9M	3	-61%	3
PROZEF	Cefprozil	J01DC	Jan-04	R25.27M	R26.0M	23.7		-9%	R16.6M		-36%	R13.8M		-47%	R19.6M		-25%	R17.2M		-34%	
LESCOL	Fluvastatin	C10AA	Nov-03	R24.39M	R48.9M	52.4		7%	R37.3M		-24%	R31.7M		-35%	R15.0M		-69%	R13.5M		-72%	
PLAVIX	Clopidogrel	B01AC	Feb-08	R23.98M	R24.9M	18.7	4	-25%	R14.2M	5	-43%	R12.7M	5	-49%	R1.9M	6	-92%		6		6
NORVASC	Amlodipine	C08CA	Apr-07	R23.00M	R18.9M	14.4	13	-24%	R11.3M	14	-40%	R9.1M	16	-52%	R8.1M	16	-57%	R6.2M	16	-67%	16
CO-RENITEC	Enalapril+hydroc	C09BA	Dec-99	R22.91M	R31.3M	28.9	1	-8%	R22.0M	2	-30%	R18.7M	2	-40%	R5.7M	2	-82%	R4.7M	2	-85%	2
Min (All Product)					**R.0M**	**ZAR.0M**	**1**	**-100%**	**R.0M**	**1**	**-100%**	**R.0M**	**1**	**-100%**	**R.0M**	**1**	**-100%**	**R.0M**	**1**	**-99%**	**0**
Max (All Products)					**R269.7M**	**ZAR240.1M**	**13**	**20%**	**R254.2M**	**14**	**4%**	**R204.5M**	**16**	**-10%**	**R220.4M**	**16**	**697%**	**R168.0M**	**16**	**968%**	**20**
Average (All Products)					**R18.8M**	**ZAR17.4M**	**2.72**	**-28%**	**R16.2M**	**3.28**	**-56%**	**R14.5M**	**3.74**	**-68%**	**R12.8M**	**4.02**	**-13%**	**R11.8M**	**4.23**	**-2%**	**5**
Count (All Products)					**R.0M**	**206**	**57**	**214**	**R.0M**	**69**	**214**	**R.0M**	**81**	**214**	**R.0M**	**88**	**162**	**R.0M**	**94**	**140**	**112**
SD (All Products)					**R36.7M**	**ZAR33.0M**	**2.14**	**26%**	**R32.6M**	**2.73**	**27%**	**R28.7M**	**3.23**	**24%**	**R27.1M**	**3.43**	**104%**	**R23.2M**	**3.60**	**151%**	**4**
Total for Top 30					**R2440.8M**	**ZAR2192.1M**	**44**	**-**	**R1925.4M**	**73**	**-**	**R1644.2M**	**100**	**-**	**R526.8M**	**123**	**-**	**R927.9M**	**144**	**-**	**188**
Total for All Products					**R4068.5M**	**ZAR3591.3M**	**155**	**-11.7%**	**R2961.2M**	**226**	**-27.2%**	**R2475.4M**	**303**	**-39.2%**	**R2076.7M**	**354**	**-49.0%**	**R1673.8M**	**398**	**-58.9%**	**532**

The anti-infectives and antiparasitic categories had two drugs apiece that left the market in the first year following the loss of patent expiry. One product of the anti-infectives, Cedax® (Ceftibuten, ATC 4 J01DD) experienced competition from 3 other products in the same therapeutic class without experiencing generic competition. The second anti-infective (Relenza® [Zanamivir, ATC 4 J015AH]) did not experience competition from neither close substitutes nor generic drugs. On the other hand, neither of the antiparasitic drugs (Wellvone® [Atovaquone, ATC 4 P01AX)]) and Halfan® [Halofantrine, ATC 4 P01BX]) experienced competition from either generics or close-substitutes.

The second year following the loss of patent protection resulted in overall sales of innovator products falling by 27.3% from their original sales at patent expiry. Forty four percent (n = 54) of the innovator products that left the market exited in the second year following the loss of their patent protection. Their average sales in the year preceding the loss of their exclusivity was R 1.4M (SD = R 2.9M). Four products apiece belonged to the sensory organs therapeutic class and the anti-infectives. Two of the products Okacyn® (Lomefloxacin) and Voltaren Opthalmic ® (Diclofenac)) that act on the sensory organs experienced generic entry from both generics and other chemical entities in the same therapeutic class, S01AX and S01BC respectively. The other two products Trusopt® (Dorzolamide) and Rhinolast® (Azelastine)) that act on the sensory organs did not experience competition from generics but from other products in the same therapeutic classes, S01EC and S01GX respectively.

Two of the anti-infectives Azactam® (Aztreonam, ATC 4 J01DF) and Baraclude® (Entecavir, ATC 4 J05AF)) that left the market in the second year following the loss of their patent protection did not experience competition from either generics or other chemical entities in the same therapeutic class. The other two anti-infectives Lorabid® (Loracarbef, ATC 4 J01DC) and Noroxin® (Norfloxacin, J01MA)) experienced competition from other chemical entities in the same therapeutic classes as them. Additionally, Noroxin® experienced generic competition from generics as well.

Furthermore, three products apiece left the market in the second year following the loss of their patent protection, these were antineoplastic agents, drugs that act on the alimentary tract and the respiratory system. Except for Etopophos® (Etoposide, ATC 4 L01CB) which experienced generic competition, all other antineoplastic drugs Leustatin® (Cladribine, ATC 4 L01BB) and Suprefact® (Buserelin, ATC 4 L02AE) did not experience competition from either close-substitutes or generics. Only Dipentum® (Olsalazine, ATC A07EC) lacked competition from both the generics and close-substitutes. The remaining two products (Antizid® (Nizatidine, ATC A02BA) and Navoban® (Tropisetron, ATC 4 A04AA) that act on the alimentary canal experienced competition from close-substitutes. None of the drugs that act on the alimentary canal experienced competition from generic drugs.

None of the drugs that act on the respiratory system experienced generic competition. Only Tilade M® (Nedocromil, ATC 4 R03BB) experienced competition from close-substitutes. The other two drugs that act on the respiratory tract Accolate® (Zafirlukast, ATC 4 R03DC) and Semprex® (Acravastine, ATC R06AX) did not experience competition from either generic drugs or close-substitutes. Additionally, there were two products apiece that belonged to the therapeutic class dermatologicals and central nervous system. None of the products Nizovules® (Ketoconazole) and Elidel® (Pimecrolimus) that belong to the dermatologicals experienced competition from close-substitutes. Only Elidel® experienced generic competition. On the other hand, none of the products that belong to the central nervous system Naramig® (Naratriptan, ATC 4 N02CC) and Rilutek® (Riluzole, ATC 4 N07XX) experienced competition from neither generics nor close-substitutes.

Finally, there was one product apiece that belonged to the antiparasitic Co-artem® (ArtemetherLumefan, ATC 4 P01BE), cardiovascular system Zanidip® (Lercanidipine, ATC 4 C08CA) and genitourinary system Estracombitis TTS® (EstrogensNorethist, ATC 4 G03CA). None of these products experienced generic competition. Except for Co-artem®, the other two cardiovascular drugs did not experience competition from close-substitutes. In the second year following the loss of patent protection, there were 39

innovator products whose sales declined by between 97.0% and 61.0%. The average sales of these products in the year preceding loss of their patent protection was R 1.86M (SD = R 2.10M).

Five drugs in the worst performing category belonged to the cardiovascular system (ATC C), 4 drugs apiece acted on the alimentary canal (ATC A), skin (dermatologicals, ATC D), antineoplastic drugs (ATC L), musculoskeletal system (ATC M), central nervous system (ATC N), and drugs that acts on the sensory organs (ATC S). There were 27 innovator products that left the market by the end of their second year following the loss of their patent protection. Only 11.1% (n = 27) had experienced generic competition whereas 55.6% (n = 27) of these molecules faced competition from close-substitutes. Albeit competition from Adco-Simvastatin, Zocor posted a 10.94% increase in sales from R 78.6M in 2001 to R 87.2M in 2003. No other products experienced a growth in their sales in their second year following the loss of patent protection.

There were 14 innovator products (25.9%, n = 54) that left the market at the end of the third year following the loss of their patent protection. These products had average sales of R 0.98M (SD = R 0.39M) and R 0.83M (SD = R 0.14M) in the year preceding their loss of patent expiry and at patent expiry respectively. Overall sales of the innovator products contracted by 39.2% (n = R 4079.6M) at the end of the third year following the loss of patent protection. None of these molecules had experienced competition from generics. Thirty six percent (n = 14) of these molecules also did not experience competition from close substitutes.

The drugs that act on the central nervous system (Zolmitriptan, N02CC), (Entacapone, N04BX) and (Rivastigmine, N06DA)) dominated the list of products that left the market in the third year following the loss of their patent protection. Two drugs apiece belonged to the cardiovascular system (Esmolol, C07AA) and FosinoprilHydrochloride, C09BA)), anti-infectives (Enoxacin, J01MA) and (Ganciclovir, J05AB), antineoplastic (Topotecan, L01XX) and Tacrolimus, L04AD) and the sensory organs (Fucidic acid, S01AA) and Brinzolamide, S01EC). Finally, there was one drug that acts on the musculoskeletal

system (Pamidronic acid, M05BA), respiratory system (Mizolastine, R06AX), and Cinacalcet (H05BX) which is a systemic hormonal preparation.

On the other hand, 39 products posted considerable losses of the market share with their sales declining by between 97.4.0% to 61.5%. Thirteen percent (n = 39) of the products that left the market in the third year following the loss of their exclusivity belonged to the cardiovascular system. Four products apiece belonged to the dermatologicals, antineoplastic preparations, musculoskeletal system, central nervous system, sensory organs, and alimentary canal. Three products apiece belonged to the anti-infectives and genitourinary system and sex hormones. One product apiece belonged to the systemic hormonal preparations and blood and blood-forming organs therapeutic classes. None of the innovator products experienced a growth in their sales by the end of the third year following the loss of their exclusivity.

3.2.3. The Impact of Generic Entry on Price Erosion

Figure 3.3 shows the aggregate impact of a specified number of generic drugs on price erosion. The higher the number of generic drugs the greater the price erosion.

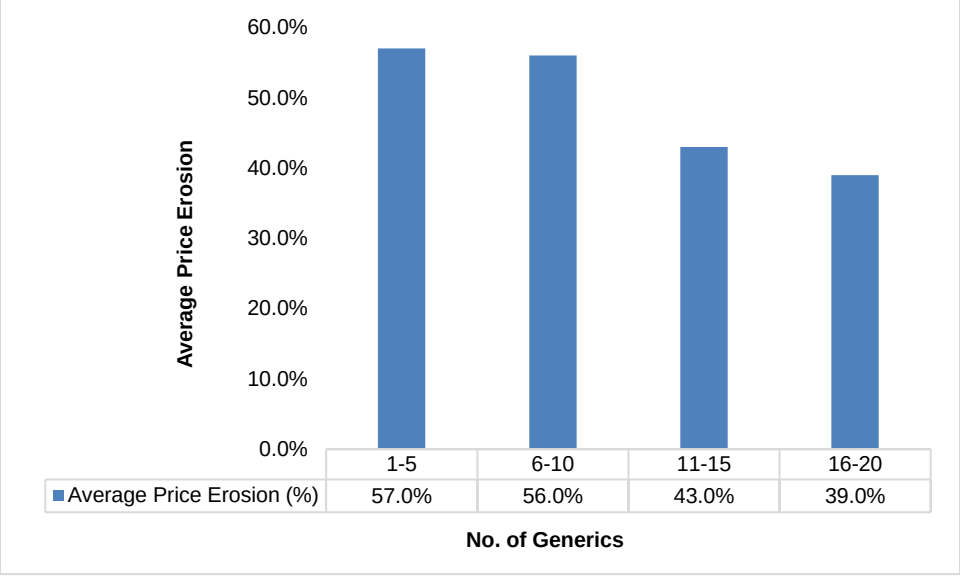


Figure 3.3 - Generic Entry and Price Erosion, 1999 - 2012.

3.2.4. Prices of Other Generic Drugs at Entry

The entry prices of generic drugs in the same formulation market were computed with a view to establish whether the prices of the foregoing entrants have a bearing on the price of the new entrant. An average entry price of other generic drugs in the same formulation market was found to be R2.54 (SD = R3.97).

3.2.5. Frequency Distributions of Therapeutic Categories

Table 3.4 depicts the market shares by value for the total pharmaceutical market (TPM), innovators' market and the generics' market. There were no differences in the rankings of the market shares by the ATC 1 system between the innovators products and the TPM. The most dominant therapeutic class in the total pharmaceutical market and the innovators' market were the general anti-infectives (ATC J) which accounted for 26.0% (n = 257) of the market by value. By contrast, the anti-infectives ranked 3rd (3.01%, n = 24) in the generics market. Except for the generics market, the drugs that work on the cardiovascular system ranked second in terms of the ATC 1 categories for both the TPM market as well as the innovators. They accounted for 24.3% (n = 445) of the market share by value whereas the drugs for cardiovascular disease ranked 1st (8.07%, n = 330) in the generics market.

Similarly, there were further differences in the rankings of the remainder of the Top 5 therapeutic classes by value between the generics market and the markets of the innovators and the overall market. The drugs belonging to the central nervous system (ATC class N) and the respiratory system (ATC class R) ranked 3rd (18.1%, n = 291) and 4th (9.66%, n = 130) in the innovators' market as well as the total pharmaceutical market by value respectively. The corresponding rankings for the generics' market were 4th (2.36%, n = 83) for the central nervous system and 5th (0.97%, n = 1) for the respiratory drugs.

Finally, the Top 5 ATC 1 categories comprised of the drugs for the alimentary canal (ATC class A), the accounted for 8.68% (n = 162) by value for the innovators market and the total pharmaceutical market respectively. The drugs for the alimentary canal ranked 2nd

(3.14%, n = 112) for the generics' market by value. There was no generic representation for the anti-parasitic products, insecticides and repellents (ATC class P) as well as various (ATC class V).

Table 3.4 Leading Therapeutic Classes, 1999 – 2012

		Total Pharmaceutical Market			Innovators			Generics		
ATC 1 Code	Description	Rank	Market Share (Value)	N	Rank	Market Share (Value)	N	Rank	Market Share (Value)	N
J	Anti-infectives for systemic use	1	26.0%	257	1	23.0%	95	3	3.01%	24
C	Cardiovascular system	2	24.3%	445	2	16.2%	115	1	8.07%	330
N	Central Nervous system	3	18.1%	291	3	15.7%	103	4	2.36%	83
R	Respiratory system	4	9.66%	130	4	8.69%	47	5	0.97%	1
A	Alimentary tract and metabolism	5	8.65%	162	5	5.51%	50	2	3.14%	112
M	Musculo-skeletal system	6	3.66%	60	6	2.88%	31	6	0.78%	188
L	Antineoplastic and immunomodulating agents	7	2.99%	49	7	2.87%	25	8	0.12%	29
D	Dermatologicals	8	2.37%	52	8	2.06%	27	7	0.30%	25
B	Blood and blood forming organs	9	1.75%	17	9	1.65%	11	9	0.10%	6
G	Genito-urinary system and sex hormones	10	0.97%	29	10	0.87%	19	9	0.10%	9
H	Systemic hormonal preparations, excluding sex hormones	11	0.73%	8	11	0.73%	8	-	0.00%	162
S	Sensory organs	12	0.56%	13	12	0.51%	12	10	0.06%	1
P	Antiparasitic products, insecticides and repellents	13	0.27%	4	13	0.27%	4	-	0.00%	0
V	Various	14	0.04%	2	14	0.04%	2	-	0.00%	0

3.2.6. Frequency Distributions of Dosage Forms

Table 3.5 shows the Top 20 dosage forms by value; the results suggest that a handful of dosage forms drive the market. The top 10 pharmaceutical dosage forms accounts for 93.3% (n = R44724.6M), 92.2% (n = R36220.7M) and 99.4% (n = R8503.9M) for the total pharmaceutical market, innovators and generics markets respectively. Table 3.5 indicates that 5 dosage forms accounts for 97.5% of all the dosage forms in the generics' market. The most prominent dosage form were the tablets that accounted for three-quarters of the market (75.7%, n = R8503.9M) by value. This was followed by capsules and injections at 13.5% (n = R8503.9M) 6.50% (n = R8503.9M) respectively.

Table 3.5 Leading Dosage Forms, 1999 – 2012

Total Pharmaceutical Market					Innovators Market					Generics Market				
Dosage Forms	**Rank**	**Sales (ZAR)**	**Market Share**	**N**	**Dosage Forms**	**Rank**	**Sales (ZAR)**	**larket Shar**	**N**	**Dosage Forms**	**Rank**	**Sales (ZAR)**	**Market Share**	**N**
TAB	1	ZAR22780.3M	50.93%	1000	TAB	1	ZAR16342.1M	45.12%	252	TAB	1	ZAR6438.3M	75.71%	748
INJ	2	ZAR8879.3M	19.85%	170	INJ	2	ZAR8326.6M	22.99%	88	CAP	3	ZAR1148.4M	13.50%	82
CAP	3	ZAR4126.7M	9.23%	130	CAP	3	ZAR2978.3M	8.22%	52	INJ	2	ZAR552.6M	6.50%	78
INF	4	ZAR978.9M	2.19%	22	SRT	7	ZAR914.7M	2.53%	15	INF	4	ZAR84.9M	1.00%	7
ACC	5	ZAR928.3M	2.08%	14	ACC	5	ZAR908.7M	2.51%	6	CRE	11	ZAR67.9M	0.80%	8
SRT	6	ZAR921.5M	2.06%	19	INH	4	ZAR896.5M	2.48%	11	SYR	13	ZAR38.1M	0.45%	8
INH	7	ZAR918.8M	2.05%	17	INF	6	ZAR894.0M	2.47%	13	SRC	10	ZAR37.6M	0.44%	4
DSP	8	ZAR872.9M	1.95%	13	DSP	8	ZAR872.9M	2.41%	6	SOL		ZAR35.1M	0.41%	7
SUS	9	ZAR872.2M	1.95%	17	SUS	9	ZAR871.2M	2.41%	16	OPD	18	ZAR26.4M	0.31%	1
SYR	10	ZAR429.0M	0.96%	5	SYR	10	ZAR391.0M	1.08%	4	INH	6	ZAR22.3M	0.26%	1
CRE	11	ZAR419.8M	0.94%	7	SOL	12	ZAR375.2M	1.04%	6	ACC	5	ZAR19.6M	0.23%	1
SOL	12	ZAR410.4M	0.92%	12	CRE	11	ZAR351.8M	0.97%	10	SHA	8	ZAR11.8M	0.14%	2
AQS	13	ZAR271.8M	0.61%	4	AQS	13	ZAR271.8M	0.75%	2	SRT		ZAR6.8M	0.08%	2
OPD	14	ZAR269.1M	0.60%	19	OPD	14	ZAR242.7M	0.67%	11	CHU	9	ZAR5.5M	0.06%	8
SRC	15	ZAR195.1M	0.44%	5	SRC	15	ZAR157.5M	0.43%	3	GEO	7	ZAR4.3M	0.05%	2
DRP	16	ZAR134.9M	0.30%	5	DRP	16	ZAR133.7M	0.37%	1	UNG	17	ZAR1.4M	0.02%	4
GRA	17	ZAR121.4M	0.27%	6	GRA	17	ZAR121.4M	0.34%	5	DRP	21	ZAR1.2M	0.01%	1
CHU	18	ZAR114.6M	0.26%	3	EFT	20	ZAR111.8M	0.31%	1	SUS	14	ZAR1.1M	0.01%	2
EFT	19	ZAR111.8M	0.25%	5	OIN	18	ZAR111.1M	0.31%	3	LOT		ZAR.8M	0.01%	2
OIN	20	ZAR111.1M	0.25%	3	CHU	19	ZAR109.1M	0.30%	2	PTD		ZAR.1M	0.00%	1
Total for Top 20		**ZAR43867.9M**	**98.1%**		**Total for Top 20**		**ZAR35382.4M**	**97.7%**		**Total for Top 20**		**ZAR8503.9M**	**100.0%**	
Total for All Dosage Form		**ZAR44724.6M**	**100.0%**		**Total for All Dosage Form**		**ZAR36220.7M**	**100.0%**		**Total for All Dosage Form**		**ZAR8503.9M**	**100.0%**	
Min (All Dosage Form)		**ZAR2.8M**	0.01%		**Min (All Dosage Form)**		**ZAR2.8M**	0.01%		**Min (All Dosage Form)**		**ZAR.8M**	0.0%	
Max (All Dosage Form)		**ZAR22780.3M**	50.93%		**Max (All Dosage Form)**		**ZAR16342.1M**	45.12%		**Max (All Dosage Form)**		**ZAR6438.3M**	75.7%	
Average (All Dosage Form)		**ZAR993.9M**	**2.22%**		**Average (All Dosage Form**		**ZAR804.9M**	**2.22%**		**Average (All Dosage Form**		**ZAR425.2M**	**5.00%**	
Count (All Dosage Form)		**45**	-		**Count (All Dosage Form)**		**45**	-		**Count (All Dosage Form)**		**20**	-	
SD (All Dosage Form)		**ZAR3618.9M**	-		**SD (All Dosage Form)**		**ZAR2703.5M**	-		**SD (All Dosage Form)**		**ZAR1441.4M**	-	

Legend: TAB - Tablets, INJ - Injections, CAP - Capsules, INF - Infusions, ACC - Accuhaler, SRT - Slow Realese Tablets, INH - Inhaler, DSP - Dispersible Tablets, SUS - Suspensions, SYR - Syrup, CRE - Cream, SOL - Solutions, AQS - Aqueous Nasal Spray, OPD - Eye Drops, SRC - Slow Release Capsules, DRP - Drops, GRA - Granules, CHU - Chewable Tablets, EFT - Effervescent Tablets, OIN - Ointments, SHA - Shampoo, GEO - Gels, UNG - Ointment, LOT - Lotion, PTD - Transdermal Patch

3.3. Market Segmentation of the South African Pharmaceutical Industry

The breakdown of the pharmaceutical industry by sector in terms of its sales by value was conducted with a view to understand the segmentation in the context of the sector's responsiveness to legislative reforms.

3.3.1. Market Segmentation by Pharmaceutical Companies

Notwithstanding the fact that the innovator companies held just a fifth of the market share by value, they had a considerably low number of products in their portfolios; Table 3.6. The product portfolios of each company in the different markets were M = 23 (SD = 33, range = 176), M = 20 (SD = 29, range = 109) and M = 14 (SD = 18, range = 66) for the total pharmaceutical market, generics' and innovators' markets respectively. Both Aspen Pharmacare and Sandoz had 110 products apiece which represented the highest number of products in a portfolio of a company in all the markets. This paradoxical difference is indicative of the high average unit price for the innovator products in comparison to the generics as shown in Table 5.1.

As depicted in Table 3.6, the Top 4 and Top 20 companies accounted for 42.4% and 98.4% of the generics market by value respectively. The 4 leading generic companies controlled 59.4% of the market by value with minor differences between the two leading companies, Cipla-Medro (18.7%, n = R1591.1M) and Aspen Pharmacare (18.8%, n = R1602.1M). Save for Sandoz the remainder of these companies are South African by origin and were all listed in the Johannesburg Stock Exchange (JSE) by end of 2012. The Top 4 and Top 20 companies accounted for 49.8% (n = R 18029.1M) and 98.1% of the innovators' market by value correspondingly.

Table 3.6 Top 20 Leading Pharmaceutical Companies, 1999 – 2012.

Total Pharmaceutical Market: 1999 - 2012				Total Pharmaceutical Market: 1999 - 2003				Total Pharmaceutical Market: 2004 - 2012			
Total Pharmaceutical Market	**Rank**	**Sales**	**Market Share**	**N**	**Total Pharmaceutical Market**	**Rank**	**Sales**	**Market Share**	**N**	**Total Pharmaceutical Market**	**Rank**	**Sales**	**Market Share**	**N**
Sanofi-Aventis	1	ZAR7030.9M	15.72%	99	Sanofi-Aventis	1	ZAR2387.7M	16.61%	21	Sanofi-Aventis	1	ZAR4643.1M	15.30%	78
Aspen Pharmacare	2	ZAR6505.8M	14.55%	177	Aspen Pharmacare	2	ZAR1981.8M	13.79%	40	Aspen Pharmacare	2	ZAR4524.0M	14.90%	137
MSD	3	ZAR3717.5M	8.31%	72	MSD	3	ZAR1749.7M	12.17%	43	MSD	3	ZAR1967.8M	6.48%	29
Pfizer Laboratories	4	ZAR2820.2M	6.31%	42	Pfizer Laboratories	4	ZAR1243.3M	8.65%	20	Astrazeneca	4	ZAR1738.3M	5.73%	20
Bayer	5	ZAR2471.3M	5.53%	20	Roche	5	ZAR1150.9M	8.01%	13	Pfizer Laboratories	5	ZAR1576.9M	5.20%	22
Astrazeneca	6	ZAR2400.6M	5.37%	33	Bayer	6	ZAR964.3M	6.71%	11	Cipla Medro	6	ZAR1545.6M	5.09%	88
Roche	7	ZAR2384.0M	5.33%	31	Novartis	7	ZAR672.0M	4.68%	14	Bayer	7	ZAR1507.0M	4.96%	9
Novartis	8	ZAR1861.3M	4.16%	56	Astrazeneca	8	ZAR662.3M	4.61%	13	Roche	8	ZAR1233.1M	4.06%	18
Janssen Pharmaceutica	9	ZAR1763.8M	3.94%	33	Janssen Pharmaceutica	9	ZAR597.2M	4.16%	15	Adcock Ingram	9	ZAR1217.3M	4.01%	60
Cipla Medro	10	ZAR1591.1M	3.56%	97	Wyeth	10	ZAR528.7M	3.68%	1	Novartis	10	ZAR1189.3M	3.92%	42
Wyeth	11	ZAR1570.9M	3.51%	8	Abbott	11	ZAR469.6M	3.27%	5	Janssen Pharmaceutica	11	ZAR1166.6M	3.84%	18
Adcock Ingram	12	ZAR1369.9M	3.06%	74	Bristol-Myers Squibb	12	ZAR458.9M	3.19%	10	Wyeth	12	ZAR1042.2M	3.43%	7
Bristol-Myers Squibb	13	ZAR1337.4M	2.99%	20	Boehringer Ingelheim	13	ZAR341.1M	2.37%	4	Bristol-Myers Squibb	13	ZAR878.6M	2.89%	10
Abbott	14	ZAR1022.4M	2.29%	17	AHN Pharma	14	ZAR296.7M	2.06%	6	Pharma Dynamics	14	ZAR599.1M	1.97%	60
Nycomed	15	ZAR678.0M	1.52%	8	Adcock Ingram	15	ZAR152.6M	1.06%	14	Sandoz	15	ZAR566.2M	1.87%	102
Boehringer Ingelheim	16	ZAR627.3M	1.40%	20	Nycomed	16	ZAR146.4M	1.02%	2	Abbott	16	ZAR552.8M	1.82%	12
Sandoz	17	ZAR606.7M	1.36%	110	Elli Lilly	17	ZAR122.5M	0.85%	6	Nycomed	17	ZAR531.7M	1.75%	6
Pharma Dynamics	18	ZAR604.0M	1.35%	65	Servier Laboratories	18	ZAR79.5M	0.55%	1	Biogaran	18	ZAR464.3M	1.53%	3
Elli Lilly	19	ZAR517.8M	1.16%	14	Johnson & Johnson	19	ZAR47.1M	0.33%	2	Elli Lilly	19	ZAR395.4M	1.30%	8
AHN Pharma	20	ZAR506.6M	1.13%	12	Cipla Medro	20	ZAR45.6M	0.32%	9	Astellas Pharma	20	ZAR341.4M	1.12%	32
Total for Top 20		**ZAR41387.7M**	**92.54%**		**Total for Top 20**		**ZAR14097.9M**	**98.09%**		**Total for Top 20**		**ZAR8503.9M**	**100.0%**	
Total for All Companies		**ZAR44724.6M**	**100.00%**		**Total for All Companies**		**ZAR14370.4M**	**99.99%**		**Total for All Companies**		**ZAR30324.6M**	**99.91%**	
Min (All Companies)		**ZAR.1M**	**0.00%**		**Min(All Companies)**		**ZAR1.4M**	**0.01%**		**Min(All Companies)**		**ZAR7.2M**	**0.02%**	
Max (All Companies)		**ZAR7030.9M**	**15.72%**		**Max(All Companies)**		**ZAR2387.7M**	**16.61%**		**Max(All Companies)**		**ZAR4643.1M**	**15.30%**	
Average (All Companies)		**ZAR677.6M**	**1.52%**		**Average(All Companies)**		**ZAR378.2M**	**2.63%**		**Average(All Companies)**		**ZAR631.8M**	**2.08%**	
Count (All Companies)		**66**	**-**		**Count(All Companies)**		**38**	**-**		**Count(All Companies)**		**48**	**-**	
SD (All Companies)		**ZAR1358.9M**	**3.04%**		**SD (All Companies)**		**ZAR599.4M**	**4.17%**		**SD (All Companies)**		**ZAR998.3M**	**3.29%**	

3.3.2. Market Segmentation by Pharmaceutical Products

As shown in Table 3.7, there were no differences in the 11 top ranked products between the innovators market and the total pharmaceutical market by value. Insofar as the total pharmaceutical market is concerned, the 12th ranked (1.41%, n = R 44714.6M) product (Adco-Simvastatin) by value, was ranked 1st in the generics' market. Notably, Adco-Simvastatin was the only generic product in the total pharmaceutical market of the Top 20 products by value.

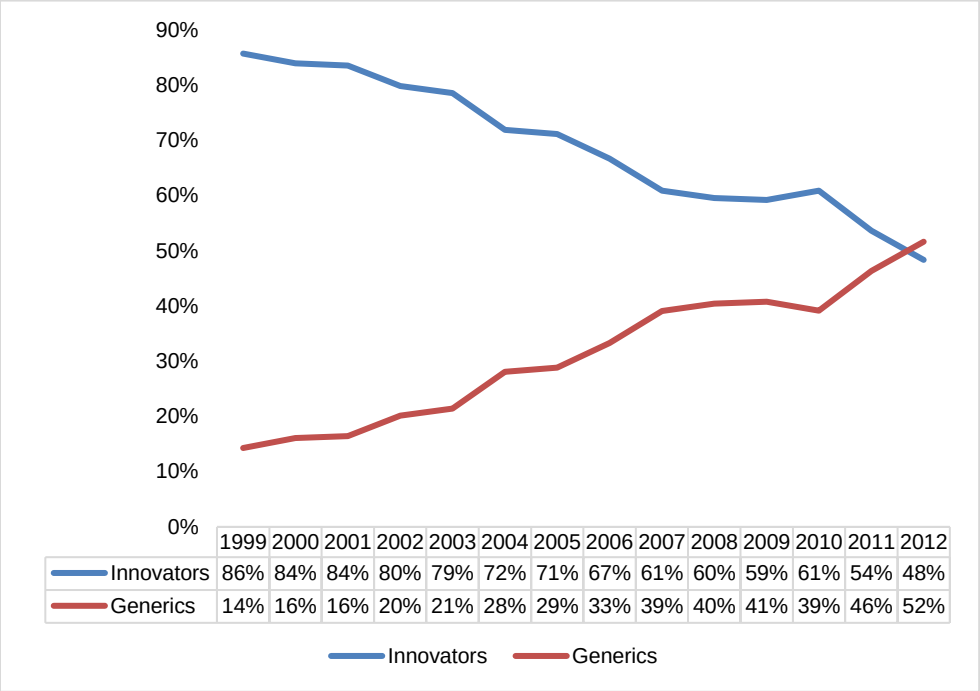
The generics sector appeared to be primarily driven by a handful of products by value, The Top 20 ranked generic products accounted for just over half of the market (51.7%, R8503.9M) by value for the period 1999 to 2012. Adco-Simvastatin (Simvastatin) and Ciprobay (Ciprofloxacin) as bestselling drugs for the generics' market and innovators' market respectively had sales that were 37 (7.42%, n = R8503.9M) and 12 (5.46%, n = R36220.7M) times more than their respective industry's average by value. As seen in Table 3.7, Simvastatin as a chemical entity jointly held the second position with Amlodipine in terms of having the highest number of generic equivalents. Both chemical entities (Simvastatin and Amlodipine) attracted 16 generic entrants whereas Ciprofloxacin attracted 15 generic entrants.

Table 3.7 Top 20 Pharmaceutical Products, 1999 – 2012

Total Pharmaceutical Market				Innovator Market				Generic Market			
Pharmaceutical Product	**Chemical Entity**	**Sales (ZAR)**	**Market Share**	**Innovator Products**	**Chemical Entity**	**Sales (ZAR)**	**Market Share**	**Generic Products**	**Chemical Entity**	**Sales (ZAR)**	**Market Share**
Ciprobay	Ciprofloxacin	ZAR1976.5M	4.42%	Ciprobay	Ciprofloxacin	ZAR1976.5M	5.46%	Adco-Simvastatin	Simvastatin	ZAR630.9M	7.42%
Rocephin	Ceftriaxone	ZAR1591.2M	3.56%	Rocephin	Ceftriaxone	ZAR1591.2M	4.39%	Pantoloc	Pantoprazole	ZAR392.6M	4.62%
Lamictin	Lamotrigine	ZAR1534.0M	3.43%	Lamictin	Lamotrigine	ZAR1534.0M	4.24%	Zetomax	Lisinopril	ZAR284.7M	3.35%
Efexor	Venlafaxine	ZAR1208.3M	2.70%	Efexor	Venlafaxine	ZAR1208.3M	3.34%	Coxflam	Meloxicam	ZAR259.6M	3.05%
Flixotide	Fluticasone	ZAR1137.7M	2.54%	Flixotide	Fluticasone	ZAR1137.7M	3.14%	Prexum	Perindopril	ZAR234.3M	2.76%
Tavanic	Levofloxacin	ZAR1137.1M	2.54%	Tavanic	Levofloxacin	ZAR1137.1M	3.14%	Prexum Plus	Perindoprilindapamide	ZAR230.0M	2.71%
Targocid	Teicoplanin	ZAR818.2M	1.83%	Targocid	Teicoplanin	ZAR818.2M	2.26%	Pharmapress	Enalapril	ZAR215.8M	2.54%
Meronem	Meropenem	ZAR763.7M	1.71%	Meronem	Meropenem	ZAR763.7M	2.11%	Aspavor	Atorvastatin	ZAR210.1M	2.47%
Lanzor	Lansoprazole	ZAR721.0M	1.61%	Lanzor	Lansoprazole	ZAR721.0M	1.99%	Amloc	Amlodipine	ZAR198.6M	2.34%
Maxipime	Cefepime	ZAR682.3M	1.53%	Maxipime	Cefepime	ZAR682.3M	1.88%	Venlor	Venlafaxine	ZAR195.2M	2.30%
Klacid	Clarithromycin	ZAR668.5M	1.49%	Klacid	Clarithromycin	ZAR668.5M	1.85%	Altosec	Omeprazole	ZAR195.1M	2.29%
Adco-Simvastatin	Simvastatin	ZAR630.9M	1.41%	Risperdal	Risperidone	ZAR593.4M	1.64%	Carloc	Carvedilol	ZAR188.7M	2.22%
Risperdal	Risperidone	ZAR593.4M	1.33%	Tritace	Ramipril	ZAR581.5M	1.61%	Lansoloc	Lansoprazole	ZAR183.9M	2.16%
Tritace	Ramipril	ZAR581.5M	1.30%	Renitec	Enalapril	ZAR559.5M	1.54%	Epitec	Lamotrigine	ZAR175.3M	2.06%
Renitec	Enalapril	ZAR559.5M	1.25%	Topamax	Topiramate	ZAR545.8M	1.51%	Topzole	Pantoprazole	ZAR165.5M	1.95%
Topamax	Topiramate	ZAR545.8M	1.22%	Clexane	Enoxaparin	ZAR527.9M	1.46%	Aspen Ceftriaxone	Ceftriaxone	ZAR157.3M	1.85%
Clexane	Enoxaparin	ZAR527.9M	1.18%	Cibadrex	BenazeprilHydrochlorothiazide	ZAR474.7M	1.31%	Fluzol	Fluconazole	ZAR143.6M	1.69%
Cibadrex	BenazeprilHydrochlorothiazide	ZAR474.7M	1.06%	Seretide	FluticasoneSalmeterol	ZAR467.4M	1.29%	Adco-Zolpidem	Zolpidem	ZAR139.9M	1.65%
Seretide	FluticasoneSalmeterol	ZAR467.4M	1.05%	Norvasc	Amlodipine	ZAR449.4M	1.24%	Omez	Omeprazole	ZAR100.7M	1.18%
Norvasc	Amlodipine	ZAR449.4M	1.00%	Aprovel	Irbesartan	ZAR447.3M	1.23%	Hexal-Lisinopril	Lisinopril	ZAR93.0M	1.09%
Min (All Product)		**ZAR.1M**		**Min (All Product)**		**ZAR.3M**		**Min (All Product)**		**ZAR.1M**	
Max (All Products)		**ZAR1976.5M**		**Max (All Products)**		**ZAR1976.5M**		**Max (All Products)**		**ZAR630.9M**	
Average (All Products)		**ZAR62.7M**		**Average (All Products)**		**ZAR160.3M**		**Average (All Products)**		**ZAR17.3M**	
Count (All Products)		**713**		**Count (All Products)**		**226**		**Count (All Products)**		**491**	
SD (All Products)		**ZAR172.1M**		**SD (All Products)**		**ZAR272.6M**		**SD (All Products)**		**ZAR50.0M**	
Total for Top 20		**ZAR17068.9M**	**38.2%**	**Total for Top 20**		**ZAR16885.3M**	**46.6%**	**Total for Top 20**		**ZAR4394.8M**	**51.7%**
Total for All Products		**ZAR44724.6M**	**100.0%**	**Total for All Products**		**ZAR36220.7M**	**100.0%**	**Total for All Products**		**ZAR8503.9M**	**100.0%**

3.3.3. Shifts in the Market Segmentation of the South African Pharmaceutical Industry

Figure 3.4 provides a graphical representation of the shifting patterns of the local pharmaceutical industry. The industry was previously dominated by the innovator companies. However, the generic sector of the market has since gained traction and is demonstrably growing at a steady rate.



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Innovators	86%	84%	84%	80%	79%	72%	71%	67%	61%	60%	59%	61%	54%	48%
Generics	14%	16%	16%	20%	21%	28%	29%	33%	39%	40%	41%	39%	46%	52%

Figure 3.4 Market Segmentation of the Local Industry, 1999 - 2012.

3.4. Emerging Themes in the South African Pharmaceutical Industry

A description of the nuanced features of the (emerging themes) the local pharmaceutical market that have a bearing on the prices of generic drug is provided in this section.

3.4.1. The Influence of Generic Entry on the Prices of an Off-Patent Innovator Product

A one-way ANOVA was conducted to compare the effect of generic entry on the price of an off-patent innovator product in the genericized (M = R19.77, SE = R3.34) and not genericized (M = R53.45, SE = R3.19) chemical entities. The difference of the effect of generic entry on the price of the off-patent innovator product between the two conditions was statistically significant at $p < 0.05$, [F(1,5594) = 53.02]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the genericized and not genericized chemical entities were statistically significantly at *p*-value < 0.05.

3.4.2. The Influence of Authorized Generics on the Prices of Generic Drugs

A one-way ANOVA was conducted to compare the effect of authorized generics on the price of generic drugs in the formulation markets with authorized generics (M = R2.66 and SE = R0.20) and in the formulation markets without authorized generics (M = R2.53 and SE = R0.06) conditions. The difference of the effect of authorized generics on the price of a generic drug between the two conditions was not statistically significant at $p < 0.05$, [F(1,4596) = 0.34]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the formulation markets with and without authorized generics was not statistically significantly at *p*-value < 0.05.

3.4.3. The Influence of Authorized Generics on Price Erosion

A one-way ANOVA was conducted to compare the effect of authorized generics on price erosion in the formulation markets with authorized generics (M = 0.79 and SE = 0.01) and in the formulation markets without authorized generics (M = 0.55 and SE = 0.004) conditions of price erosion. The difference of the effect of authorized generics on price erosion between the two conditions was statistically significant at $p < 0.05$, [F(1,4402) = 252.55]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the formulation markets with and without authorized generics was statistically significantly at *p*-value < 0.05.

3.4.4. The Influence of Close Substitutes (Me-Too Drugs) on the Price of Generic Drugs

A one-way ANOVA was conducted to compare the effect of me-too drugs on the price of generic drugs in the therapeutic markets with me-too drugs (M = R5.93 and SE = R0.44) and in the therapeutic markets without me-too drugs (M = R2.48 and SE = R0.06) conditions of the price of a generic. The difference of the effect of me-too drug on the price of a generic between the two conditions was statistically significant at $p < 0.05$, [F(1,4596) = 61.49]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the therapeutic markets with and without me-too drugs was statistically significantly at *p*-value < 0.05.

3.4.5. The First-Mover Advantage and the Price of a Generic Drug

A one-way ANOVA was conducted to compare the effect of first-mover advantage in the formulation market on the price of a generic drug between the first-mover generics (M = R2.77 and SE = R0.10) and follow-on generics (M = R2.44 and SE = R0.07) conditions. The difference of the effect of first-mover advantage on the price of generics between the two conditions was statistically significant at $p < 0.05$, [F(1,4596) = 6.87]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the first-mover generics and the follow-on generics was statistically significantly at *p*-value < 0.05.

3.4.6. The Impact of Legislative Reforms on Pharmaceutical Sales

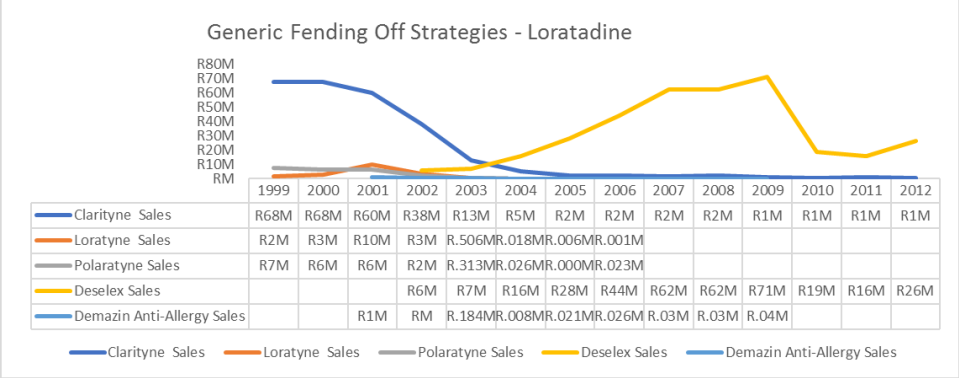
A one-way ANOVA was conducted to compare the effect of legislative reforms on the annual sales of generic products between the period before the reforms (M = R2.60M and SE = R0.19M) and the period after the reforms (M = R1.78M and SE = R0.07M) conditions. The difference of the effect of legislative reforms on the sales revenue of a generic product between the two conditions was statistically significant at $p < 0.05$, [F(1,4551) = 16.71]. Post hoc comparisons using the Tukey HSD test indicated that the difference in the mean scores for the period before the reforms and after the reforms was statistically significantly at *p*-value < 0.05.

3.4.7. The Impact of Patent Expiry on the Prices of Innovator Products

A one-way ANOVA was conducted to compare the effect of loss of patent protection on the price of the innovator product in the before patent expiry (M = R49.22 and SE = R3.97) and the after-patent expiry (M = R31.23 and SE = R2.86) conditions. The difference of the effect of the loss of patent protection on the innovator product between the two conditions was statistically significant at $p < 0.05$, [F(1,5594) = 13.53]. Post hoc comparisons using the Tukey HSD test indicated that the difference mean scores for the before and after patent expiry were statistically significantly at p-value < 0.05.

3.5. Generic Fending Off Strategies

Certain innovator companies tend to employ a wide range of strategies to maximize patent protection of their drugs with a view to maximize the commercial lifecycle.[35] The study identified two generic fending off strategies that are employed by the innovator companies with a view to mitigate generic competition. Figure 3.5 presents a case study involving Loratadine in which both strategies were employed.



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Clarityne Sales	R68M	R68M	R60M	R38M	R13M	R5M	R2M	R2M	R2M	R2M	R1M	R1M	R1M	R1M
Loratyne Sales	R2M	R3M	R10M	R3M	R.506M	R.018M	R.006M	R.001M						
Polaratyne Sales	R7M	R6M	R6M	R2M	R.313M	R.026M	R.000M	R.023M						
Deselex Sales				R6M	R7M	R16M	R28M	R44M	R62M	R62M	R71M	R19M	R16M	R26M
Demazin Anti-Allergy Sales			R1M	RM	R.184M	R.008M	R.021M	R.026M	R.03M	R.03M	R.04M			

Figure 3.5 Generic Fending Off Strategy - Case Study of Loratadine

3.5.1. Introduction of Authorized Generics into a Formulation Market

As seen in Table 3.2, the study identified 25 cases of authorized generics into formulation markets. The case study of Loratadine as depicted in Figure 3.5 demonstrates how the innovator company was able to keep this chemical entity viable despite the loss of patent protection.

Between 1999 and 2001 Loratadine was a viable chemical entity whose sales begun plummeting following the loss of its exclusivity in 2001. It is noteworthy that Loratadine traded under 5 different proprietary names during its on-patent and off-patent periods. The innovator product, Clarityne® was launched in Dec 1990 followed by Polaratyne ® 10 months later, Oct 1991. Furthermore, Loratyne ® was introduced to the market in Jan 1998 followed by Demazin Anti-Allergy in Apr 2001. All these products were launched by the same company, Schering-Plough which later merged with MSD.[36]

3.5.2. Use of 'Evergreening' Tactics

As seen in Figure 3.5, having come on stream in 2002, the sales of Desloratadine (an active metabolite of Loratadine marketed as Deselex®) rose sharply even exceeding the initial sales of Loratadine in 2009. Table 3.8 shows that the study identified 6 cases (including Loratadine) where modifications were effected on the prior art by filing for a new patent to secure exclusivity on the near expiry molecule. The most prominent form of line extension was the use of stereo selectivity where medicines that have a chiral center that comprise of a mixture of two enantiomers were used strategically.[37] In this regard, a line extension is achieved by developing and marketing a pure form of one enantiomer, this phenomenon is also known as chiral switching.[37] As shown in Table 3.8, the study identified the following cases of chiral switching: Nexiam® (Esomeprazole), Xyzal® (Levoceterizine), and Cipralex® (Escitalopram).

Table 3.8 **Generic Fending Off Strategies, 1999 – 2012**

		Invention 1 (Prior Art)						Invention 2 (Line Extension)					
Generic Fending Off Strategy	**Additional Years Gained**	**Trade Name**	**Generic Name**	**Dosage Form**	**Launch Date**	**Patent Expiry Date**	**Effective Patent Life (Yrs)**	**Trade Name**	**Generic Name**	**Dosage Form**	**Launch Date**	**Patent Expiry Date**	**Effective Patent Life (Yrs)**
Stereoselectivity	20	Losec	Omeprazole	Tab & Inj	Feb-90	Apr-99	9	Nexiam	Esomeprazole	Tab & Inj	Apr-02	Jul-13	11
Stereoselectivity	7	Cipramil	Citalopram	Tab	Sep-94	Jan-98	3	Cipralex	Escitalopram	Tab	Jun-04	Apr-08	4
New Indication	27	Proscar	Finasteride	Tab	Feb-93	Feb-05	12	Propecia	Finasteride	Tab	May-99	Oct-14	15
Active Metabolite	14	Clarityne	Loratadine	Tab, Eff & Syr	Dec-90	Jun-01	11	Deselex	Desloratadine	Tab, Syr, Srt	May-02	Jun-05	3
Active Metabolite	25	Risperdal	Risperidone	Tab, Sol & Inj	Nov-93	Mar-06	12	Invega	Paliperidone	Tab	Feb-11	Jul-23	12
New Dosage Form	18	Efexor	Venlafaxine	Tab & Cap	Feb-95	Dec-03	9	Efexor	Venlafaxine	Srt	Feb-95	Dec-03	9

As seen in Figure 3.5, the two-generic fending off strategies that were employed in terms of early generic entry as well as a line extension resulted in a significant preservation of revenue for the MSD without benefiting the patient.

3.6. Discussion

The study found a reasonably high rate of annual patent expirations (M = 39.2 patents, SD = 4.7 patents). The period under which the study was conducted, 1999 to 2012, coincided with patent expirations of some of the leading best-selling drugs of all time. Forbes' Pharma and Healthcare report lists Top 20 best-selling drugs of all time which included products such as: Lipitor® (Atorvastatin), Seroquel® (Quetapine), Seretide® (Fluticasone), Singulair® (Montelukast), Losec® (Omeprazole), Zyprexa® (Olanzapine), Diovan® (Valsartan) and Zocor (Simvastatin). Save for Seretide all the best-selling products attracted generic competition in South Africa.

Except for Clexane® (Enoxaparin) which had an effective patent life of 19.6 years, the average effective patent life in South Africa is 9.24 years (SD = 3.95 years). This is 3.88 years shorter than the USA.[38]

Grabowski *et al.* conducted a study that looked at 161 innovator molecules between 1994 and 2011 that experienced patent challenges and considered the implications of such challenges on innovation and generic competition. They found that an average effective patent life in the USA was 13.12 years (SD = 3.48 years). Effective patent life is a period between product launch and patent expiration.[39] Typically, a pharmaceutical innovator files a patent application as soon as they discover a chemical structure of the API.[40] This is done with a view to mitigate the chances of competitors filing for a patent covering the same molecule. The differential in effective patent life between the USA and South Africa can be attributed to the registration backlogs at the Medicines Control Council (MCC). The reduced effective patent life from a South African point of view has revenue implications to innovator companies who seek to recoup their sunk costs related to research and development of bringing new therapies to the market.

This study found the level of generic penetration in the South African market less than optimal on two levels. In terms of international standards, generic entry is considerably slow in South Africa. For instance, the sales of Zocor® (Simvastatin) continued to grow in the first two years following the loss of its patent protection. Hitchings *et al.* reports that

generic competition for Zocor® in the United Kingdom (UK)resulted in its sales collapsing from £250m to £2m in only two years.[38] As shown in Table 3.3, the generic equivalent of Zocor® only entered the market in the second year following its loss of patent protection.

Furthermore, Table 3.3 shows that the average rate of generic entry per chemical entity that lost its patent protection was 2.72 generics/chemical entity (SD = 2.14 generics/chemical entity), 3.28 generics/chemical entity (SD = 2.73 generics/chemical entity), and 3.74 generics/chemical entity (SD = 3.23 generics/chemical entity) in the first, second and third years following the loss of exclusivity respectively. Kanavos conducted a research of 12 European Union (EU) member states that investigated the performance of the off-patent markets relative to their pharmaceutical laws with specific focus on generic drugs.[41] At 1.0 generics/chemical entity, Greece had the lowest generic penetration rate in the first year following the loss of patent protection of an innovator product. South Africa's generic entry rate per chemical entity was comparable to that of Austria at 2.8 generic drugs across all molecules.[41] The best performing country was Germany that enrolled 10.8 generic drugs per chemical entity within the first year following loss of patent protection.[41]

The average rate of generic entry rate per chemical entity within the first year following loss of patent protection was 3.55 across all the countries.[41] The low generic penetration rate within the first year following the loss of patent protection in South Africa can also be attributed to the registration delays at the Medicines Control Council (MCC). A recent study that looked at registration timelines of the MCC found that it takes between 24 months to 36 months to register a medicine in South Africa.[42] The registration timelines by leading international regulatory authorities are 18 months and 12 months for the United States Food Drug Administration (US FDA) and the European Medicines Agency (EMA) respectively.[43]

The delays to market access by generic equivalents of chemical entities that have lost patent protection have an impact on access to medicines by patients.[42] Additionally, the registration delays undermine the cost saving impact of generic drugs as an expenditure

optimization tool for health systems and patients alike.[41] The rate of generic entry was at its slowest in the period 1999-2002. In 2003, the generic uptake increased by over 50.0% of the rate of entry of the previous year. The dramatic increase post 2002 can be attributed to legislative reform[42] as it pertains to the introduction of section 22F and other pro generic legislative changes.

The market performance of generics was found to depend on whether a drug was a first-mover in its therapeutic class following the loss of exclusivity. For instance, Lipitor® (Atorvastatin) and Zocor® (Simvastatin) accounted for 42.0% and 32.0% of global sales for statins.[44] In the case of the latter, Simvastatin, upon its loss of exclusivity in South Africa, Adcock Ingram was the first-mover to launch its generic version. The first mover status on Adcock's generic equivalent secured it a 12th spot in the Top 20 ranked products. Save for Adco-Simvastatin, the remainder of the Top 20 ranked products by value in the in South African' total pharmaceutical market were all innovator products for the period spanning 1999 to 2012.

Secondly, less than half of the chemical entities that lost patent protection between 1999 and 2012 lacked generic competition. A moderate correlation (r = 0.49, p < 0.01) was found between the market size of the innovator product prior to the loss of exclusivity and the subsequent extent of generic penetration. As demonstrated in Figure 3.2, the higher the sales of a chemical entity prior to loss of exclusivity the higher the average rate of generic entry. However, the study found that where the high sales of an innovator product were driven by a specialized technology in terms of a dosage form generic penetration was constrained. For instance, despite being the most successful product in terms of sales in the year preceding the expiry of its patent protection, Flixotide® (Fluticasone) did not experience generic competition since losing patent protection in 2001.

The selective generic entry is indicative of the fact that the choice of products by generic companies is driven by commercial interests. This is consistent with the tenets of the theory of a firm as a profit maximizing entity.[45] Craig contends that where the levels of differentiation are high, buyers' power is weakened resulting in sub-optimal social welfare

in terms of affordability and access to care.[34] This finding raises pertinent questions with considerable policy implications insofar as the NDP is concerned. As aforementioned, the goal of the NDP is to reduce the prices of medicines in South Africa with a view to improve access to medicines. The policy interventions have thus far borne fruit in certain respects, as demonstrated in Table 4.1 there was a statistically significant difference ($p < 0.01$) on price erosion in the periods before and after the institution of legislative reforms. However, it is evident that policy making ought to be agile and evolving to address the nuances of the market.

Loss of patent protection on innovator products results in a removal of a significant barrier to market entry. In certain cases, this results in multiple generic equivalents, e.g. Loratadine (n = 20) and Simvastatin/Amlodipine (n = 16), of the innovator product entering the market to compete for market share.[34] The aggregate impact of generic drugs in eroding the price of an innovator product is known as price erosion.[19] Economic theory avers that product differentiation dampens price competition, however; where products are essentially the same, price competition can be intense.[34]

It was found that the average price of generic drugs when there are 1 to 5 generic copies of the innovator drug competing was 57.0%. The price erosion dropped marginally when the number of generics is between 6 to 10. However, an entry of between 11 to 15 generics resulted in an average price erosion of 56.0% of the innovator price. The aggregate impact of between 16 to 20 generics was found to result in an average price erosion of 39.0%. Caves *et al.*, found that in the USA market the effect of generic competition is such that if the number of generic manufacturers increased from 1 to 10 the average price of the generic drug drops significantly, from 60% to 34%.[46]
Furthermore, Caves *et al.* found that if the number of the manufacturers of generic drugs reaches 20, the average price of the generic drug is 20%.

As shown in Table 3.2, the study identified 25 cases of authorized generics. The price erosion of the innovator products that had authorized generics was significantly lower (M = 79.2%, SD = 30.2%) than that of products that did not have authorized generics (M =

55.4%, SD = 25.6%); t(4401) = 15.91, $p < 0.01$. The authorized generics are common place in the pharmaceutical market,[47] in 2014 the Innovative Pharmaceutical Association South Africa (IPASA) commissioned a cross-sectional study. The study sought to establish the status of outstanding regulatory submissions on 308 drug applications made by some of their member companies.[48] The study found that the drug applications for 'clones' were about a third (32.1%, n = 308) of all the applications of a segment of their member companies at the point of research.[48] Elsewhere, Appelt conducted a research into the impact of authorized generics (pseudo generics) on price erosion of the innovator product and found that early entry is often done through a licensee or a subsidiary.[47] Appelt also found that the first-mover status confers a sustainable competitive advantage over follow on entrants. Fending off legitimate generic competition by insulating the innovator product from the dynamic forces of the generic market is driven by commercial interests. Since access to medicines is contingent upon affordability of medicines, this practice could potentially have dire health implications to patients whose access to care is compromised due to unaffordability.

Table 3.4 shows the therapeutic rankings (at ATC 1) of products that are sold on the South African pharmaceutical market. Albeit minor differences between the generics and the innovators as shown in Table 3.4, the rankings of ATC1 categories are reflective of the current developments globally and in the country with respect to the use of anti-infective agents.

On the 21st of September 2016, a high-level meeting comprising of the heads of states and governments of various member countries of the United Nations (UN) met to discuss antimicrobial resistance.[49] They acknowledged that the resistance of bacterial, viral and fungal microorganisms to antimicrobial agents that were previously effective in treating infections is because of inappropriate use of these agents. South Africa is evidently not an exception to this global concern as demonstrated by the fact that the general anti-infectives for systemic use dominates (ATC J) the market share by value for the period spanning 1999 to 2012. The government has devised a three-pronged approach encompassing surveillance, infection prevention and control as well as antimicrobial

stewardship as part of its Antimicrobial Resistance National Strategy Framework Commitments. [50]

The rankings of the therapeutic categories and the products as shown in Table 3.7 are consistent with the report of the Medical Research Council (MRC) that South Africa is experiencing a quadruple burden of disease. The MRC avers that in addition to the epidemic of acquired immuno-deficiency syndrome (AIDS), high rates of trauma and other infectious diseases; the non-communicable diseases (NCDs) are on the rise in South Africa. Furthermore, the report lists the major NCDs in South Africa as comprising of cardiovascular diseases, diabetes, cancers, chronic respiratory diseases as well as mental health.[51]

Table 3.7 shows that apart from the 4th ranked Coxflam® (Meloxicam) which accounted for 3.05% (n = R 8503.9M) of the generics' market by value, all other products in the Top 20 Products were treatments for the NCDs and infectious diseases. In the total pharmaceutical market as well as the innovators' market the only exception to the top 20 ranked pharmaceutical products was Clexane® (Enoxaparin) ranked 16th (1.31%, n = R 36220.7M) and 17th (1.18%, n = R 44714.6M) for the innovators' market and the total pharmaceutical market respectively by value.

As demonstrated in Table 3.5, the dosage forms that present with little technological complexity (e.g. tablets, capsules, creams etc) in manufacturing were the most prominent in generic entry. This finding is consistent with Sinclair who argues that upon expiration of patent protection of the innovator product, the more technologically advanced formulations do not attract a lot of competition amongst the generic manufacturers as opposed to standard oral tablets.[52] As discussed in Section 2.5.3, Aulton contends that inherent in the choice of the dosage form are the challenges that are associated with the technical aspects (skills, technology, capital etc) of manufacture. [52]

There are several important considerations that need to be made in designing a dosage form. Such considerations include biopharmaceutical properties (the rate and the extent

of drug absorption into the body), physicochemical properties (stability of the drug), and therapeutic properties (duration of action and dose frequency). As depicted in Table 3.5, the injections and infusions ranked 3rd and 4th in the generics sector of the market by value. This can be attributed to the fact that notwithstanding the onerous requirements of sterile dosage forms, registration of injections and infusions does not require the costly bioequivalence studies.[53]

A dosage form is a key feature in demonstrating a bioequivalence of a generic drug to the innovator product. As such it stands to reason that the dosage forms that do not require bioequivalence tests or that are simple to demonstrate bioequivalence (e.g. immediate release tablets, capsules etc) will be attractive to generic drugs.[54] The converse is true, the technologically advanced dosage forms (e.g. accuhalers, slow release tablets, transdermal patches etc) were found to be less attractive to generic manufacturers. Insufficient market entry by technologically advanced dosage forms keeps prices high.

In cases where there was generic entry following the loss of patent protection on innovator products, several key dynamics that appear to have had a bearing in shaping the market emerged. As seen in Figure 3.4, there have been institutional forces at work accelerating the growth trajectory of the generic industry. It is evident that the rates of generic entry were spurred by legislative reforms related to 69(A), 22F, and Regulation 8 of the Patents Act, Medicines Act and Medical Schemes Act respectively. The growth of the generics' sector is critical in terms of the impact as an expenditure optimization tool that results in cost savings for health systems and nations alike.

This finding is consistent with the research study that was commissioned by the National Association of National Pharmaceutical Manufacturers (NAPM). The study found that in South Africa, the use of generic drugs as a percentage of the prescription market has been increasing significantly from 35.3% in 2002 to 53.5% in 2006.[55] The growth of the generics' sector is of critical importance as good health is essential for individuals to succeed as citizens, families, workers and consumers. [56]

The results also suggest that there are innovator products that exit the market shortly following LOE. A common thread amongst the earlier exits were products that had low sales a year preceding loss of their patent protection, products that were in therapeutic classes that presented with intense competition (e.g. cardiovascular drugs) or small markets (e.g. antineoplastic drugs). As seen in Table 3.3, the study found a fair incidence of me-too drugs; M = 3 and SD = 3. Even though competition from 'me-too' drugs enhance buyers' power it is duplicative research, the resources spent on research could have been spent on novel research. There are several neglected diseases such as malaria, tuberculosis, sleeping sickness amongst others that require resources to be directed at.[57] The Médecins Sans Frontières argues that "the human suffering caused by infectious diseases could be reduced; with billions of dollars dedicated to health R&D it should be possible to develop effective treatments for these diseases. However, the lack of R&D for diseases common in developing countries means that very few new drugs have been brought to market for them." [57]

Other than the unwarranted suffering that many people in developing countries endure because of affliction by neglected diseases, the impact of 'me-too' drugs is wide ranging as it includes the use of scarce healthcare resources. Stephane argues that me-too drugs are generally launched 2.5 years after the breakthrough drug, with 20.0% more expenditure on marketing and often gains 38.0% of the market by year 4.[31] A cross-sectional study that was conducted by Innovators Pharmaceutical Association of South Africa (IPASA) identified 11.0% (n = 308) drug applications belonging to 'me-too' drugs at a single point of investigation in 2014.[48]

Patents are granted with a view to stimulate and recompense innovation, allocate resources efficiently, optimize consumer welfare, and ought to be granted in circumstances where true innovation can be demonstrated.[39] As such, it can be argued that the presence of the me-too drugs in the market undermines the innovation into the real breakthrough drugs.

The registration of patents that present with minimal innovation as seen in Table 3.8 can be attributed to the depository system that is used in South Africa. This presents with flaws in that there is no rigorous scientific critique to establish whether a patent for a drug that is undergoing registration has the required attributes, viz; novelty, newness, obviousness and usefulness to trade or agriculture.[58] This problem is compounded by the lack of the pre-and post-grant opposition procedures that are in place in other countries (Brazil, India and Egypt) of similar economies to South Africa. The Brazilian system is such that their medicines regulatory authority (equivalent of the MCC) is required to vet the granting of medicines' patents prior to approval by the country's patent office.[58] This affords the patent registration office an opportunity to access the expertise that is not available internally about the novelty of the new therapy undergoing registration.

Roox *et al.* identified several factors that lead to issuance of weak patents from a European perspective.[59] Such factors consisted of, *inter alia*, lack of rigorous assessment of the patentability requirements such as the inventive step, examiners' inability to check data presented to them, not enough consideration of third-party observations by examiners, and weaknesses in the opposition procedure. [59]

In 2014, the Supreme Court of Appeal of South Africa upheld an earlier court ruling in favour of Bayer Pharma AG which sought to prevent Pharma Dynamics from marketing a generic equivalent (Ruby®) of Yasmin® (Drospirenone 3mg and ethylestradiol 20 mcg). The court held that the marketing of Ruby® by Pharma Dynamics constituted an infringement of Bayer Pharma AG's patent. Pharma Dynamics argued that the multiple patents that Bayer seeks to enforce lacked novelty and should not be regarded as an inventive step that qualifies for further protection from competition. Pharma Dynamics had earlier cited a court ruling by the European Patent Office in the case between *Bayer Pharma AG vs Teva Pharmaceutical Industries* where an application for revocation of an additional patent on Yasmin® was upheld. The Doctors Without Borders South Africa had run a campaign at the margins of this court case entitled "fix the patent laws!", commenting on the outcome of the case, they pointed out that Ruby® was 30.0% cheaper

than the innovator product and that it would also give women more choices about their reproductive health. [68]

On the other hand, in 2013 the Supreme Court of India had rejected an application for an update of Norvatis' antineoplastic drug, Glivec® (Imatinib). The court ruled that Glivec® did not pass the muster of invention and patentability to warrant a secondary patent. The patient groups pointed out that the cost of treatment with Glivec® amounted to $5,000 monthly (in the US) whilst a generic equivalent of the same product was available at $200 monthly in India.[61]

The South African government argues that "a patent in the area of medicines is important since drugs are approved after clinical trials have been conclusive. Drugs, therefore, are based on a valid patent. It is contended that if "weak" patents are granted, it stifles the possibility of having access to public health. This means that if a patent is granted, even if there is no innovation on the original or dependent, access to public health may be difficult to attain." The government is in the second round of consultations with a view to tighten the legislation that will stop evergreening as the practice is often called. [58]

As seen in Section 3.4.7, the South African pharmaceutical industry does not present with Generic Competition paradox in that the average unit price of the off-patent innovator product is less than the on-patent average unit price. The difference between the prices of innovator products before and after patent expiry is statistically significant. However, the results suggest that for the formulation markets that did not attract generic entry the prices are comparatively higher than in the corresponding markets where there is generic entry. This underscores the role of generic competition in applying downwards pressure on the prices of innovators' products.[21]

Notwithstanding the fact that the presence of authorized generics does not have an influence on the price of a generic drug,[62] the presence of authorized generics in the formulation markets presented with less price erosion in comparison to the markets that did not have authorized generics. This highlights the fact that authorized generics

cushions the innovator product from the effects of generic competition[63] particularly because of the first-mover advantage that accrues on authorized generics. [47]

Therapeutic markets that presented with me-too drugs were found to have less profound impact on the average unit price of a generic drug than those that did not have me-too drugs in the therapeutic market. This can be attributed to the fact that where there is no therapeutic alternative, competition is not spread out over a few molecules, but it is focused on one chemical entity.[64] Finally, the results found that the annual sales revenue of generic products had a statistically significant contraction in the period following the implementation of the legislative reforms. In the light of several pharmaceutical plant closures in South Africa as reported by the Department of Trade and Industry (DTI) it is not implausible that the effect of pricing reforms has had an adverse effect on local production pharmaceuticals as discussed in Section 6.2.

3.7. Conclusion

The levels of generic entry into the local pharmaceutical industry following the loss of patent protection are considerably low; where generic entry was lacking the prices of off-patent innovator products were found to be considerably high in comparison to formulation markets with generic entry. Furthermore, generic competition in markets with me-too drugs was found to be less intense in comparison to markets without me-too drugs. Generic entry was found to be slow by international standards. The criteria for generic entry appeared to be driven primarily by the commercial viability of the chemical entity whilst under patent protection. Additionally, the formulations that present with complexity of manufacture were found to be less attractive to generic producers. The prices of generic drugs have come down significantly following the pricing legislative reforms. Price erosion was found to be inversely related to the number of generics in the formulation market. Formulation markets with authorized generics presented with a considerably low-price erosion.

Notwithstanding the impact of legislative reforms on the sales revenue of pharmaceutical products, a paradigm shift is afoot in the local pharmaceutical industry with the generic

industry becoming more dominant. The prominence of generics in drug therapy is likely to optimize social welfare in line with the pharmaceutical policy of the South African government.

CHAPTER FOUR

4. THE IMPACT OF THE TRANSPARENT PRICING SYSTEM ON THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY

Comparative analysis was drawn between the period foregoing the introduction of the transparent pricing system and the subsequent period by appraising several structural variables of the pharmaceutical industry in South Africa. The current chapter presents the results of this analytical comparison. Section 4.1 deals with the bivariate descriptive statistics between the study variables and the periods before and after the implementation of legislative reforms. To establish the statistical significance of the observations in the preceding section, inferential statistics are employed in Section 4.2. Finally, Section 4.3 considers the overall impact of the pricing reforms with a view to establish if they resulted in a fundamental realignment of the market and possibly improved access to medicines. A discussion and concluding remarks are presented in Sections 4.4 and 4.5 respectively.

4.1. Bivariate Descriptive Statistics of the Study Variables

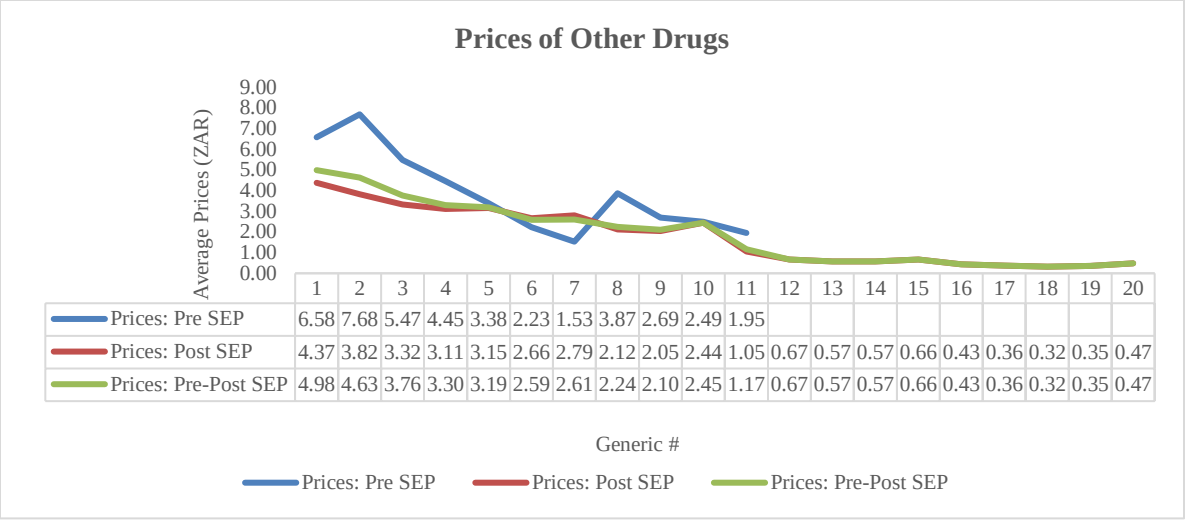
The period preceding the implementation of the transparent pricing system, 1989 (due to early entrants) to 2004, recorded an average of 4.86 generics (SE = 0.35 generics) per chemical entities that lost patent protection in comparison to an average of 3.88 generics (SE = 0.35 generics) per chemical entity that lost patent protection in the post implementation phase. There was a marginal decline (4.34%, n = R2.4M) in the sales of the innovator product in the year preceding the loss of patent protection following the implementation of the legislative reforms related to transparent pricing system. There was a low rate (4.92 months) of generic entry in the period preceding the implementation of the transparent pricing system in comparison to the 49.5 months following the implementation of the transparent pricing system.

Table 4.1 Bivariate Descriptive Statistics of the Study Variables

Market Variables	Implementation of the Transparent Pricing System			
	Before		After	
	Mean	SE	Mean	SE
No. of Generic Manufacturers Per Chemical Entity	4.86	0.35	3.88	0.35
Market Size of the Innovator Product Prior to LOE	R2.4M	R2.7M	R2.3M	R2.6M
Rate of Generic Entry (Months)	4.92	3.06	49.6	1.47
Price Erosion	0.67	0.01	0.56	0.00
Average Unit Price of an Innovator Product	R42.08	R3.61	R34.03	R3.03
Average Unit Price of a Generic Drug	R4.04	R0.18	R2.38	R0.06
Average Entry Price of Other Generics	R4.24	R5.47	R3.46	R4.48

The price erosion exerted by generic drugs on the price of the innovator product was the greatest in the period following the legislative reforms, the price erosion was 0.67 and 0.56 for the period before and after respectively. The average unit price of the innovator products and generic products declined by 23.7% and 69.7% respectively in the period following the introduction of the transparent pricing system.

As shown in Figure 4.1, the average entry price of other generics in the same formulation market underwent a contraction following the implementation of the legislative reforms. As shown in Table 4.2 below, Schedule 5 care products were the least sold in the private sector whereas the Schedules 3 and 4 dominated the market. Generally, the use of over-the-counter care products in either of the periods related to the implementation of the legislative reforms were found to be low.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Prices: Pre SEP	6.58	7.68	5.47	4.45	3.38	2.23	1.53	3.87	2.69	2.49	1.95									
Prices: Post SEP	4.37	3.82	3.32	3.11	3.15	2.66	2.79	2.12	2.05	2.44	1.05	0.67	0.57	0.57	0.66	0.43	0.36	0.32	0.35	0.47
Prices: Pre-Post SEP	4.98	4.63	3.76	3.30	3.19	2.59	2.61	2.24	2.10	2.45	1.17	0.67	0.57	0.57	0.66	0.43	0.36	0.32	0.35	0.47

Figure 4.1 Prices of Other Generic Drugs at Entry, 1999 - 2012.

The of over-the-counter drug market comprising of Schedules 1 and 2 experienced the biggest negative differential, -2.95% and -6.63% respectively from the period preceding and following the implementation of the pricing reforms. On the other hand, Schedules 3 and 5 posted the increases of 4.01% and 7.38% respectively from the period prior to the implementation of the legislative reforms to the period following the implementation.

Table 4.2 Frequency Distribution of Schedules Before and After the SEP Regime

	Implementation of the SEP Legislation			
	Pre-SEP		**Post-SEP**	
Schedule	Count	Frequency	Count	Frequency
S4	209	42.31%	1674	40.50%
S3	186	37.65%	1722	41.66%
S2	72	14.57%	328	7.94%
S1	19	3.85%	37	0.90%
S5	8	1.62%	372	9.00%

Save for the alimentary canal (ATC1 A), central nervous system (ATC1 N) and the general anti-infectives that resulted in differentials of -9.35%, -15.3%, and 12.6%, respectively;

the remainder of the therapeutic categories posted marginal changes in the period before and after the implementation of the transparent pricing system, Table 4.3.

Table 4.3 Frequency Distribution of ATC1 Before and After the SEP Regime

ATC 1	Implementation of the SEP Legislation			
	Pre-SEP		Post-SEP	
	Count	Frequency	Count	Frequency
A	10	2.02%	470	11.37%
C	184	37.25%	1507	36.46%
D	43	8.70%	93	2.25%
R	72	14.57%	333	8.06%
J	155	31.38%	776	18.78%
L	4	0.81%	50	1.21%
S	4	0.81%	8	0.19%
M	14	2.83%	142	3.44%
N	8	1.62%	700	16.94%
G	0	-	34	0.82%
B	0	-	20	0.48%

As depicted in Table 4.4 below, there were no major changes in the frequency distribution of pharmaceutical dosage forms in the period before and after the implementation of the transparent pricing system. However, there were marked increases in two dosage forms; namely, the tablets and the syrups. The former increased by 6.28% from 71.1% to 77.3% in the period before and after the implementation of the transparent pricing system respectively. It is noteworthy that the capsules which were the 3rd leading pharmaceutical dosage form in the period before the implementation of the reforms increased by 5.54% in the intervening period. On the other hand, the syrups posted the biggest decline of -2.86% in the intervening period.

Table 4.4 Frequency Distributions of Dosage Forms Before and After the SEP Regime

Dosage Form	Implementation of the SEP Legislation			
	Pre-SEP		Post-SEP	
	Count	Frequency	Count	Frequency
TAB	351	71.05%	3196	77.33%
CRE	15	3.04%	23	0.56%
LOT	7	1.42%	0	0.00%
UNG	10	2.02%	4	0.10%
SYR	19	3.85%	41	0.99%
INJ	49	9.92%	325	7.86%
OPD	4	0.81%	8	0.19%
CAP	22	4.45%	413	9.99%
GEO	4	0.81%	5	0.12%
SHA	6	1.21%	16	0.39%
SOL	4	0.81%	32	0.77%
INF	2	0.40%	19	0.46%
DRP	1	0.20%	4	0.10%
SRT	0	0.00%	5	0.12%
SRC	0	0.00%	16	0.39%
SUS	0	0.00%	7	0.17%
PTD	0	0.00%	3	0.07%
ACC	0	0.00%	3	0.07%
INH	0	0.00%	2	0.05%
CHU	0	0.00%	10	0.24%
GRA	0	0.00%	1	0.02%

4.2. Evaluation of the Impact of the Transparent Pricing System on Study Variables

A combination of ANOVA tests (Table 4.1) and crosstabulation analyses (Table 4.5) were employed with a view to establish whether the introduction of the transparent pricing system had an impact on the realignment of the industry dynamics that have a bearing on affordability of medicines and access.

4.2.1. ANOVA Between the Number of Generic Manufacturers in the Formulation Market and the Transparent Pricing System

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the number of generic manufacturers in the formulation market in the before and after conditions related to the implementation of the SEP legislation. The difference of the effect of the implementation of the SEP legislation between the two conditions was statistically significant at $p < 0.05$, [F(1,219) = 3.95]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after related to the implementation of the SEP legislation were marginally significantly different at *p*-value = 0.05.

4.2.2. ANOVA Between the Sales of the Innovator Product Prior to LOE and Transparent Pricing System

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the sales of the innovator product prior to LOE. The difference of the effect of the implementation of the SEP legislation between the two conditions was not statistically significant at $p < 0.05$, [F(1,544) = 0.09]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after conditions pertaining to the implementation of the pricing reforms were not significantly different (*p*-value = 0.76).

4.2.3. ANOVA Between the Rate of Generic Entry and the Transparent Pricing System

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the rate of generic entry in the before and after conditions related to the implementation of the SEP legislation. The difference of the effect of the implementation of the SEP legislation between the two conditions was statistically significant at $p < 0.001$, [F(1,968) = 173.0]. Post hoc comparisons using the Tukey HSD test indicated that the

mean scores for the before and after conditions with regards to the implementation of the SEP legislation were significantly different (p-value <0.001).

4.2.4. ANOVA Between Price Erosion and the Transparent Pricing System

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on price erosion in the before and after conditions related to the implementation of the SEP legislation. The difference of the effect of the implementation of the SEP legislation between the two conditions was statistically significant at $p < 0.001$, [$F(1,4402) = 76.5$]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after conditions with regards to the implementation of the SEP legislation were significantly different (p-value <0.001).

4.2.5. ANOVA between the Transparent Pricing System and the Average Unit Price of an Innovator Product

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the average price of the innovator product in the before and after conditions related to the implementation of the SEP legislation. The results suggest that the difference of the effect of the implementation of the SEP legislation between the two conditions is not statistically significant at $p < 0.001$, [$F(1,5594) = 2.92$]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after conditions with regards to the implementation of the SEP legislation were significantly different (p-value = 0.08).

4.2.6. ANOVA between the Transparent Pricing System and the Average Unit Price of a Generic Drug

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the average unit price of a generic drug in the before and after conditions related to the implementation of the SEP legislation. The difference of the effect of the implementation of the SEP legislation between the two conditions was statistically significant at $p < 0.001$, [$F(1,4596) = 71.3$]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after conditions with regards to the implementation of the SEP legislation were significantly different (p-value <0.001).

4.2.7. ANOVA between the Transparent Pricing System and the Prices of Other Generic Drugs at Entry

A one-way ANOVA was conducted to compare the effect of the transparent pricing system on the prices of other generic drugs at entry in the before and after conditions related to the implementation of the SEP legislation. The difference of the effect of the implementation of the SEP legislation between the two conditions was statistically significant at $p < 0.001$, [$F(1,4621) = 575.7$]. Post hoc comparisons using the Tukey HSD test indicated that the mean scores for the before and after implementation of the SEP legislation conditions were significantly different (p-value <0.001).

4.2.8. Crosstabulation Analysis Between the Type of Drug Therapy and the Transparent Pricing System

As shown in Table 4.5, crosstabulation analysis was carried out to establish the impact of the introduction of the transparent pricing system on the type of the drug therapy. The results of the Chi-square suggest that there is no statistically significant difference in the type of drug therapy between acute and chronic groupings, $\chi^2 = 5.83$, df = 1 at $p = 0.16$.

4.2.9. Crosstabulation Analysis Between the Type of Drug Market and Transparent Pricing System

As shown in Table 4.5, crosstabulation analysis was carried out to establish the impact of the introduction of the transparent pricing system on the type of the drug market. Chi-square results suggests that there is a statistically significant difference in the type of drug market between the over-the-counter and prescription groupings, $\chi^2 = 45.7$, df = 1 at $p < 0.001$.

4.2.10. Crosstabulation Analysis Between the Complexity of Manufacture and the Transparent Pricing

As shown in Table 4.5, crosstabulation analysis was carried out to establish the impact of the introduction of the transparent pricing system on the complexity of manufacture of a pharmaceutical dosage form. Chi-square results suggests that there is no statistically significant difference in the complexity of manufacture between not complex and the complex groupings, $\chi^2 = 1.89$, df = 1 at $p = 0.17$.

Table 4.5 Crosstabulation Analyses of the Type of the Markets

	Implementation of the Transparent Pricing System		
Type of Drug Therapy	**Before**	**After**	**Total for the Row**
Acute	109 (22.1%)	729 (17.6%)	838
Chronic	385 (77.9%)	3404 (82.4%)	3789
All Groups	494	4133	4627
Type of Drug Market			
Over-the-Counter	91 (18.4%)	365 (8.83%)	456
Prescription	403 (81.6%)	3768 (91.2%)	4171
All Groups	494	4133	4627
Complexity of Manufacture			
Not Complex	439 (88.9%)	3752 (90.8%)	4191
Complex	55 (11.1%)	381 (9.22%)	436
All Groups	494	4133	4627

4.3. Transparent Pricing System and the Realignment of the Local Pharmaceutical Industry

4.3.1. Market Structure of the South African Pharmaceutical Industry

Table 4.6 provides an appraisal of the outlook of the market structures in the periods before and after the implementation of legislative reforms (the introduction of SEP and pro-generic policies). The results suggest that the four leading pharmaceutical companies in terms of market shares, declined from 49.5% to 42.5% in the period following the implementation of the legislative reforms.

Table 4.6 Total Pharmaceutical Market Before and After Legislative Reforms

Total Pharmaceutical Market					
Before Transparent Pricing System			**After Transparent Pricing System**		
Rank	**Company**	**Market Share**	**Rank**	**Company**	**Market Share**
1	Sanofi-Aventis	16.7%	1	Aspen Pharmacare	14.9%
2	Aspen Pharmacare	14.2%	2	Sanofi-Aventis	14.8%
3	MSD	10.1%	3	MSD	6.68%
4	Pfizer Laboratories	8.48%	4	Cipla-Medro	6.18%
5	Roche	7.60%	5	Astra-Zeneca	5.90%
6	Bayer	6.48%	6	Bayer	4.66%
7	Astra-Zeneca	4.78%	7	Pfizer Laboratories	4.34%
8	Novartis	4.57%	8	Adcock Ingram	4.00%
9	Wyeth	4.23%	9	Novartis	3.80%
10	Janssen Pharmaceutica	4.12%	10	Janssen Pharmaceutica	3.78%
11	Bristol-Myers Squibb	3.43%	11	Roche	3.28%
12	Abbott	3.01%	12	Wyeth	2.86%
13	Adcock Ingram	2.02%	13	Bristol-Myers Squibb	2.60%
14	Boehringer Ingel	1.86%	14	Pharma Dynamics	2.44%
15	AHN Pharma	1.79%	15	Sandoz	2.05%
16	Nycomed	1.24%	16	Biogaran	1.90%
17	Elli Lilly	0.90%	17	Nycomed	1.77%
18	Servier Laboratories	0.75%	18	Abbott	1.64%
19	Cipla-Medro	0.65%	19	Elli Lilly	1.39%
20	Sandoz	0.59%	20	Astellas Pharma	1.33%

4.3.2. Market Concentration of the South African Pharmaceutical Industry

The Herfindahl-Hirschman Index (HHI) was computed to elucidate the market concentration of the pharmaceutical industry in the periods before and after the implementation of the legislative reforms. The HHI for the period spanning 1999 to 2004 presented with an HHI of 0.91 in comparison to the HHI of 0.72 for the period following the implementation of the legislative reforms.

4.3.3. Market Segmentation of the South African Pharmaceutical Industry

There is a considerable growth of the generics sector of the market as shown in Figure 3.4. Insofar as the year-on-year growth for the generics sector is concerned, the year 2004 represented the biggest growth (7.0%) since 1999 and has continued to grow at an average of 3.0% annually since then as opposed to a growth rate of 1.0% between 1999 and 2003.

The number of generic companies in the post implementation phase doubled in comparison to the period preceding the introduction of the policies. In addition to Aspen Pharmacare, Adcock Ingram and Cipla-Medro which were the only three generic companies in the Top 20 companies in the total pharmaceutical market for the period 1999 to 2003, Sandoz, Biogran and Astellas made the Top 20 list of leading companies for the period 2004 to 2012. Save for Aspen Pharmacare, the rankings of Adcock Ingram (15) and Cipla-Medro (20) improved from their low positions in the period before the implementation of the legislative reforms to improved rankings following the implementation. Aspen Pharmacare retained its second position in the total pharmaceutical market followed by Cipla-Medro rising to position 6 in the post implementation phase. On the other hand, Adcock Ingram also improved its position to 9.

4.4. Discussion

In “perfect markets” willing buyers and sellers ought to be left to transact with each other without interference from the government as the markets have the capacity to effect an optimal allocation of resources.[65] However, the WHO argues that the conditions for a perfect market are seldom fully met in pharmaceutical markets where market failure is often the norm warranting regulation. Accordingly, the South African government

intervened in the pharmaceutical industry with a view to optimise social welfare derived from medicines.

Following the implementation of the transparent pricing system there were several changes in the performance of structural variables of the market. The contrast between the number of generic manufacturers per chemical entity that lost patent protection between the two periods (before and after implementation of the pricing reforms) was statistically significant. This can be attributed to the high incidence of patent expirations in the period preceding the implementation of the transparent pricing system. Furthermore, the intervening period was characterised by a marked increase in the abbreviated new drug applications (ANDA) following the implementation of the pro-generic drug policies, Figure 3.1. There was a statistically significant difference between the rates of generic entry between the two periods, before and after the implementation of the transparent pricing system. This can be attributed to a high incidence of authorized generics in the period preceding the implementation of transparent pricing system as shown in Table 3.2.

As seen in Figure 4.1, the increase in generic entry following the implementation of the pricing reforms resulted in price competition as each producer reduces their price with a view to protect and/or secure their market share.[17] Such price competition exerts a downward pressure on the prices of drugs. As the number of generic products in the market increases the average unit price of generic drugs continue to decline.[17] The aggregate impact of increased generic competition resulted in a statistically significant price erosion in the intervening period. Accordingly, the median entry price of the other drugs in the same formulation market presented with a statistically significant contraction of entry prices in the intervening period, Figure 4.1.

In line with the price erosion, the decline of the average unit prices of generic drugs in the period following the implementation of the legislative reforms was statistically significant. This can be attributed to the intense competition in the generic market.[66] By contrast, the period following the implementation of the pricing reforms resulted in a statistically

insignificant decline in the average unit prices of innovator products. The government instructed the pharmaceutical companies to recalibrate their prices in 2004 prior to the implementation of the SEP. This entailed the removal of the 'fat' related to perverse incentives (including bonusing and discounts) that were commonplace in the industry.[9]

Since the prices of innovator products were higher than the generics, it follows that the percentage movement following the implementation of the new regulations did not have as much impact as the generics. This finding is consistent with the research conducted by Mediscor, one of the leading Medical Scheme Administrators in South Africa. In 2007, Mediscor reported that the overall medicine expenditure decreased by 9.7% between 2004 and 2005. Mediscor attributes these developments mainly to the enactment of the pricing reforms, as the SEP for generic drugs decreased more than that of innovator products. [67]

The low frequency distribution of Schedule 5 products can be attributed to their high risk-to-benefit ratio. There are strict controls in place and onerous recordkeeping related to the handling of products that belong to this schedule.[68] The dominance of Schedules 3 (mainly chronic medicines) is in line with the prevalent diseases patterns in South Africa particularly as it relates to NCDs.[51] The foregoing discussion in Section 3.4 provided an explanation of high usage of Schedule 4 products (mainly anti-infective agents).

The statistically significant decline in the frequency distributions of over-the-counter medications can be attributed to, *inter alia*, several products that were rescheduled from the non-prescription market to the prescription market in the intervening period with a view to avoid abuse in certain cases and due to risk in other cases.[69] In the intervening period there was also a change in marketing practices resulting in the exclusion of Schedule 2 products from the category of the direct to consumer advertisement.[70] Insofar as the Schedules 3 and 5 are concerned, the increased frequencies for the intervening period can be attributed to the institution of the prescribed minimum benefits (PMB). PMB is aimed at ensuring that the members of the medical aid schemes who present with certain chronic diseases can access their treatment by not having their funds run out.[71] Similarly, the increases in the frequencies related to the therapeutic categories of the

alimentary canal and the central nervous system can be attributed to, *inter alia*, the institution of the PMBs in the intervening period. Notwithstanding the introduction of the PMBs and the growing prevalence of NCDs in South Africa, there was no statistically significant difference, particularly with respect to chronic diseases, between the type of drug therapy before and after the implementation of the legislative reforms.

Since tablets are the most frequently used form of pharmaceutical preparation by generic drugs, their increase in the intervening period can be viewed as a proxy for increased generic penetration in the same period. Notwithstanding the changes in the tablets, capsules and injections dosage forms there was no statistically significant difference between the complexity of manufacture before and after the implementation of the legislative reforms.

The intervention of the South African government to regulate the price of pharmaceuticals is consistent with economic theory. Economic theory holds that where there is market failure it is the responsibility of a government to regulate the market to make for an efficient allocation of resources.[65] South Africa has recently (2010) become a member of BRICS which constitute of Brazil, Russia, India and South Africa. BRICS is a conglomerate of emerging economies playing a prominent role in the world development platforms.[72] In comparison to another BRICS counterpart, Brazil, South Africa made a significant progress in terms of generic penetration at the end of the 10-year anniversary since the enactment of pro-generic laws. In 2009 which marked the 10th anniversary since the enactment of the Generic Law (Law Decree 9787/99), the generics sector constituted a mere 14.0% and 18.0% market share by value and volume respectively. [73]

On the other hand, South Africa proved to be a lot more successful in terms of the levels of generic penetration. The country attained generic penetration rates comparable to global trends even before the 10th anniversary since the enactment of the pro-generic laws. Tellingly, the intervention of the South African government in terms of legislative reforms aimed at stimulating competition, directly and indirectly, has had a significant impact in making medicines affordable. The impact of the legislative reforms has been

two-fold, on the one hand it encouraged competition by making the market conditions conducive for generic entry. Secondly, the direct price controls have also borne fruit albeit somewhat with the average unit price of the innovator products.

By contrast, the impact of the legislative reform was somewhat modest insofar as the market structure and market concentrations of the local pharmaceutical industry. Economic literature defines a market structure wherein the four leading firms control more than 40.0% of the market as an oligopoly.[34] In an oligopoly, the market is characterized by a small number of large firms who are market leaders. This market displays significant interdependence amongst role players. Decisions and actions of any of the large firms can influence the market share and profitability of its competitors and as such there is always a need to consider the possible reactions of competitors in making decisions about marketing and pricing.[34] From an enumerate definition of an oligopoly the results suggest that the legislative reforms effected changes to the market shares of the local industry. However, the movement of market shares of the four leading firms from 52.1% before the implementation of the transparent pricing system to 42.4% following the implementation of the reforms did not elicit a structural change in the market.

Similarly, the assessment of the market concentration of the local pharmaceutical industry has revealed that the industry is highly concentrated. The HHI is a tool that is used to measure the level of market concentration in a given industry. The level of market concentration has a bearing on market competition and thus on prices. There are three interval boundaries for assessing the extent of market concentration in an industry. The interval boundaries are determined by the value of HHI. If the value of HHI is less than 0.15 the market is classified as unconcentrated. If the value of HHI is in the range between 0.15 – 0.25 the market is classified as moderately concentrated. Finally, if the value of the HHI is greater than 0.25 the market is classified as highly concentrated. The period preceding the implementation of the transparent pricing system presented with an HHI of 0.91 in comparison to an HHI of 0.72 following the implementation of the reforms.

The legislative reforms effected a downward movement in the value of the HHI, however; the industry has not moved an interval boundary. It is noteworthy that the high HHI is not unique to the South African mark*et al.*one. In a study that was commissioned by the European Commission to look at the competitiveness of the EU's pharmaceutical market, it was found that the HHI ranged from 0.92 to 1.22 amongst the EU's member states.[74] Economic development of a nation is, in part, contingent upon the health of its citizenry; given the central role that pharmaceuticals play in healthcare, legislative reforms aimed at optimizing the social welfare of South Africans who consume pharmaceuticals was an imperative. Additionally, the reforms sought to comply with Section 27(2) of the Constitution of the Republic of South Africa, Act 108 of 1996 as it relates to the State having to take progressive steps to ensure the achievement of the right to healthcare by the South Africans. Whereas there are evident gains, the structural arrangement of the industry has not undergone a fundamental change. The local industry remains highly concentrated and dominated by a handful of pharmaceutical companies which undermines competitiveness and social welfare.

4.5. Conclusion

The intervention by the South African government to effect pharmaceutical pricing regulation was consistent with economic theory as it pertains to intervening in markets where there is market failure. The legislative reforms resulted in both intended and unintended outcomes. With respect to the latter the intervening period presented with prolonged rates of generic entry because of increased applications emanating from a conducive environment for generics.

On the positive note, the increase in the market share of generics in the market resulted in reduced prices of generic drugs in the intervening period. Additionally, the price erosion was at its greatest in the period following the introduction of the legislative reforms. South Africa was found to have fared better than one of its BRICS' counterparts, Brazil, with respect to the responsiveness of the market to its policy interventions. Notwithstanding the positive attributes of the pricing legislative reforms, the market has not undergone a

structural shift and remains an oligopoly and highly concentrated; which are market conditions that are not optimal for a competitive industry.

CHAPTER FIVE

5. MODEL FOR THE PRICING OF GENERIC DRUGS IN SOUTH AFRICA

This chapter comprises of four main sections. Section 5.1 presents the results of univariate descriptive statistics of the explanatory variables that are going to be used in the regression analysis of the price of a generic drug. This is followed by Section 5.2 which provides an appraisal of the structural relationships (ANOVA and correlational analysis) between the price of a generic drug and the explanatory variables. Section 5.3 presents a model for pricing generic drugs in South Africa, the first part of this section deals with univariate regression analysis followed by the multivariate regression analysis. The discussion and concluding remarks are presented in Sections 5.4 and 5.5 respectively.

5.1. Univariate Descriptive Statistics of Variables

The market size of the innovator product in the year preceding the loss of patent protection was discussed under Section 3.2.2. As shown in Table 5.1, the results suggest that the price of the innovator product is higher than its corresponding price of a generic drug in the formulation market. Furthermore, the results suggest that the lagged entry prices of the earlier generics in the formulation market is higher than the average price of the new entrant. The average market share of a generic company is low suggestive of market dominance by a handful of generic companies.

The dominant therapeutic category was found to be the cardiovascular system category, it accounted for just over a third of the market, Table 5.2. The average unit price of the cardiovascular system was the second lowest of all the therapeutic classes. The general anti-infectives were almost a fifth of the market by value and presented with an average unit price that is the third highest of all the therapeutic classes. The respiratory system was found to be the third leading therapeutic class with an average unit price being the lowest of all the therapeutic categories.

Table 5.1 Univariate Descriptive Statistics of Study Variables

Variables	Mean	SD
Sales of the Innovator Product in the Year Preceding its LOE: Formulation Level (Product Level)	R4.01M (R39.6M)	R5.79M (R48.3M)
Price of the Off-Patent Innovator Product at Corresponding Price Points with Generics	R8.29	R37.04
Average Price of a Generic Drug	R2.54	R3.97
Lagged Average Entry Price of Other Generics in the Formulation Market	R3.54	R1.77
Average Market Share of a Generic Company	2.08%	3.29%

The results suggest that the generic drugs that belong to Schedule 4 of the pharmaceutical market were cost drivers in the pharmaceutical market, Table 5.3.

Table 5.2 Frequency Distribution of ATC1 Categories

ATC1	Mean	SE	Count	Frequency
L	R14.96	R.47	52	1.13%
S	R11.25	R1.02	11	0.24%
J	R4.82	R0.11	907	19.7%
A	R3.84	R0.15	480	10.4%
D	R3.46	R0.29	134	2.91%
G	R2.70	R0.58	34	0.74%
N	R2.54	R0.13	708	15.4%
B	R1.82	R0.76	20	0.43%
M	R1.22	R0.27	156	3.39%
C	R0.97	R0.08	1691	36.8%
R	R0.91	R0.17	405	8.81%

Noteworthy in this category are groups of drugs such as the statins, proton pump inhibitors, antineoplastic agents, antibiotics amongst others. This was followed by drugs that predominantly act on the central nervous system, Schedule 5. Finally, Schedule 2

which belongs to the over-the-counter drug market was to be the least costly category; products that belong to this category were the third leading category of most sold medicines in the market.

Table 5.3 Frequency Distribution of Scheduling Statuses

Schedule	Mean	SE	Count	Frequency
S4	R4.38	R0.08	1855	40.34%
S5	R2.65	R0.19	380	8.26%
S1	R1.56	R0.49	56	1.22%
S3	R1.11	R0.08	1907	41.47%
S2	R0.90	R0.18	400	8.70%

As discussed in Section 3.2.6, over 90.0% of the generics' market is driven by three dosage forms, namely the tablets, capsules and injections. As shown in Table 5.4, the latter was the second highest cost driver in the market after the ophthalmic preparations. The solutions and shampoos were the least expensive pharmaceutical dosage forms respectively. The market size of the innovator product in the on-patent market was comprehensively dealt with under Section 3.2.2. Table 5.5 shows that the sales category R21.7M – R43.3 presented with the highest average unit price for medicines in the generics' market. This category of the market was found to comprise of products such as the antineoplastic agents, inhalers and respiratory corticosteroids (accuhalers), blood and blood-forming organs etc.

The second highest average unit price belonged to the R86.8M – R108.4M category. This category comprised primarily of agents that act on the respiratory tract and the general anti-infectives. The least expensive category in terms of the average unit price was the R65.1 – R86.7M category. This category comprised of the agents that act on the cardiovascular system, the alimentary tract and the respiratory tract.

Table 5.4 Frequency Distribution of Dosage Forms

Dosage Form	Mean	SE	Count	Frequency
OPD	R11.25	R1.10	11	0.24%
INJ	R7.40	R.19	359	7.81%
PTD	R6.07	R2.10	3	0.07%
SRT	R5.21	R1.62	5	0.11%
CAP	R3.82	R.17	435	9.46%
UNG	R3.08	R1.01	13	0.28%
LOT	R2.94	R1.37	7	0.15%
CHU	R2.02	R1.15	10	0.22%
TAB	R1.97	R.06	3537	76.92%
DRP	R1.90	R1.62	5	0.11%
SRC	R1.83	R.91	16	0.35%
CRE	R1.65	R.60	37	0.80%
ACC	R1.55	R2.10	3	0.07%
INH	R0.58	R2.57	2	0.04%
SUS	R0.49	R1.37	7	0.15%
INF	R0.36	R.81	20	0.43%
SYR	R0.34	R.47	60	1.30%
GRA	R0.31	R3.63	1	0.02%
GEO	R0.30	R1.21	9	0.20%
SOL	R0.20	R.61	36	0.78%
SHA	R0.19	R.77	22	0.48%

Table 5.5 Descriptive Statistics of the Sales of the Innovator Product Prior to LOE

Sales of the Innovator Product Prior to LOE	Mean	SE	Count	Frequency
R0.0M - R21.6M (1)	R2.87	R0.11	1158	25.2%
R21.7M - R43.3M (2)	R4.15	R0.18	461	10.0%
R43.4M - R65.0M (3)	R2.54	R0.09	1936	42.1%
R65.1M - R86.7M (4)	R0.93	R0.15	663	14.4%
R86.8M - R108.4M (5)	R4.41	R0.50	60	1.30%
R108.5M - R130.1M (6)	R1.37	R3.88	1	0.02%
R151.9M - R173.4M (7)	R2.21	R0.62	39	0.85%
R195.2M - R216.8 (8)	R2.11	R0.23	280	6.09%

The results suggest that the type of drug therapy that is least dominant in the generics' sector of the market is acute care products, Table 5.6. This category of drug therapy was also found to present with the highest average unit price in the market. The chronic care products represented over three-quarters of the generics' market. Furthermore, the results suggest that the type of drug market that dominates in the generics' sector is prescription market, Table 5.6. The prescription drug market was also found to present with the highest average unit price in the market. Over-the-counter medicines represented only a tenth of the drug market.

Table 5.6 Descriptive Statistics of the Types of Drug Therapy and Drug Market

Market Variables	Mean	SE	Count	Frequency
Type of Drug Therapy				
Acute (1)	R5.97	R0.13	822	17.9%
Chronic (2)	R1.79	R0.06	3776	82.1%
Type of Drug Market				
Over-the-Counter Market (1)	R0.98	R0.18	456	9.92%
Prescription Market (2)	R2.72	R0.06	4142	90.1%

As shown in Table 5.7, the highest number of generics for a chemical entity in a formulation market was twenty. The results suggest that the average unit price of the generic drug is higher in the lower order of entry and the converse holds true.

As depicted in Table 5.8, the period preceding the implementation of the legislative reforms (encompassing the transparent pricing system, the Bolar amendment and the mandatory generic substitution) presented with a higher average unit price for generic drugs.

Table 5.7 Descriptive Statistics of Order of Generic Entry

Market Variables	**Mean**	**SE**	**Count**	**Frequency**
Order of Generic Entry				
1 (1)	R3.19	R0.11	1205	26.2%
2 (2)	R3.32	R0.14	819	17.8%
3 (3)	R2.47	R0.16	599	13.0%
4 (4)	R2.33	R0.18	453	9.85%
5 (5)	R2.19	R0.21	358	7.79%
6 (6)	R1.92	R0.23	298	6.48%
7 (7)	R1.88	R0.25	239	5.20%
8 (8)	R2.04	R0.31	157	3.41%
9 (9)	R1.40	R0.32	150	3.26%
10 (10)	R1.49	R0.42	86	1.87%
11 (11)	R0.70	R0.49	63	1.37%
12 (12)	R0.74	R0.54	53	1.15%
13 (13)	R0.50	R0.56	49	1.07%
14 (14)	R0.51	R0.63	38	0.83%
15 (15)	R0.58	R1.13	12	0.26%
16 (16)	R0.40	R1.18	11	0.24%
17 (17)	R0.35	R2.26	3	0.07%
18 (18)	R0.32	R3.91	1	0.02%
19 (19)	R0.35	R3.91	1	0.02%
20 (20)	R0.45	R2.26	3	0.07%

Finally, the results suggest that the non-complex drug formulations dominate the formulation market, Table 5.8. The complex formulations presented with the highest average unit price in the market.

Table 5.8 Descriptive Statistics - Pro-Generic Policies and Complexity of Manufacture

Market Variables	Mean	SE	Count	Frequency
Implementation of Pro-Generic Policies				
Before Implementation (1)	R4.03	R0.30	173	3.76%
After Implementation (2)	R2.49	R0.06	4425	96.2%
Complexity of Manufacture of a Pharmaceutical Dosage Form				
Not Complex Dosage Forms (1)	R2.11	R0.06	4179	90.9%
Complex Dosage Forms (2)	R6.84	R0.18	419	9.11%

5.2. Structural Relationship Between the Price of a Generic Drug and Market Variables

Inferential statistical techniques comprising of an ANOVA and correlational analysis was employed to establish the relationship between the market variables that impacts on the price of a generic drug and how they influence the price.

5.2.1. Price of a Generic Drug and the Number of Generic Manufacturers in the Formulation Market

A one-way ANOVA was conducted to compare the effect of categorised number of generics on the price of a generic drug. There was a significant effect of the categorised number of generic drugs on the price of a generic drug at $p < 0.001$ for the four conditions [$F(1,3) = 99.2$]. Post hoc comparisons using the Tukey HSD test indicated that the mean score for the 1-5 condition was significantly different (p-value <0.001) to the 6-10 condition, the 11-15 and the 16-20 conditions. However, the 11-15 condition did not differ significantly from the 16-20 condition.

5.2.2. Price of a Generic Drug and the Market Size of the Innovator Product

A one-way ANOVA was conducted to compare the effect of the categorized sales of innovator products in the year preceding the LOE on the price of a generic drug. There was a significant effect of the categorized sales on the price of a generic drug at $p < 0.001$ for the eight conditions [$F(71,4590) = 31.4$].

Post hoc analysis was also carried out for the conditions above. Six pairs of conditions were found to be statistically different at $p < 0.001$. Firstly, the differences between condition 1 (R0.0M - R21.6M), condition 2 (R21.7M - R43.3M) and condition 4 (R65.1M - R86.7M) were found to be statistically significant. Secondly, the following conditions presented with differences that were statistically significant: conditions 2, condition 3 (R43.4M - R65.0M), condition 4 and condition 5 (R86.8M - R108.4M). Thirdly, statistically significant differences were detected in the following conditions: condition 3, condition 2, condition 4 and condition 5.

Furthermore, statistically significant differences were found in the following conditions: condition 4, condition 1, condition 2, condition 5 and condition 8 (R195.2M - R216.8). Similarly, the following pairs of conditions also presented with differences that were statistically significant: condition 5, condition 3, condition 4 and condition 8. Finally, the following pairs of conditions presented with differences that were statistically significant: condition 8, condition 2, condition 4 and condition 5.

5.2.3. Price of a Generic Drug and the Type of Drug Therapy

A one-way ANOVA was conducted to compare the effect of the type of drug therapy on the price of a generic drug. There was a significant effect of the type of drug therapy on the price of a generic drug at $p < 0.001$ for the acute and chronic conditions [$F(71,4596) = 891.7$]. Post hoc test was conducted given the statistically significant outcome for the one-way ANOVA test. The differences between the acute condition and the chronic condition were found to be statistically significant at $p < 0.001$.

5.2.4. Price of a Generic Drug and the Order of Generic Entry

A one-way ANOVA was conducted to compare the effect of the order of generic entry into the formulation market on the price of a generic drug. There was a significant effect of the order of generic entry into the formulation market on the price of a generic drug at $p < 0.001$ for the twenty conditions [$F(19,4578) = 8.59$]. Post hoc analysis was also carried out for the conditions above. Fourteen pairs of conditions were found to be statistically different at $p < 0.001$. Firstly, the differences between condition 1, 3–7 and 9-14 were found to be statistically significant. The following conditions presented with differences that were statistically significant: conditions 2 and conditions 3-14. Save for condition 8, conditions 3-14 presented with differences that were statistically significant with conditions 1 and 2. Condition 8 presented with a difference that was statistically significant with condition 2. Finally, no differences that were statistically significant ($p < 0.005$) were detected at condition 15 henceforth.

5.2.5. Price of a Generic Drug and the Pricing Legislative Reforms

A one-way ANOVA was conducted to compare the effect of the implementation of the pro-generic policies on the price of a generic drug. There was a significant effect of the implementation of the pro-generic policies on the price of a generic drug at $p < 0.001$ for the before implementation and the after implementation conditions [$F(20,4577) = 45.7$]. Post hoc test was conducted to establish whether the differences are statistically significant. The results suggest that the differences between the before implementation of the pro-generic policies and the after implementation of the pro-generic policies conditions are statistically significant at $p < 0.001$.

5.2.6. Price of a Generic Drug and the Type of Drug Market

A one-way ANOVA was conducted to compare the effect of the type of the drug market on the price of a generic drug. There was a significant effect of the type of the drug market on the price of a generic drug at $p < 0.001$ for the over-the-counter and the prescription conditions [$F(1,4596) = 80.131$]. Post hoc test was conducted given the statistically significant outcome for the one-way ANOVA test. The differences between the over the counter condition and the prescription condition were found to be statistically significant at $p < 0.001$.

5.2.7. Price of a Generic Drug and the Complexity of the Manufacturing Process Related to a Dosage Form

A one-way ANOVA was conducted to compare the effect of the complexity of manufacture of the pharmaceutical dosage form on the price of a generic drug. There was a significant effect of the complexity of manufacture of the pharmaceutical dosage form on the price of a generic drug at $p < 0.001$ for the not complex and the complex conditions [$F(1,4596) = 610.9$]. Post hoc test was conducted to establish whether the differences are statistically significant. The results suggest that the differences between the not complex condition and the complex condition are statistically significant at $p < 0.001$.

5.2.8. Correlation Analysis Between the Price of a Generic Drug and Study Variables

Correlational analyses were employed to examine the relationship between the price of a generic drug and the sales of the innovator product before LOE, lagged number of generics in the same formulation market, price of the innovator product in the formulation market at corresponding price points, average market shares of the generic companies, lagged average price of the generic drug at entry and lagged price erosion.

As shown in Table 5.9, the results suggest a none to extremely weak relationship between the price of a generic drug and the market size of the on-patent innovator product, average market shares of generic companies and the lagged price erosion. Furthermore, the results suggest a weak relationship between the price of a generic drug and lagged average price of other generic drugs at entry, and lagged number of generics in the formulation market. Finally, the results suggest a moderate relationship between the price of a generic drug and the price of the innovator product at corresponding price points as the generic drug in the formulation market. Save for the average market shares of generic companies which was correlated to the price at $p = 0.02$, the correlations of the foregoing variables and the price of a generic drug are all statistically significantly at $p < 0.001$

Table 5.9 Correlational Analyses Between Prices and Predictor Variables.

Variables that are Correlated to Generic Price	**Pearson's r**	***p*-value**
Sales of the Innovator Product in the Year Preceding Loss of Patent Protection	-0.11	$p < 0.001$
Lagged Number of Generics in the Formulation Market	-0.24	$p < 0.001$
Price of the Innovator Product at Corresponding Price Points	0.41	$p < 0.001$
Average Market Shares of the Generic Companies	0.04	$p < 0.05$
Lagged Average Entry Price of Other Generics	0.28	$p < 0.001$
Lagged Price Erosion	0.07	$p < 0.001$

Furthermore, the results suggest that both the market size of the on-patent innovator product and the lagged number of generics in the formulation market are negatively correlated to the price of a generic drug.

5.3. Development of a Model for Pricing Generic Drugs in South Africa

In addition to an account of the univariate descriptive statistics of the possible predictor variables that was presented in Section 5.1, their statistical significance as per Section 5.2. The results of univariate regression are presented in this section, as shown in Table 5.10. Univariate regression analysis was conducted to establish the possible influence of the variables that were identified as predictors of the price of a generic product. Tables 5.10 and 5.11 presents the results of the analyses and the description of the acronyms of the variables respectively.

5.3.1. Univariate Regression Analysis for the Type of Drug Therapy

Regression analysis provides tools for building models that describe relationships between a dependent variable and one or more independent variable (s), all of which are numerical.[80] The simplest type of regression model deals with one independent variable and one dependent variable.[80]

Given that when one plots two variables against each other in a scattergram, the values generally don't fall exactly in a perfect straight line, linear regression analysis attempts to find the line that best estimates the relationship between the dependent variable and the independent variable.[80] A linear regression model that deals with more than one variable is known as a multiple linear regression.[80] Multiple linear regression analysis quantifies the impact of various simultaneous influences (multiple independent variables) on a dependent variable.[80]

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + \varepsilon$, where Y represents the dependent variable, $X_1 \ldots X_k$ are the independent variables, β_0 represents the intercept term, $\beta_1 \ldots \beta_k$ represents the regression coefficients for the independent variables, and ε represents the error term, i.e. unpredictable random disturbance term.[80]

Multiple linear regression analysis was used in this study to estimate the impact of the following independent variables on the dependent variable, as follows:

The price equation (Explanations of terms is provided in Table 5.11) for the influence of the type of drug therapy on the price of a generic drug can be expressed as follows:

$$GP = \beta_0 + \beta_1 TDT + \varepsilon \quad (1)$$

As shown in Table 5.10, the results suggest that the price of a generic drug is inversely related to the type of drug therapy. The price of a generic drug will be -4.18 less if it is a chronic care product than it would if it were an acute care product.

5.3.2. Univariate Regression Analysis for the Sales of the Innovator Product in the Year Preceding the LOE

Equation 2 below provides a model specification for the influence of sales of the innovator product on the price of the generic drug.

$$GP = \beta_0 + \beta_1 SYPPE + \varepsilon \quad (2)$$

The results as depicted in Table 5.10 suggest that there is a positive relationship between the relative market size of the on-patent innovator product and the price of a generic drug following the loss of patent protection. The results of the correlational analysis as depicted in Table 5.6 bears repetition. A statistically significant negative correlation was found between the price of a generic drug and the sales of an on-patent innovator product in the year preceding its LOE. Furthermore, the univariate regression output between the price of a generic drug and the sales of an on-patent innovator product in the last year before LOE suggest a negative statistically significant relationship. Notwithstanding the foregoing, the results suggest that a unit increase in the sales of the on-patent innovator product in the year preceding the loss of patent protection is associated with a negligible decrease (no change) in the price of the generic drug upon entry.

5.3.3. Univariate Regression Analysis for the Order of Generic Entry into the Formulation Market

Equation 3 below provides a model specification for the influence of the order of generic entry into the formulation market. The results suggest an inverse relationship between the price of a generic drug and the sequence of generic entry into the formulation market, Table 5.10. A unit increase in the positioning (sequence) of a generic drug in the formulation market results in a decrease of 0.22 in the price of a generic drug.

$$GP = \beta_0 + \beta_1 OGE + \varepsilon \quad (3)$$

5.3.4. Univariate Regression Analysis of the Lagged Number of Generics in the Formulation Market

Equation 4 below provides a model specification for the lagged number of generics in the formulation market and its influence on the price of a generic drug. The results suggest an inverse relationship between the price of a generic drug and the lagged number of generics in the formulation market. A unit increase in the number of generics in the formulation market results in a decrease of a price of a generic drug by 0.20.

$$GP = \beta_0 + \beta_1 LNUGEN + \varepsilon \quad (4)$$

5.3.5. Univariate Regression Analysis of the Lagged Average Price of Other Generics at Entry

Equation 5 below provides a model specification for the influence of lagged average price of other generics at entry in the same formulation market. The results suggest a positive relationship between the price of a generic drug and the lagged average price of other generics at entry, Table 5.10. A unit increase in the lagged average price of other generic drugs at entry in the same formulation market results in an increase of 0.65 in the price of a generic drug.

$$GP = \beta_0 + \beta_1 LAEP + \varepsilon \quad (5)$$

5.3.6. Univariate Regression Analysis of the Price of the Innovator Product in the Formulation Market

Equation 6 below gives a model specification for the influence of the price of an innovator product at the corresponding price points with the generic product in the formulation market. The results suggest a positive relationship between the price of the generic drug and its corresponding price of an innovator product in the same formulation market, Table 5.10. A unit increase in the price of the innovator product results in an increase of 0.05 in the price of a generic drug.

$$GP = \beta_0 + \beta_1 IP + \varepsilon \quad (6)$$

5.3.7. Univariate Regression Analysis of the Implementation of the Pro-Generic Policies

Equation 7 below provides a model specification for the influence of the pro-generic policies on the price of a generic drug. As depicted in Table 5.10, the result suggests an inverse relationship between the price of the generic drug and the implementation of the pro-generic policies. Pricing in the period following the implementation of the pricing legislative reforms results in a price decrease of 1.55 in comparison with the period preceding the implementation of the reforms.

$$GP = \beta_0 + \beta_1 IPGP + \varepsilon \quad (7)$$

5.3.8. Univariate Regression Analysis for the Complexity of Manufacture

Equation 8 below gives a model specification for the influence of the complexity of manufacture of a dosage form on the price of a generic drug. The results suggest a positive relationship between the price of the generic drug and the complexity of

manufacture of a dosage form, Table 5.10. The price of a generic drug will be 4.72 high if it is a complex formulation than it would if it were a non-complex formulation.

$$GP = \beta_0 + \beta_1 CMDF + \varepsilon \quad (8)$$

Table 5.10 Results of Univariate Regression Results

	b	**SE**	***p*-value**
Type of Drug Therapy	-4.18	0.14	$p < 0.001$
Sales of the Innovator Company Prior to LOE	-0.00	0.00	$p < 0.001$
Order of Generic Entry	-0.22	0.02	$p < 0.001$
Lagged Number of Generic Drugs in the Formulation Market	-0.20	0.01	$p < 0.001$
Price of the Innovator Product at Corresponding Price Points	0.05	0.00	$p < 0.001$
Lagged Average Entry Price of Other Generics in the Formulation Market	0.65	0.03	$p < 0.001$
Type of Drug Market	1.74	0.19	$p < 0.001$
Impact of Pricing Reforms	-1.55	0.31	$p < 0.001$
Complexity of Manufacture of a Dosage Form	4.72	0.19	$p < 0.001$

Table 5.11 Description of Variables

Variable	Definition of Variable
TDT	Type of drug therapy in terms of acute or chronic as per the WHO's 3-digit anatomical therapeutic chemical classification (ATC3). This is a binary variable taking a value of one if the drug therapy is chronic otherwise zero
SYPPE	Annual sales of the innovator product a year preceding the expiry of patent protection at formulation level. Used as a proxy of the market size of the product prior to loss of exclusivity. Sales are in real terms following deflation with consumer price index (CPI) using 1999 as the base year
OGE	Order of generic entry as a measure of a position of the new generic entrant in the formulation market of generic drugs
LNUGEN	Lagged Number of generic drugs at formulation level, n - 1
IP	Average unit price of the innovator product at the corresponding price point as the generic drug
LAEP	Lagged average entry price of generic drugs per unit of measure with respect to dosage forms. The price was lagged by 12 months. Prices are in real terms following deflation by CPI using 1999 as the base year
IPGP	Introduction of pro-generic policies encompassing the introduction of Section 22F and Section 69(A) of the Medicines Act and Patents Act respectively. This is a binary variable taking a value of one for the period following the introduction of the pro-generic policies otherwise zero
TDM	Benefit-to-risk ratio as it relates to the requirements for a prescription in accordance with Section 22A of the Medicines Act. This is a binary variable taking a value of one if the product requires a prescription otherwise zero
LPE	Lagged price erosion represents the aggregate impact of the generic drugs in eroding the price of the innovator product. The price erosion was lagged by 12 months.
CMDF	Complexity of manufacture of a dosage form is a binary variable taking a value of one if the manufacture of a dosage form is complex otherwise zero.
GP	Generic price is an average unit price of a drug computed by dividing the average annual price of a drug by its pack size.
β_0	represents the intercept term, $\beta_1 \ldots \beta_k$ represents the regression coefficients for the independent variables, and ε
ε	represents the error term

5.3.9. Multivariate Analysis of Generic Price and Predictor Variables

The hypothesized price equation for the influence of structural relationships in the pharmaceutical market on the price of a generic drug is presented in Equation 9.

$$GP = \beta_0 + \beta_1 TDT + \beta_2 OGE + \beta_3 IPGP + \beta_4 CMDF + \beta_5 LAEP + \beta_6 TDM + \beta_7 SYPPE + \beta_8 IP + \varepsilon \quad (9)$$

As shown in Table 5.12, the results suggest that the type of drug therapy and the price of a generic drug are negatively correlated. If all variables are held constant, the chronic care products are 3.12 cheaper than the acute care products. Furthermore, the results suggest a negative correlation between the price of a generic drug and the order of generic entry into the formulation market. If all variables are held constant, a unit increase in the order of entry into the formulation market is associated with a decline of 0.06 in the price of a generic drug. The results also suggest that the sales of the innovator product in the year preceding the loss of patent protection are negatively correlated with the price of a generic drug. If all variables are held constant, a unit increase in the sales of the innovator product in the year preceding the loss of patent protection is associated with a negligible decline in the price of a generic drug upon generic entry. Finally, a negative correlation was detected between the price of a generic drug and the impact of the implementation of the pricing reforms. If all variables are held constant, the post implementation phase with regards to the pricing reforms is associated with a decline of 1.28 in the price of a generic drug.

On the other hand, the results suggest a positive correlation between the price of a generic drug and the complexity of manufacture of a formulation, the lagged average price of other generics at entry into the formulation market, the type of the drug market and the price of the innovator product at corresponding price points in the formulation market. Accordingly, if all variables are held constant, pricing in the formulation market suggests that a complex formulation will be 0.55 more expensive than the non-complex formulation, a unit increase in the lagged average price of other generic drugs at entry will result in an increase of 0.30 in the price of a generic drug; finally, pricing in the drug market suggests that a prescription product will be 1.16 more expensive than an over-the-counter product.

Table 5.12 Results of Multivariate Regression Analysis

Explanatory Variables	b	SE	*p*-value
Type of Drug Therapy	-3.12	0.16	$p < 0.001$
Order of Generic Entry	-0.06	0.02	$p < 0.001$
Price of the Innovator Product at Corresponding Price Points	0.04	0.00	$p < 0.001$
Complexity of Manufacture	0.55	0.22	$p < 0.05$
Lagged Average Entry Price of Generics in the Formulation Market	0.30	0.03	$p < 0.001$
Type of Drug Market	1.16	0.17	$p < 0.001$
On-Patent Sales of the Innovator in the Year Prior to LOE	0.00	0.00	$p < 0.001$
Impact of Pricing Reforms	-1.28	0.17	$p < 0.001$

The adjusted R^2 emanating from the regression results suggests that the model (equation 9) accounts for 35.0% of the structural relationships that influenced the price of a generic drug in the market.

5.4. Discussion

As shown in Table 5.6, chronic care products command a higher market share in comparison to the acute care products. Magazzini *et al.* conducted a research study into dynamic competition in pharmaceuticals in 2004, they found that the products that treat chronic diseases are inclined to attract generic competition as opposed to acute care products. Cook devised a new product forecast algorithm which provides a pragmatic guide to how market dynamics are likely to shape the commercial success of a new product. The algorithm puts epidemiological data at the centre of the forecasting mechanism.[28] Cook argues that chronic care products present with a high carryover rates than acute care products. Carryover rates are specific to the prevailing market conditions, therapeutic categories and reflect the customer's loyalty to a product.[28] As aforementioned, South Africa has a quadruple burden of disease carving out a market for

chronic care products.[51] Insofar as the type of drug market is concerned, Cook also argues that the prevalence of chronic diseases in most societies is supportive of medicine launches in the prescription market of the pharmaceutical industry.[51]

This proposition is consistent with the findings of the current research study which suggests that the chronic care products are priced cheaper than acute care products possibly due to intense competition in the former market. The level of generic penetration can serve as a proxy of demand within therapeutic categories. As such, generic penetration is likely to be intense within areas of therapy that presents with high demand for pharmaceuticals resulting in low prices due to competition.

The results of this research study suggest that the generic manufacturers can carve out market niches particularly where they are well adept in the manufacture of technologically advanced dosage forms. The complexity of the manufacture of a dosage form was found to have a bearing on the probability of generic entry, number of possible generic entrants into the formulation market, and the price of a generic drug. These results are consistent with Tenn *et al.*[33] and Sinclair. [52]

The results suggest that the market size of the innovator product prior to loss of patent protection explicitly influences generic entry and implicitly the price of a generic drug. This finding is consistent with the findings of Hudson. As aforementioned, see Section 1.1.2, in 2000, Hudson examined generic uptake in Japan, UK, Germany and the USA following the loss of patent protection and determined that the generic entry was driven by the market size of the innovator product before loss of patent protection. This finding was found to be in line with Magazzini *et al.* who also held that the commercial success (relative market size) of the innovator product facilitates generic entry.[20] The results of the current study suggests an inverse relationship between the level of generic penetration as induced by the sales of the innovator brand prior to LOE. The findings of the current research study, Hudson and Magazzini *et al.* are consistent with the theory of a firm in neoclassical economics as it pertains to a firm as a profit maximizing entity.[45]

The commercial interests of generic firms guide the type of drug markets, drug therapy and chemical entities to market as opposed to epidemiological imperatives of the country.

In 2016, during the state of the nation address, the South African president announced that plans to have a state owned pharmaceutical company were afoot.[75] Ngozwana argues that a state owned pharmaceutical company can help solve the problem of medicine shortages in South Africa.[76] The country's leading labour movement (Congress of South African Trade Unions, Cosatu) has over the years advocated for a state owned pharmaceutical company. Cosatu argues that South Africa as a developmental state, needs to intervene decisively in key sectors of the economy that presents with problems or with a capacity to stimulate the growth of the economy.[77] Potentially, a state owned pharmaceutical company could produce various formulations of essential medicines in South Africa indiscriminate of the market size of the innovator product prior to LOE and the complexity of manufacture. As shown in Table 3.1, only 47.5% of the innovator products that lost patent protection attracted generic entry. The results also suggest that where entry took place, the market size and complexity of manufacture were the key influential factors.

The results suggest that legislative reforms had the intended impact in terms of exerting a downward pressure on the price of a generic drug. The introduction of pro-generic policies had an impact in terms of stimulating generic competition in the market. The foregoing illustration, Figure 3.4, provided an account of how the market segmentation of the local pharmaceutical industry underwent a paradigm shift from satisfying demand with innovators to generic drugs.

The primary goal of generic drugs policies is to optimize the efficiency of drug expenditures by substituting expensive innovator products with affordable generics.[78] The rationale is that bioequivalent generic drugs made in pharmaceutical plants that operate under cGMP present with the same safety and clinical profiles as the innovator products. This finding, impact of the implementation of pro-generic policies, is consistent with a study that sought to appraise the experiences of generics in multiple countries. de

Joncheere *et al.* reported that the use of generics is high in countries that implemented pro-generic policies. Specifically, de Joncheere *et al.* found that the Netherlands, Canada, Denmark's use of the same policy options (generic substitution and reference pricing system) as the ones adopted by South Africa has had a positive impact in terms of stimulating generic competition.

The results suggest a negative correlation between the order of generic entry and the price of a generic drug wherein the first mover advantage accrues for being the first to market. Generic entry is precarious and is not under the control of the entrant,[78] not only is the date of regulatory approval by the MCC uncertain but each applicant does not know when and/or how many other generic applications have been filed on the same formulation. Section 34 of the Medicines Act forbids the medicines registration officers from disclosing any information to third parties that they gained in carrying out their duties. Whilst the resultant order of generic entry will be sequential, the entry decisions are likely to be simultaneous.[78]

The firms that receive marketing authorization ahead of rival generic firms gets a first-mover advantage. This allows the firm to sell their generic products sooner with minimal competition and often maintains the market leader position in terms of market shares in subsequent years. In their investigation of the generic drug industry dynamics, Reiffen *et al.* contends that a generic company that gets early approval is likely to have a sizable market share and good return on investment in comparison to the late entrants.[78] This finding is consistent with the findings of Adriaen *et al.* who explored the pricing strategies of originator and generic medicines following patent expiry in Belgium. They found that the price differential between the generics in the formulation market and the corresponding innovator product grew larger with the increase in the number of entrants.[22]

A positively correlated relationship between the price of the innovator product at corresponding price points with generics and the price of a generic drug suggest that the local off-patent market conforms to the Stackelberg leadership model.[79] The innovator products are price leaders and the generic drugs are price takers. Empirical evidence

from the US suggests that in the pharmaceutical industry the originators and generic drug manufacturer's use price differently, a situation known as, 'Generic Competition Paradox'.[80]

Generic Competition Paradox refers to a situation where generic entry has paradoxical effects on the prices of generic drugs and originator drug. The fact that 'Generic Competition Paradox' does not hold in South Africa can be attributed to the influence of market forces that are in operation in South Africa in comparison to the market of the United States of America (USA). The USA operates a free market system[20] for the pharmaceutical industry as opposed to the heavily regulated market in RSA.

South Africa spends 8.30% of its gross domestic products on healthcare, well above the 5% that is recommended by the WHO.[73] The NDoH reports that this 8.3% is split as 4.2% and 4.1% for the public sector and private sector respectively. The 4.1% spend in the private sector covers a mere 16.2% of the population who have private insurance.[81] At a staggering expenditure of R 22.3 Billion (16.1%, n = R 138.6 Billion), medicines (and consumables) were the second highest benefit after private hospitals that was paid out by all medical aid schemes in RSA.[82] It is therefore evident that the South African medicines' market is lucrative. Evidently, the price of innovator products following loss of exclusivity is subject to the efficient allocation of resources as dictated by market forces and thus results in a downward trend in the light of generic competition. Conformance to the phenomenon of generic competition paradox would imply being left out of the medically insured in South Africa as they impose internal reference pricing systems.[8] This is also in line with the finding that following patent expiry the price drop is significant, see Section 3.4.6.

Pharmaceutical manufacturers and medicines in South Africa are required to be registered with the MCC in terms of Section 22C(1b) and Section 15 of the Medicines Act respectively. If therapeutic equivalence is proven, in economic terms, generic products in the same formulation market are homogenous non-differentiated goods. Craig contends that where manufacturers of homogenous goods face flat marginal costs, the firms are

inclined to compete on price than on market share.[34] The current research study undertook to investigate the determinants of generic price. The results suggest a statistically significant inversely proportional relationship between the number of companies, including the order of entry, and a generic price in the formulation market. In this sense, the higher the number of rival generic firms in the formulation market, the lower the price. As such the number of competitors acts as a proxy for generic price.

5.5. Conclusion

The price of a generic drug in South Africa was found to respond to the policy interventions in terms of regulating the market. Overall, seven market variables were found to have an influence on the price of the generic drug in South Africa. Five of the variables were negatively correlated to price with two variables been positively correlated. It is noteworthy that the off-patent market of the local industry conforms to the Stackelberg leadership model. This has far reaching implications in the light of the imminent price reforms related to international benchmarking as discussed in the following chapter.

CHAPTER SIX

6. SOUTH AFRICAN INDUSTRIAL PHARMACEUTICAL POLICY: REVIEW AND RECOMMENDATIONS

Medicines are not ordinary articles of trade, they present with both positive and negative externalities; as such pharmaceutical markets are amongst the most regulated in the world.[83] Policy makers must strike a balance between contrasting objectives whilst securing the health policy objectives.[84] Health policy objectives such as protecting public health, safeguarding the patients' human rights of access to safe and efficacious medicines, improving the quality of care and reigning in the pharmaceutical budget. [84]

This chapter seeks to provide an appraisal of the policy interventions in the local pharmaceutical industry and offer recommendations where the policy intervention presented with unintended consequences. The first section deals with the optimization of the rates of generic entry into the South African pharmaceutical industry in Section 6.1. This is followed by Section 6.2 which deals with the erosion of pharmaceutical manufacturing capacity in South Africa. The challenges related to the current pricing regime are appraised in Section 6.3. Finally, Section 6.4 reviews a case that has been made about the negative impact of authorized generics on access to medicines which is followed by concluding remarks.

6.1. Optimization of the Rates of Generic Entry into the South African Pharmaceutical Industry

Notwithstanding the paradigm shift in the market segmentation of the South African pharmaceutical industry as pointed out in Figure 3.4, generic penetration rate was found to be a mere 47.0% of all chemical entities that lost patent protection. Furthermore, the study found that generic entry was selective particularly to innovator products that generated high revenues whilst under patent protection. Additionally, generic entry was also found to be discriminative based on dosage forms and therapeutic areas. In 2009, a Ministerial Task Team on Procurement identified, *inter alia*, extensive utilization of single-source medicines and drugs for which there were no generics, high usage of costly drugs

particularly in oncology as some of the key challenges that had a bearing on access to medicines.[85]

These findings are consistent with the results of this study with regards to selective and low levels of generic entry in South Africa. The WHO identifies two critical success factors for the successful implementation of an NDP. The critical factors are an installation of a monitoring and evaluation programme and a periodical review of the policy.[86] Pharasi *et al.* argues that there has never been a comprehensive review of the policy responsiveness following the implementation of the NDP as there is lack of a comprehensive monitoring and evaluation programme (s).[85] It has been 21 years since the adoption of the NDP but the sector presents with several key challenges related to its implementation.

The low generic penetration rates are compounded by a considerably slow rate of generic entry into the South African market as pointed out in Section 3.2. It is well documented that the regulatory authority presents with considerable registration backlogs emanating from increased volumes of applications for registration.[42] Leng *et al.* argues that the implementation of pro-generic policies opened the flood gates to numerous registration applications by generic companies.[42] They also point out that a sizable number of the applications in the system relates to a practice of submitting multiple dossiers of the same drug by a single manufacturer resulting in the system being clogged up at the regulatory authority.[42]

Evidently, robustness and agility need to be effected into the pharmaceutical policy. This can be achieved by first implementing a monitoring and evaluation programme that will identify the implementation challenges with a view to respond timeously before the unintended consequences manifests. The government should consider in its monitoring and evaluation programme the assessment of various aspects of generic entry such as therapeutic categories and dosage forms that are largely neglected with a view to incentivise the manufacturers to consider launching generics in such poorly penetrated

areas. As seen in Section 3.4.1, in instances where generic entry was lacking, innovator prices remained considerably high which could potentially affect access.

6.2. Erosion of Pharmaceutical Manufacturing Capacity: Tension between Public Health Policy and Industrial Policy

As depicted in Table 1.1, at the dawn of democracy, the NDP outlined the health, economic and industrial objectives for the pharmaceutical sector in South Africa. The health goals pertained to ensuring the availability of drugs of good quality, safety and efficacy. The economic objectives sought to facilitate access to drugs by ensuring that the prices were affordable. On the other hand, the industrial goals of the NDP was to promote local production of pharmaceuticals and increase pharmaceutical exports.

The Green Paper on National Health Insurance reports that South Africa has poor health outcomes despite spending 8.50% of its GDP on health. The WHO recommends countries to spend at least 5.00% of its GDP on health. Notwithstanding the poor prognosis on health outcomes, strides have been made in one of the key measures of health outcomes, life expectancy.[88] Stats SA reports that life expectancy of South Africans increased from 52 years in 2005 to 61 years in 2014.[89] This can be attributed to the massive roll-out programme of ARVs, South Africa bears the biggest disease burden of HIV/AIDS in the world.[89] As such the South African ARVs tender is the biggest ever awarded by a single government.[90] In the tender contracting period, 2010 – 2011, the South African negotiated a 53.0% overall reduction in the prices of ARVs.[90] By 2015, 42.2% (n = 6.4 million) of HIV-infected South Africans were on ARVs. The scale up of the ARVs treatment in South Africa resulted in the AIDS-related deaths falling from 51.0% to 31.0% of the country's overall mortality.[90]

The reduction of the prices of ARVs in the public sector is an example of reduction of prices in line with the economic objectives of the NDP. This research study found that the legislative reforms that were enacted by the South African government yielded statistically significant price reductions. As seen in Chapter 4, the average unit price of medicines in

South Africa following the implementation of pricing reforms resulted in a marked decrease.

A review of the policy responsiveness of the NDP would, albeit problems, suggest considerable policy success on multiple fronts (health and economic objectives). On the other hand, the industrial objectives of the NDP have largely failed. Despite the Department of Trade and Industry (dti) listing the pharmaceutical industry as one of the five prioritized sectors of the economy in its Industrial Policy Action Plan (IPAP), the sector has major challenges. The pharmaceutical industry has experienced a significant erosion of its manufacturing capacity following a widespread closure of pharmaceutical plants in South Africa. According to the IPAP 2013/14 – 2015/16, 37 plants were closed in the last 20 years or so.[91]

The South African pharmaceutical market is the biggest in Africa (ahead of Nigeria, Egypt, and Kenya) and yet the pharmaceutical import penetration rate in South Africa is a staggering 65.0%. In 2015, the ratio of pharmaceutical imports (R 22.51 Bn) to pharmaceutical exports (R 5.02 Bn) stood at 4.48:1 resulting in a negative trade balance of R 17.49 Bn, the pharmaceutical industry is the fifth leading driver of the current account deficit in South Africa.[92] Business Monitor International (BMI) forecasts an 8.60% Compound Annual Growth Rate (CAGR) increase in pharmaceutical imports in South Africa, from R 20.63 Bn in 2014 to R 31.16 Bn by 2019.

South Africa has recently adopted the Universal Test to Treat (UTT) programme which is advocated for by the WHO. UTT dictates that every individual who tests positive for HIV should be initiated on ARVs' treatment right away irrespective of their CD4 count.[93] The policy of the South African government had previously been to only initiate therapy when the CD4 count of the patient had reached 350. In 2010, the MRC reported that NCDs accounted for 39.0% of total deaths in the country; the deaths due to NCDs matched those as result of HIV/AIDS and TB combined. The MRC study attributed the rising incidence of NCDs to changes in lifestyle and urbanization.[51]

Despite a disproportionate burden of both infectious and chronic diseases and legislative regimes that spans the Preferential Procurement Policy Framework Act (PPPFA) and the IPAP which both encourage local production, pharmaceutical manufacturing contributes a meagre 1.60% to the country's GDP.[94] The security of supply of medicines has been threatened on several occasions with medicines stock outs at healthcare facilities being commonplace. On the 5th of June 2015, the Minister of Health convened an urgent meeting with 32 executives of pharmaceutical companies with a view to respond to a national crisis related to medicines stock outs.[95] The medicines stock outs affected several critical medicines such as drugs that act on the central nervous system, cardiovascular system, analgesics and anesthetic agents. Several reasons were advanced for the medicines stock outs and these included challenges with sourcing of the raw materials (active pharmaceutical ingredients and excipients), unexpected delays in the manufacture and packaging of medicines, and erratic medicines forecasts.[95] Insofar as the former is concerned, South Africa imports more than 90.0% of its raw materials. [95]

The pursuit for low prices in the public and private sectors of the healthcare system in South Africa appears to have had unintended consequences with respect to local production of pharmaceuticals. As aforementioned pursuit of policies aimed at securing public health is often complex and at times might yield unintended consequences. The supply side health policy instruments to achieve equity and efficiency (i.e. optimal use of limited resources to maximize population health) appear to have undermined the industrial policy objectives. This problem poses a serious threat to the security of supply of medicines in South Africa particularly in the light of UTT which in itself represents an excellent window of opportunity to embed local production of pharmaceuticals.

6.3. Pharmaceutical Pricing Policy in South Africa and the Computation of Single Exit Price Adjustments (SEPA)

As outlined in the NDP, the appointment of a pricing committee, introduction of transparent pricing system, and regulation of price increases were amongst some of the key supply side policy instruments that the government sought to implement with a view to control the prices of medicines in South Africa. Following protracted litigation between

the pharmaceutical industry and the South African government these policy instruments formed part of the legislative reforms which were promulgated in 2004.[97]

As discussed in Section 1.1.1, the amendment to the Medicines Act introduced Section 22G which empowered the Minister of Health to establish a pricing committee and the transparent pricing regime. Ngozwana points out that amongst the various skills sets and stakeholders that comprise the pricing committee, there is no representative of the pharmaceutical industry in the committee.[1] In April 2004, the government published a framework for the annual computation of the single exit price adjustments (SEPA), Regulations Relating to a Transparent Pricing System for Medicines and Scheduled Substances, Gazette No. 26304. Singularly, the South African governments' policy of single exit price (health policy of the NDP) appears to present with a mirage of problems that has (d) a bearing on local production of pharmaceuticals (industrial policy of the NDP). Chief amongst the challenges of computing the ceiling price increase that pharmaceutical companies can implement annually is the apparent non-adherence to the prescribed methodology.

The pricing regulations identified several economic indicators that ought to be considered in computing an annual SEPA. These included the following: "*average CPI for the preceding year, the average producer price index (PPI) for the preceding year, changes in the rates of foreign exchange and purchasing power parity, comments received from interested persons and the need to ensure the availability, affordability and quality of medicines and scheduled substances in the Republic."* [9]

Representatives of pharmaceutical firms under the auspices of Pharmaceutical Task Group (PTG) have often decried the lack of transparency on the side of government in how it computes the SEPA.[1] For instance, the use of the widely-accepted methodology to compute the SEPA does not provide the expected SEPA. Save for 2009 and 2011, the computation of SEPA by the PTG using the methodology has always resulted in a differential with the SEPA granted by the government.[1]

The PTG's computations are based on the following formula:
SEPA = 70.0% CPI + 15.0% (Rand/US Dollar Variance) + 15.0% (Rand/Euro Variance).

Pharmaceutical manufacturers in South Africa operate under a harsh economic climate. Some of the direct costs such as utilities, labour and raw materials are worth appraising.[1] Pharmaceutical manufacturing involves use of water that has undergone various levels of purification for it to become pharmaceutical grade. Furthermore, there are requirements for the treatment of air in the manufacturing environment with a view to avoid airborne contaminants. The heating, ventilation and air-conditioning (HVAC) also make extensive use of electricity. The National Electricity Regulator of South Africa (NERSA) approved an annual price hike of 8.00% from 2013 to 2018. Eskom, the main supplier of electricity in South Africa, had requested the regulator (NERSA) for a 16.0% increase. It is worth noting that even the 8.00% increase that has been authorized by NERSA is well above the CPI. [97]

South African' s labour force is not as competitive as that of peer countries.[98] The World Economic Forum (WEF)'s Global Competitiveness Report of 2014/2015 ranks South Africa 136th (out of 144 countries) for income versus productivity. The WEF's report also ranks South Africa 144th (out of 144 countries) in terms of industrial relations.[99] Pharmaceutical manufacturing is a knowledge based industry that requires an input of high end skills such as pharmacists, chemists, engineers amongst others. The country has an acute shortage of these skills which imposes high costs of recruitment and staff retention. [100]

South Africa imports more than 95.0% of active pharmaceutical ingredients (APIs), and this reliance on imported raw materials leaves local manufacturers vulnerable to exchange rate fluctuations and vagaries.[1] Deterioration of the local currency against major currencies, specifically the US dollar and the Euro, results in additional transaction costs for local companies leading to constraints in cash flows and profits. [1]

On the other hand, the NDoH in its quest to achieve its health objective as stated in the NDP with respect to the quality, safety, and efficacy of the pharmaceuticals in South Africa sought accreditation of an international quality organization. Section 22C 1(b) of the Medicines Act empowers the government, through the Medicines Control Council (MCC), to prescribe the quality standard for manufacture of medicines in South Africa.[27]

In 2007, the MCC in its endeavor to raise the quality standard of pharmaceutical manufacturing in South Africa, took up the membership of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).[101] PIC/S is a leading international organization that comprise of the members of the European Union (EU) and other developed countries. Members of PIC/S observe stringiest quality standards and GMP insofar as the manufacture of pharmaceuticals is concerned. South Africa is the only African country with this exclusive membership.[101]

Attainment of PIC/S membership is a key milestone for the MCC with respect to its mandate of regulating medicines in South Africa and allows for cooperation with other peer countries that are members of the same scheme.[101] However, the cost of compliance under PIC/S is onerous against the backdrop of reduced income because of the harsh economic climate that the local manufacturers operate under. It is probable that either directly or indirectly some of the legislative reforms related to pricing might be attributable to the erosion of manufacturing capacity in the country.

The departure of the NDoH from the widely-accepted methodology (30/70, Forex/CPI) poses a lack of uncertainty to manufacturers as they cannot make accurate projections about their overheads versus potential income from their sales. Furthermore, other provisions that had been made by the pricing regulations at the time of publishing in April 2004 has not been used. For instance, the regulations recommended that the SEPA should consider availability of medicines in the country as a guiding principle for the pricing committee.

Additionally, the regulations made a provision for the use of historic PPI data. Stats SA defines PPI as: "*a measure of the change in the prices of goods either as they leave their place of production or as they enter the production process"*[102]

A formula that provides for changes in the historical PPI would probably account for the cost pressures that the local manufacturers of pharmaceuticals are faced with and would grant prices that allows a fair recovery of inputs costs. Whereas the use of CPI is aimed at protecting the consumers of pharmaceutical products, in the long run it has a negative impact if the security of supply of critical pharmaceuticals is at risk.

Several studies have revealed that there is an inherent tension between health and trade (industrial) policies of many governments around the world.[103] This experience of the South African pharmaceutical landscape holds true to this notion. In its publication that came out in 2015 entitled: "Trade and Health: Towards building a National Strategy", the WHO provides several case studies of an inherent tension between the health and the trade (industrial) policies of governments around the world.[103] The WHO recommends its member states to adopt an all-inclusive approach in the form of sector development strategies. Given its multi-disciplinary nature, a sector development strategy is likely to install adequate safeguards that avoids unintended consequences downstream.[103]

The WHO was instrumental in helping the government of Ethiopia in its crafting of sector development strategy for the pharmaceutical industry. There are several pragmatic points that draws a sharp contrast with the South African situation that emanated from the Ethiopian strategy. For instance, the awarding of a state tender to a manufacturer is followed by a 50.0% upfront payment that allows manufacturers to make all the necessary working capital expenditures that would facilitate uninterrupted supply of pharmaceuticals to the state.[104] In its report entitled: "Medicines Procurement Reform in the Public Sector", the NDoH concedes that some of the medicines stock outs that are experienced in the country are related to the withholding of supplies by pharmaceutical companies because of non-payments by provinces. [105]

Secondly, the tender cycles as per the Ethiopian sector development strategy are 5 yearly as opposed to the 2 yearly cycles in South Africa. A long tender cycle allows for stability as the manufacturer is able to effect efficiencies into their manufacturing environment and employ the staff that is required for the execution of the orders.[104] This points to a need for prudency in policy making within the South African' context.

6.4. Authorized Generics and their Impact on Access to Medicines

Authorized generics are increasingly forming a part of the innovator's products lifecycle management strategies. The US FDA describes authorized generics as "[a]ny marketing by an [New Drug Application (NDA) holder or authorized by an NDA holder, including through a third-party distributor, of the drug product approved under the NDA in a manner equivalent to the marketing practices of holders of an approved [Abbreviated NDA (ANDA) for that drug"[106]

Authorized generics are produced by, or under a licensing agreement with, the innovator company and are marketed by the same innovator company or through an affiliate, or alternatively, another third party such as a generic company. In this case, the generic company is required to split the sales revenue or pays royalties to the innovator company.[106] In the USA, the marketing of authorized generics is usually linked to either the expiry of patent protection of the innovator product before there is generic competition. In other cases, the launch of an authorized generics is made to coincide with generic company's 180-day exclusivity.[107]

The legal framework in the USA allows for what is known as some Paragraph IV generic drug applications. Such drug applications are filed with the FDA under Section 21 of the U.S. Codes § 355(j)(2)(A)(vii)(IV). This involves challenging an existing patent of the innovator product on the basis that it is invalid or that the marketing of its generic equivalent will amount to a non-infringement of the patent.[107]

A successful challenge of the patent results in the awarding of what is known as a Paragraph IV certificate which under Section 505(j)(5)(B)(iv) of the Federal Food, Drug

and Cosmetic Act establishes a 180-day exclusivity period.[107] Under this code, the FDA is not allowed to approve other ANDAs for the same drug product. Notwithstanding the exclusivity for the first filer of an ANDA, the holder of the NDA, its distributors and licensees can continue marketing their products throughout the 180-day exclusivity period. In 2004, the US FDA invoked this clause in its response to an earlier citizens' petitions by Mylan Pharmaceuticals Inc (Mylan) and Teva Pharmaceuticals USA Inc (Teva) that sought to challenge the marketing of authorized generics.[107]
In its response, the US FDA held that "[t]the marketing of authorized generics during the 180-days exclusivity period is a longstanding, pro-competitive practice, permissible under the [*Federal Food, Drug and Cosmetic Act (FD&C Act*)].[107]

Dissatisfied with this viewpoint of the US FDA, the two companies approached the United States District Court for the District of Columbia a month later.[107] Both companies argued in court that the FDA's response to their petitions was inconsistent with the fundamental premise of the Hatch-Waxman Act related to striking a balance between the competing interests of the innovator and generic companies.[107] Effectively the two companies petitioned the court to rule against the marketing of the authorized generics prior to the expiration of the 180-day exclusivity period. The court affirmed the earlier decision of the US FDA and stated in its judgement that the *FD&C Act* "only prohibits the FDA from approving subsequent ANDAs until after the 180-day exclusivity period has expired. Nothing in the statute provides any support for the argument that FDA can prohibit any support for the argument that FDA can prohibit NDA holders from entering the market with a brand generic drug during the exclusivity period". Teva took the case on appeal and lost the case.[107]

Notwithstanding this legal precedent, in 2011 the Federal Trade Commission was sanctioned to examine the competitive effects of authorized generic drugs in the USA.[107] Given that the authorized generics are marketed at price below the innovator products, the investigation held that authorized generics present with cost savings for the patients and the healthcare system in the short-term. However, the Federal Trade Commission found that the authorized generics reduce the profits of independent generic

manufacturers particularly because they act as *de facto* first-movers thus captures and retains a significant portion of the market share.[107]

The Commission concluded that although the presence of authorized generics does not appear to have had a negative impact on patent challenges, this could possibly be due to the agreements between the innovator and generic companies.[107]
Such agreements could entail an innovator company agreeing not to launch an authorized generic in an exchange for delayed entry by the generic company. The Commission argued that the frequency and profitability of these practice is enticing enough to coerce independent generic manufacturers to settle. The effect of these settlements is a sub-optimal social welfare.[107]

In Europe, the legal framework also facilitates for the entry of authorized generics in the member states of the European Union (EU). The European Commission, executive arm of the EU, issued a directive in 2001 (Directive 2001/83/EC) that sets forth a framework for authorized generics. Article 10c of this directive contends that a holder of marketing authorization may permit use of the pharmaceutical, pre-clinical and clinical documentation already filed during an NDA to subsequent applications relating to other medicinal products containing the same qualitative and quantitative composition in terms of the active substances and dosage forms.[108]

In 2009 the Commission conducted a Pharmaceutical Sector Inquiry with a view to establish whether authorized generics have negative aspects. Upon its conclusion, the Commission undertook to monitor patent settlements on an annual basis.[108] Patent settlements agreements were defined by the EC as commercial agreements to settle patent-related disputes such as patent infringement or patent validity. The 7th Report on the Monitoring of Patent Settlements, (covering the period spanning 1 Jan 2015 to 31 Dec 2015), by the EC sought to better understand the patent settlements between innovator and generic companies. The patent settlements were classified broadly on; firstly, whether the agreement anticipates a limitation on the generic company's capability to

market its own product. Secondly, whether the agreement anticipates a value transfer from the innovator to the generic company.[108]

The report found that the ability of a generic company to enter the market can be limited when the settlement agreement contains a clause that explicitly forbids the generic company from challenging the validity of the innovator's patent (s); "non-challenge clause". Furthermore, the ability of a generic company to enter the market can be constrained by a commercial agreement that includes a clause that explicitly forbids the generic company from entering the market until the patent (s) has (ve) expired; "non-compete clause".[108]

The Commission affirmed the royalty free licenses that allow generic companies to carry out an immediate product launch without conditions related to quantities that can be sold, pricing of their products and the supplier of the active pharmaceutical agreements as in line with the applicable competition laws.[108] However, the Commission held that licenses granted by the innovator company that facilitates market access for a generic company were limiting generic entry if such generic company is not allowed to enter the market with its own product or it cannot determine the conditions for the commercialization of its own product.[108] This includes patent agreements in which the innovator and generic companies agree that the latter will be a distributor of the innovator product and in cases where the generic company is required to source its active pharmaceutical ingredients from the innovator company. Furthermore, the Commission views agreements that permits for early generic entry but where such entry cannot be immediate as limiting generic entry.[108]

The Commission found that the value transfer from an innovator to the generic companies can assume various forms with a payment of a lump sum being the most clear-cut form of value transfer. Direct monetary transfer entailed buying an asset such as generic company' stock of their own generic products.[108] The terms of other patent settlements' agreements that came before the Commission involved direct monetary transfer wherein the generic company explicitly or implicitly agrees to delay a launch of their generic drug

and/or agree to discontinue a patent challenge. The Commission held that innovator companies can afford such payments given that the settlements allows the company to continue benefiting from the sales of its well-selling product.[108]

Other forms of value transfer involve distribution agreements in which an innovator company grants a commercial benefit to a generic company by allowing it to enter the market before patent expiry.[108] Furthermore, other forms of value transfer involve an agreement wherein an innovator company binds itself not to exert its rights related to invoking a patent against a generic company. Technically, this constitute value transfer in that the generic company accrues marketable value because of the patent settlement agreement.[108]

The Commission elected not to decide on whether the agreements that came before it during its investigation violated any competition laws of the EU. It held that a case-by-case analysis of the agreements will be required to establish as to whether the early generic entry constituted an antitrust behavior.[108] It further contended that there could be instances where early generic entry is pro-competitive when compared to the parties' expected outcome of the litigation. On the other hand, the Commission held that it is possible that other generic entries (e.g. through license or a distribution agreement) could potentially undermine competition. The latter could involve agreements wherein the innovator company is fully aware that their product does not meet patentability criteria such that a patent challenge could render their patent protection null and void.[108]

Finally, the Commission found that the number of patent agreements that are most likely to constitute an anticompetitive behavior declined from 22.0% to 10.0% for the periods spanning 2000 to 2008 and for the 2015's investigation respectively. The Commission avers that patent settlement agreements that delay generic entry are to the detriment of the patients.[108]

The incidence of authorized generics in Canada and Australia is 25.0% and 20.0% respectively.,[109-110] In the case of the former, Canada, the courts ruled in 2004 in the case

between Apotex Inc. and Hoffman La-Roche Limited, that under the country's' competition laws the introduction of authorized generics does not constitute an anti-competitive behavior. A similar ruling was made in the USA Despite the court's ruling the use of authorized generics in Australia, as is the case in South Africa, is yet to be systematically investigated. [110]

As discussed in Section 3.4.1, the results of this study indicate that the presence of authorized generics in the formulation market does not influence the price of a generic drug. This finding is consistent with the study that was conducted by McGee looking at the economic and pricing impact of authorized generic medicines in South Africa. This study found that the pricing levels of multiple source under conditions of presence of authorized generics and absence of authorized generics in the formulation market were similar.[62] However, as seen in Section 3.4.2 the results of the current study reveal that the presence of authorized generics does impact on the price erosion which raises questions related to access to medicines based on affordability. Following the approaches adopted by the USA and Europe with respect to instituting commissions to consider the influence of authorized generics on access, it is advisable for the South African Competition Commission to probe the matter and make findings.

Cost containment is not a primary health policy objective but a tool that governments employ with a view to attain a balance between conflicting demands.[84] Governments' use of cost containment as a regulatory measure often targets the supply side of the pharmaceutical market, namely; the pharmaceutical industry with varying degrees of success.[84] The WHO argues that most curative and preventive health actions depend on medicines and yet medicines involve powerful economic interests. Expenditure on medicines are often the second largest item after personnel's wages and salaries.[111] Furthermore, the WHO avers that in most industrialized countries the cost of pharmaceuticals is rising by 8.00-12.0%, much faster than consumer prices. Lastly, the WHO contends that health systems must make essential medicines available and affordable to all patients.[111]

6.5. Conclusion

Having identified the key features of the local pharmaceutical industry; the study developed a model that accounts for the characteristics of the drug, market, and the regulatory processes (legal framework) that influences the pricing of generic drugs in South Africa. The characteristics of a drug that has a bearing on the price of a generic drug were found to be the type of drug therapy, complexity of manufacture of a pharmaceutical dosage form, and the type of the drug market. On the other hand, the factors in the market that were found to influence the price of a generic drug were found to comprise of the order of generic entry into the formulation market, prices of the innovator product at corresponding price points with generics, market size of the on-patent innovator product, lagged average price in the formulation market. Finally, the introduction of wide ranging legislative reforms was collectively found to have had an influence in the pricing of generic drugs in South Africa.

The implementation of wide ranging policy interventions presented with both successes and challenges. Insofar as the successes are concerned, it is noteworthy that the prices of generic drugs came down significantly as a response to legislative reforms. The reduction of prices of medicines has a bearing on affordability and by extension on access. Extending access to medicines is central to the attainment of the aspirations of right to healthcare as enshrined in the constitution. Key to the reduction of prices of medicines in South Africa was the creation of a conducive environment for generic drugs by introducing pro-generic policies. On the other hand, the study found that patterns of generic entry remain unchecked and left to commercial interests of companies leaving certain sectors (e.g. dosage forms and therapeutic categories) of the pharmaceutical market uncompetitive.

The erosion of pharmaceutical manufacturing capacity presents with a considerable risk to the security of supply of medicines in South Africa. Given the country’s high burden of disease, an interruption in the supply value chain could potentially have catastrophic results. It appears that the current pricing regime constraints the growth of local production of pharmaceuticals.

The results of this study are suggestive of a tension between the health and trade policies of the South African government. It will be prudent for the stakeholders in the pharmaceutical industry to adopt the sector development approach to plan and execute in tandem.

7. APPENDICES

7.1. Appendix A

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical))

Private Bag 3, Wits 2050 South Africa

Ref. W-CJ-091130-1
30/11/2009

TO WHOM IT MAY CONCERN

Waiver:	This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).
Investigator:	**Mothobi Godfrey Keole Student no 250222**
Project title:	**Beyond patent expiry, development of a model for pricing generic drugs in South Africa. .**
Reason:	This study is an analysis of commercially available health economics information (from IMS Health) in the public domain. There are no humans involved.

UNIVERSITY OF THE WITWATERSRAND
2009 -11- 30
JOHANNESBURG

7.2. Appendix B

Appendix B is provided on pages 144 to 147 below, it can be accessed electronically from the following link:
https://www.dropbox.com/sh/50ck87ma707flrh/AACvjiQZV8CeOMskGdJj1LcNa?dl=0

						Year 1 After Patent Expiry			Year 2 After Patent Expiry			Year 3 After Patent Expiry			Year 4 After Patent Expiry			Year 5 After Patent Expiry				
Trade Nme	Generic Name	ATC 4	Date of Patent Expiry	Sales 12 Months Preceding Expiry	Sales at Patent Expiry	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Max No. of Generics	No. of Related ATC4 s
FLIXOTIDE	Fluticasone	R03BA	Feb-01	R215.90M	R186.5M	151.7		-20%	R118.6M		-37%	R124.3M		-34%	R46.3M		-74%	R46.3M		-75%	0	1
CIPROBAY	Ciprofloxacin	J01MA	Sep-01	R305.83M	R269.7M	240.1	4	-11%	R254.2M	9	-6%	R204.5M	11	-24%	R152.5M	13	-43%	R155.3M	13	-42%	15	7
CLEXANE	Enoxaparin	B01AB	Jun-11	R187.91M	R179.9M	145.7		-19%	R113.1M		-37%	R114.6M		-36%								1
EFEXOR	Venlafaxine	N06AX	Dec-03	R184.97M	R146.7M	128.2		-13%	R107.6M		-28%	R89.4M	1	-39%	R58.7M	1	-61%	R45.1M	2	-69%	3	2
TAVANIC	Levofloxacin	J01MA	Jun-06	R96.09M	R107.2M	95.0	1	-11%	R92.7M	3	-13%	R78.2M	3	-27%	R66.6M	4	-19%	R42.9M	5	-60%	7	7
SINGULAIR	Montelukast	R03DC	Oct-11	R66.00M	R78.2M	72.8	5	-7%	R61.8M	5	-21%	R59.0M	5	-25%		5			5		5	2
ZYRTEC	Cetirizine	R06AE	Feb-02	R66.34M	R67.4M	67.8	2	1%	R57.0M	3	-15%	R45.1M	9	-33%	R10.8M	10	-84%	R8.6M	11	-87%	13	1
ZOCOR	Simvastatin	C10AA	Feb-01	R69.06M	R78.6M	87.2		11%	R82.1M	1	-6%	R71.0M	2	-10%	R11.4M	5	-85%	R8.4M	8	-89%	10	4
CLARITYNE	Loratadine	R06AX	Jun-01	R67.00M	R59.8M	54.4	4	-9%	R41.6M	10	-30%	R33.5M	11	-44%	R2.2M	12	-96%	R2.2M	15	-96%	20	6
LANZOR	Lansoprazole	A02BC	Aug-05	R85.75M	R44.3M	42.8	4	-3%	R31.3M	6	-29%	R26.6M	7	-40%	R6.7M	7	-85%	R4.6M	8	-89%	8	3
TRITACE	Ramipril	C09AA	Apr-05	R61.57M	R42.2M	38.1	4	-10%	R30.5M	4	-28%	R24.4M	5	-42%	R12.2M	6	-71%	R9.8M	6	-77%	6	10
KLACID	Clarithromycin	J01FA	Mar-05	R57.95M	R37.4M	33.1	6	-12%	R27.1M	7	-28%	R22.9M	8	-39%	R17.1M	8	-54%	R20.2M	8	-46%	8	3
TARGOCID	Teicoplanin	J01XA	May-03	R56.16M	R50.0M	55.7		-7%	R44.0M		-27%	R34.2M		-43%	R55.0M		-8%	R59.0M		-3%	1	1
ZYPREXA	Olanzapine	N05AH	Apr-11	R54.57M	R40.0M	37.5	3	-6%	R29.8M	3	-26%	R24.1M	3	-40%		3			3		3	2
MAXIPIME	Cefepime	J01DE	Jan-09	R52.41M	R62.9M	59.8		-5%	R46.1M		-23%	R39.9M		-36%								2
LAMICTIN	Lamotrigine	N03AX	May-00	R50.00M	R67.7M	69.7		3%	R60.0M		-11%	R47.6M		-29%	R156.0M		131%	R160.0M	2	140%	9	3
RENITEC	Enalapril	C09AA	Dec-99	R49.29M	R202.1M	172.4	4	-15%	R176.1M	7	-13%	R126.0M	7	-38%	R23.6M	7	-88%	R16.8M	7	-92%	8	10
ROCEPHIN	Ceftriaxone	J01DD	May-99	R49.16M	R214.1M	180.0		-16%	R164.3M	2	-14%	R173.1M	2	-19%	R220.4M	6	3%	R106.9M	6	-50%	10	4
TOPAMAX	Topiramate	N03AX	Sep-04	R46.64M	R65.2M	67.1		3%	R50.2M		-14%	R44.6M	3	-32%	R49.1M	5	-25%	R47.1M	5	-28%	6	3
RISPERDAL	Risperidone	N05AX	Mar-06	R47.64M	R60.4M	56.2		-7%	R44.7M		-26%	R39.7M	6	-34%	R32.7M	9	-46%	R30.2M	10	-50%	11	1
MERONEM	Meropenem	J01DH	Jul-07	R46.95M	R64.5M	62.2		-4%	R51.8M		-20%	R43.2M	1	-33%	R65.6M	2	35%	R56.2M	2	-13%	2	2
CIPRALEX	Escitalopram	N06AB	Apr-06	R45.57M	R44.8M	46.4	2	4%	R31.8M	3	-29%	R27.3M	5	-39%	R21.1M	5	-53%		5		5	2
DIFLUCAN	Fluconazole	J02AC	Jun-02	R44.69M	R63.4M	61.5	1	-3%	R49.4M	5	-22%	R40.9M	6	-36%	R14.9M	7	-77%	R12.0M	7	-81%	9	3
PREPULSID	Cisapride	A03FA	Sep-02	R43.35M	R18.8M	13.7		-27%	R11.0M		-42%	R9.0M		-52%	R.2M		-99%	R.0M				1
LOSEC	Omeprazole	A02BC	Apr-99	R39.59M	R20.3M	14.6		-28%	R12.3M		-39%	R10.0M		-51%	R10.1M		-50%	R7.8M	3	-62%	7	3
SERETIDE	FluticasoneSalmete	R03AK	Sep-10	R37.95M	R27.1M	24.2		-11%	R17.6M		-35%	R14.0M		-48%								1
ZOFRAN	Ondansetron	A04AA	Jan-05	R34.95M	R25.7M	20.0	4	-22%	R16.3M	5	-36%	R13.4M	5	-48%	R6.3M	6	-68%	R7.4M	7	-71%	7	5
ACCUPRIL	Quinapril	C09AA	Sep-01	R33.02M	R33.5M	31.1		-7%	R24.5M		-27%	R20.6M		-38%	R13.9M	1	-59%	R7.5M	1	-76%	4	10
SEROQUEL	Quetiapine	N05AH	Mar-07	R32.61M	R38.0M	33.4		-12%	R27.3M		-28%	R23.3M		-39%	R51.9M	1	37%	R19.4M	5	-49%	5	2
FLIXONASE	Fluticasone	R03BA	Feb-01	R30.09M	R32.5M	30.0		-8%	R22.5M		-31%	R19.2M		-41%	R22.7M		-30%	R46.3M		42%	0	1
PRAVA	Pravastatin	C10AA	Nov-02	R20.60M	R38.2M	34.0		-11%	R26.5M		-25%	R23.7M	2	-38%	R12.4M	3	-68%	R8.1M	3	-79%	6	4
DESELEX	Desloratadine	R06AX	May-06	R20.15M	R44.0M	41.0		-7%	R31.1M	1	-29%	R26.2M	1	-40%	R18.7M	3	-58%	R15.9M	4	-64%	4	6
TRAMACET	Tramadol	N02AX	Sep-12	R27.16M	R33.3M	30.7		-8%	R23.7M		-29%	R19.6M		-40%								1
GEMZAR	Gemcitabine	L01BC	Mar-04	R27.00M	R28.4M	26.0		-8%	R20.3M		-29%	R16.2M		-43%	R33.5M		18%	R34.6M		23%	4	1
KYTRIL	Granisetron	A04AA	Apr-06	R26.31M	R30.5M	27.8		-10%	R21.6M		-30%	R18.4M	1	-40%	R18.7M	3	-39%	R11.9M	3	-61%	3	5
PROZEF	Cefprozil	J01DC	Jan-04	R25.27M	R26.0M	23.7		-9%	R16.6M		-36%	R13.0M		-47%	R19.6M		-25%	R17.2M		-34%		2
LESCOL	Fluvastatin	C10AA	Nov-03	R24.39M	R48.9M	52.4		7%	R37.3M		-24%	R31.7M		-35%	R15.0M		-69%	R13.5M		-72%		4
PLAVIX	Clopidogrel	B01AC	Feb-06	R23.96M	R24.9M	18.7	4	-25%	R14.2M	5	-43%	R12.7M	5	-49%	R1.9M	6	-92%		6		6	3
NORVASC	Amlodipine	C08CA	Apr-07	R23.00M	R18.9M	14.4	13	-24%	R11.3M	14	-40%	R9.1M	16	-52%	R8.1M	16	-57%	R6.2M	16	-67%	16	3
CO-RENITEC	EnalaprilHydrochlor	C09BA	Dec-99	R22.91M	R31.3M	26.9	1	-6%	R22.0M	2	-30%	R18.7M	2	-40%	R5.7M	2	-82%	R4.7M	2	-85%	2	7
TIENAM	Imipenem	J01DH	Aug-02	R21.03M	R22.8M	16.1		-29%	R13.5M		-41%	R11.0M		-52%	R21.6M		-5%	R17.2M		-25%	1	2
AMARYL	Glimepiride	A10BB	Dec-00	R21.49M	R45.4M	46.5		2%	R34.5M		-24%	R30.5M		-33%	R31.1M	1	-32%	R20.4M	3	-55%	10	1
ADVANTAN	Methylprednisolone	D07AC	Aug-02	R21.01M	R20.4M	26.6		-7%	R20.6M		-26%	R17.4M		-39%	R26.5M		-7%	R23.5M		-17%		3
Lamisil	Terbinafine	D01BA	Aug-00	R20.06M	R18.2M	12.8		-21%	R9.6M		-41%	R7.4M		-54%	R11.6M		-29%	R11.9M	2	-26%	8	1
ATACAND	Candesartan	C09CA	Apr-11	R20.09M	R18.6M	13.5		-27%	R10.9M		-41%	R8.8M		-53%								7
STILNOX	Zolpidem	N05CF	Oct-01	R20.55M	R27.7M	24.8		-11%	R18.4M	2	-34%	R14.7M	5	-47%	R9.5M	5	-66%	R8.8M	6	-68%	7	1
ZITHROMAX	Azithromycin	J01FA	Sep-05	R20.50M	R20.8M	15.2	4	-26%	R13.0M	4	-37%	R10.2M	5	-50%	R28.7M	5	39%	R27.6M	5	34%	7	3
SEREVENT	Salmeterol	R03AC	Apr-04	R20.25M	R16.8M	13.4		-20%	R9.7M		-42%	R7.8M		-54%	R6.9M		-59%	R5.9M		-65%		1
ACCURETIC	QuinaprilHydrochlor	C09BA	Jun-06	R19.75M	R12.8M	10.0	2	-22%	R7.9M	4	-38%	R6.2M	4	-51%	R3.4M	4	-74%	R2.6M	4	-80%	4	7
SERZONE	Nefazodone	N06AX	Mar-02	R18.94M	R14.8M	12.0		-19%	R8.7M		-41%	R6.8M		-54%								2
MOBIC	Meloxicam	M01AC	Dec-99	R18.40M	R22.5M	90.9		-2%	R85.5M		-6%	R75.1M	1	-19%	R26.6M	2	-71%	R10.5M	2	-89%	12	2
UNAT	Torasemide	C03CA	Aug-06	R18.14M	R13.1M	11.7	1	-10%	R8.4M	1	-36%	R6.3M	1	-52%	R8.2M	1	-37%	R8.7M	1	-49%	1	1
ZESTRIL	Lisinopril	C09AA	Dec-99	R17.02M	R51.8M	54.4	2	5%	R39.3M	2	-24%	R32.4M	4	-37%	R14.2M	6	-73%	R7.9M	8	-85%	10	10
ZOLOFT	Sertraline	N06AB	Oct-00	R17.74M	R35.1M	32.5		-7%	R26.9M		-25%	R22.1M		-37%	R34.5M	1	-2%	R20.0M	3	-43%	11	2
TARIVID	Ofloxacin	S01AX	Aug-01	R17.46M	R18.3M	13.5	2	-26%	R10.5M	3	-43%	R8.6M	3	-53%	R1.6M	3	-91%	R0.1M	3	-53%	3	2
TAZOCIN	PiperacillinTazobac	J01CR	Oct-02	R17.30M	R19.4M	14.5		-25%	R12.1M	1	-37%	R9.8M	1	-49%	R11.5M	1	-41%	R10.9M	1	-44%	2	1
TRI-PLEN	FelodipineRamipril	C09BB	Sep-07	R17.19M	R15.3M	12.5		-18%	R9.0M		-41%	R7.0M		-54%	R11.3M		-26%	R10.0M		-35%		2
VFEND	Voriconazole	J02AC	Jan-11	R16.76M	R17.9M	13.5		-24%	R10.0M		-44%	R8.2M		-54%								3
CONTROLOC	Pantoprazole	A02BC	Jun-05	R16.70M	R12.7M	9.4	3	-26%	R7.7M	3	-39%	R5.8M	3	-55%	R2.1M	3	-83%	R1.4M	4	-89%	5	3
LIPITOR	Atorvastatin	C10AA	Jul-10	R16.34M	R46.8M	47.1	5	1%	R36.1M	6	-23%	R31.4M	6	-33%		6			6		6	4
ELOCON	Mometasone	R01AD	Dec-09	R16.19M	R20.5M	15.1	6	-26%	R12.6M	6	-39%	R10.0M	6	-51%	R8.7M	6	-57%	R10.6M	6	-49%	6	2
SANDOSTATIN	Octreotide	H01CB	Nov-00	R16.15M	R18.7M	13.0		-22%	R9.7M		-42%	R7.6M		-54%	R18.0M		0%	R10.0M		-40%		1
CLARITYNE D	LoratadinePseudoe	R06AX	Jun-01	R15.06M	R12.8M	8.8	2	-30%	R7.3M	2	-42%	R5.5M	2	-56%	R5.0M	2	-61%	R1.2M	2	-91%	2	6
CEFTRON	Cefpirome	J01DE	May-02	R13.75M	R9.0M	7.4		-17%	R5.2M		-42%	R3.9M		-56%	R2.5M		-72%	R1.8M		-80%		2
CIBADREX	BenazeprilHydrochl	C09BA	Jan-10	R13.73M	R.0M			-100%			-100%			-100%								7
COSOPT	DorzolamideTimolol	S01ED	Jun-00	R13.67M	R14.1M	11.9		-16%	R8.5M		-40%	R6.7M		-53%	R4.3M		-69%					1
SPORANOX	Itraconazole	J02AC	Jun-99	R13.54M	R21.4M	15.8		-27%	R13.4M		-37%	R10.6M		-51%	R20.2M		-6%	R19.0M		-11%	2	3
TEMODAL (SHC)	Temozolomide	L01AX	Aug-02	R12.61M	R19.1M	14.4		-24%	R11.5M		-40%	R9.6M		-50%	R33.9M		77%	R22.3M		17%		1
COVERSYL PLUS	PerindoprilIndapam	C09BA	Apr-06	R12.56M	R8.5M	7.3	3	-14%	R4.8M	4	-44%	R3.5M	7	-59%	R3.1M	7	-64%		7		7	7
COVERSYL	Perindopril	C09AA	Apr-06	R12.54M	R12.2M	8.7	4	-29%	R7.0M	6	-42%	R5.0M	9	-59%	R3.9M	11	-68%		13		13	10
ZESTORETIC	LisinoprilHydrochlor	C09BA	Dec-99	R12.20M	R29.1M	27.2		-6%	R21.5M		-26%	R17.4M		-40%	R37.9M		30%	R27.5M		-5%	7	7
ZELITREX	Valaciclovir	J05AB	Aug-06	R12.24M	R10.4M	8.0		-23%	R5.6M		-45%	R4.4M	2	-58%	R0.4M	2	-20%		2		2	3
ZAMANON	Dolasetron	A04AA	Oct-07	R12.00M	R9.1M	7.5		-18%	R5.3M		-41%	R4.1M		-55%	R.5M		-95%	R.1M		-99%		5

						Year 1 After Patent Expiry			Year 2 After Patent Expiry			Year 3 After Patent Expiry			Year 4 After Patent Expiry			Year 5 After Patent Expiry				
Trade Nme	Generic Name	ATC 4	Date of Patent Expiry	Sales 12 Months Preceding Expiry	Sales at Patent Expiry	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Max No. of Generics	No. of Related ATC4 s
MAXALT	Rizatriptan	N02CC	Jan-12	R11.00M	R12.6M	9.0		-29%	R7.5M		-41%	R5.7M		-55%								4
REDUCTIL	Sibutramine	A08AA	Dec-06	R11.56M	R12.8M	9.9	1	-23%	R7.9M	1	-38%	R6.0M	2	-53%	R3.5M	2	-73%		2		2	2
TELFAST	Fexofenadine	R06AX	Jan-00	R11.53M	R27.9M	25.0		-11%	R19.4M		-31%	R15.0M		-44%	R13.7M		-51%	R11.6M		-58%	6	6
IMIGRAN	Sumatriptan	N02CC	Jul-05	R11.29M	R10.9M	8.2	1	-25%	R6.1M	1	-44%	R4.6M	4	-58%	R5.9M	4	-46%	R5.5M	4	-50%	4	4
DIOVAN	Valsartan	C09CA	Feb-11	R10.77M	R8.0M	7.4	3	-18%	R4.9M	3	-44%	R3.7M	3	-58%		3			3		3	7
KLACID P	Clarithromycin	J01FA	Mar-05	R10.46M	R11.5M	8.3	6	-28%	R7.0M	7	-39%	R4.9M	8	-57%	R5.1M	8	-56%	R20.2M	8	76%	8	3
ACTIVELLE	Estradiol Norethister	G03FA	Aug-04	R10.37M	R11.0M	8.2	1	-26%	R6.2M	1	-44%	R4.6M	1	-58%	R6.7M	1	-21%	R9.3M	1	-16%	1	1
ARIMIDEX	Anastrozole	L02BG	May-06	R10.37M	R12.3M	8.6		-29%	R7.1M		-42%	R5.2M	3	-57%	R3.7M	4	-70%		4		4	3
ESMERON	Rocuronium	M03AC	Apr-05	R10.31M	R10.3M	7.9		-23%	R5.9M		-44%	R4.4M		-58%	R6.9M		-3%					4
PERDIX	Moexipril	C09AA	Sep-01	R10.29M	R.0M			-100%			-100%			-100%	R.0M		346%	R.0M		101%		10
ZANIDIP	Lercanidipine	C08CA	Jan-05	R10.20M	R.5M	.2		-91%			-100%			-100%	R4.0M		697%	R4.7M		852%		3
ONCIT	Palonosetron	A04AA	Nov-10	R10.20M	R2.1M	1.9		-13%	R.9M		-50%	R.5M		-76%								5
HISMANAL D	Pseudoephedrine Ai	R01BA	Apr-99	R10.20M	R.0M																	2
PHYSIOTENS	Moxonidine	C02AC	Nov-99	R10.20M	R1.4M	.9		-36%	R.2M		-84%	R.1M		-95%	R6.7M		378%	R4.5M		221%	1	1
AVELON	Moxifloxacin	J01MA	Feb-10	R10.27M	R15.6M	12.6	5	-19%	R9.1M	5	-42%	R7.3M	5	-53%		5			5		5	7
ELIDEL	Pimecrolimus	D11AX	Nov-10	R10.27M	R.1M	.0		-97%			-100%			-100%								1
OXYNORM	Oxycodone	N02AA	Nov-12	R10.27M	R1.2M	.7		-38%	R.1M		-58%	R.0M		-96%								1
OXYCONTIN	Oxycodone	N02AA	Nov-12	R10.27M	R3.0M	2.5		-18%	R1.5M		-49%	R.9M		-69%								1
ATACAND PLUS	Candesartan Hydroc	C09DA	Apr-11	R9.84M	R8.4M	7.3		-13%	R4.5M		-47%	R3.1M		-63%								4
FLOMAX	Tamsulosin	G04CA	Mar-06	R9.70M	R9.6M	7.9	1	-18%	R5.7M	2	-41%	R4.3M	2	-55%	R6.0M	2	-37%	R5.6M	3	-41%	4	1
CARDURA	Doxazosin	C02CA	Nov-99	R9.46M	R25.4M	19.5		-23%	R14.4M		-43%	R13.1M		-48%	R21.9M	2	-14%	R26.3M	2	4%	3	1
AGGRASTAT	Tirofiban	B01AC	Sep-11	R9.44M	R9.5M	7.9		-17%	R5.5M		-42%	R4.3M		-55%								3
ADVIL CS	Ibuprofen/Pseudoep	R01BA	Apr-05	R9.18M	R7.7M	7.1	2	-6%	R4.3M	2	-44%	R3.0M	2	-62%	R11.1M	2	44%	R9.4M	2	22%	2	2
COZAAR	Losartan	C09CA	Jul-07	R9.09M	R6.9M	6.1	5	-10%	R3.3M	5	-52%	R2.5M	6	-62%	R6.6M	6	-4%	R6.8M	9	-2%	9	7
DIFFERIN	Adapalene	D10AD	Apr-06	R8.43M	R7.9M	7.1		-10%	R4.4M		-44%	R3.0M		-62%	R3.9M		-52%	R3.6M		-54%		1
ULTIVA	Remifentanil	N01AH	Feb-10	R8.36M	R32.7M	30.6		-6%	R22.7M		-30%	R19.3M		-41%								2
FIXIME	Ceftriaxone	J01DD	Nov-00	R8.32M	R4.9M	4.1		-18%	R2.7M		-44%	R1.8M		-63%	R1.2M		-75%	R.3M		-95%		4
PLENDIL	Felodipine	C08CA	Jun-99	R8.26M	R27.3M	24.7		-10%	R18.2M		-33%	R14.7M		-46%	R31.8M		17%	R23.7M	1	-13%	1	3
NIZSHAMPOO	Ketoconazole	D01AC	Jan-99	R8.23M	R7.9M	7.2		-9%	R4.5M	1	-43%	R3.0M	1	-62%	R2.7M	2	-65%	R2.9M	2	-64%	2	1
COAPROVEL	Irbesartan Hydrochlc	C09DA	Mar-11	R7.81M	R4.3M	3.3	1	-23%	R2.3M	1	-46%	R1.6M	1	-64%		1			1		1	4
PREDEDEX	Dexmedetomidine	N01AB	Jul-08	R7.16M	R7.1M	6.8		-5%	R4.1M		-43%	R2.7M		-61%	R20.3M		186%					1
NIZORAL	Ketoconazole	D01AC	Jan-99	R6.80M	R7.1M	6.4		-9%	R3.7M	1	-46%	R2.7M	1	-62%	R1.1M	2	-84%	R2.9M	2	-60%	2	1
NORCURON	Vecuronium	M03AC	Aug-99	R6.55M	R10.7M	8.0		-25%	R5.9M		-45%	R4.5M		-58%	R6.0M		-44%	R4.8M		-55%	1	4
FAMVIR	Famciclovir	J05AB	Sep-05	R6.51M	R5.9M	5.2		-7%	R2.9M		-46%	R2.1M		-62%	R4.6M		-17%	R3.9M		-30%		3
CO-MICARDIS	Telmisartan/Hydroct	C09DA	Feb-12	R6.22M	R2.7M	2.4	1	-12%	R1.4M	1	-49%	R.8M	1	-70%		1			1		1	4
PROGRAF	Tacrolimus	L04AD	Sep-11	R6.13M	R6.7M	5.6		-18%	R3.1M		-54%	R2.4M		-64%	R18.8M		180%	R30.4M		472%	0	1
ARICEPT	Donepezil	N06DA	Jun-08	R6.04M	R6.5M	5.2		-17%	R3.0M	2	-53%	R2.3M	2	-64%	R2.3M	2	-63%		2		2	2
FEMARA	Letrozole	L02BG	Mar-07	R5.87M	R7.1M	6.9		-4%	R4.2M		-41%	R2.8M		-61%	R6.2M	2	15%	R5.4M	2	-25%	2	3
PEXOLA	Pramipexole	N04BC	Dec-05	R5.83M	R6.6M	5.2		-21%	R3.0M		-55%	R2.3M		-64%	R12.3M		87%	R12.9M		97%	1	3
APROVEL	Irbesartan	C09CA	Mar-11	R5.57M	R3.9M	3.1	1	-20%	R2.0M	2	-49%	R1.4M	2	-65%		2			2		2	7
DILATREND	Carvedilol	C07AG	Apr-99	R5.37M	R22.8M	16.7		-27%	R13.6M		-40%	R12.3M	1	-46%	R21.6M	1	-5%	R13.6M	1	-40%	9	1
RULIDE	Roxithromycin	J01FA	Dec-00	R5.27M	R3.0M	2.5		-18%	R1.6M	1	-47%	R1.0M	3	-66%	R.1M	3	-96%	R.1M	5	-96%	5	3
COZAAR COMP	Losartan Hydrochlor	C09DA	Jan-09	R4.99M	R5.3M	4.7		-12%	R2.8M	3	-47%	R1.9M	11	-64%		11			11		11	4
NIMBEX	Cisatracurium	M03AC	Jul-11	R4.95M	R4.0M	3.5		-28%	R2.5M		-47%	R1.7M		-64%								4
RAMACE	Ramipril	C09AA	Apr-05	R4.70M	R3.9M	3.1	4	-19%	R2.0M	4	-48%	R1.4M	5	-63%	R.9M	6	-78%	R9.8M	6	153%	6	10
LORABID	Loracarbef	J01DC	Jan-11	R4.59M	R.7M	.3		-87%	R.0M		-100%			-100%								2
BONDRONAT	Ibandronic acid	M05BA	Jul-07	R4.53M	R7.0M	6.4		-9%	R3.0M		-48%	R2.7M		-61%	R12.5M		79%	R11.7M		68%		4
LOTRIDERM	Betamethasone/Clot	D07XC	Oct-01	R4.45M	R4.2M	3.2		-24%	R2.0M		-51%	R1.5M		-65%	R1.7M		-60%	R1.4M		-67%		1
MONOPRIL	Fosinopril	C09AA	Nov-01	R4.45M	R4.0M	4.1		-15%	R2.0M		-48%	R1.5M		-63%	R2.0M	1	-50%	R1.5M	1	-59%	1	10
RAPITEN	Alfentanil	N01AH	May-99	R4.39M	R5.4M	5.1		-6%	R2.0M		-47%	R2.0M		-62%	R7.1M		32%	R6.3M		16%		2
TARKA	Trandolapril/Verapar	C09BB	Mar-12	R4.36M	R4.7M	3.5		-26%	R2.4M		-50%	R1.6M		-66%								2
MICARDIS	Telmisartan	C09CA	Feb-12	R4.34M	R3.7M	2.9	1	-21%	R1.9M	1	-48%	R1.2M	1	-67%		1			1		1	7
VOLTAREN EMULG	Diclofenac	S01BC	Apr-07	R4.25M	R3.6M	2.7	1	-26%	R1.8M	2	-50%	R1.1M	2	-68%	R2.0M	2	-24%	R3.5M	2	-2%	2	2
ARTHROTEC	Diclofenac/Misopros	M01AB	May-11	R4.19M	R3.7M	2.8		-25%	R1.8M		-51%	R1.2M		-68%								1
CLIMARA	Estradiol	G03CA	Jun-07	R4.00M	R2.2M	1.9	1	-13%	R1.0M	1	-53%	R.5M	1	-76%		1		R.0M	1	-99%	1	2
KESTINE	Ebastine	R06AX	Jul-04	R3.76M	R2.1M	1.7		-20%	R.9M		-57%	R.4M		-79%	R1.1M		-49%	R1.1M		-49%		6
CASODEX	Bicalutamide	L02BB	Jul-03	R3.75M	R13.0M	11.7		-10%	R8.0M		-39%	R6.3M		-51%	R10.1M		34%	R17.7M		36%	6	1
KEPPRA	Levetiracetam	N03AX	May-05	R3.67M	R8.9M	7.4		-17%	R5.2M		-42%	R3.8M		-58%	R6.5M		-7%	R8.6M	1	-4%	1	3
REQUIP	Ropinirole	N04BC	May-06	R3.44M	R5.1M	4.3		-15%	R2.0M		-45%	R1.9M	1	-62%	R9.4M	1	84%		1		1	3
ACTOS	Pioglitazone	A10BG	Jan-06	R3.32M	R3.0M	2.4	1	-19%	R1.4M	1	-53%	R.9M	1	-71%	R.9M	1	-71%	R.9M	1	-81%	1	1
CORALAN	Ivabradine	C01EB	Sep-12	R3.29M	R3.9M	3.0		-22%	R1.9M		-50%	R1.3M		-66%								1
BREXIDCAM	Piroxicam	M01AC	Oct-04	R3.19M	R3.1M	2.5		-20%	R1.7M		-46%	R1.1M		-66%	R1.3M		-59%	R1.2M		-61%		2
TRILEPTAL	Oxcarbazepine	N03AF	Oct-00	R3.12M	R2.6M	2.2		-18%	R1.2M		-55%	R.8M		-75%	R3.1M		19%	R3.2M		20%	1	1
ACTONEL	Risedronate	M05BA	Jan-12	R3.02M	R1.9M	1.6	1	-18%	R.9M	1	-68%	R.3M	1	-83%		1			1		1	4
INHIBACE	Cilazapril	C09AA	May-03	R3.02M	R2.6M	2.2		-18%	R1.3M		-53%	R.8M		-70%	R.6M		-78%	R.5M		-81%		10
PEPCID	Famotidine	A02BA	Feb-00	R2.87M	R1.9M	1.6		-19%	R.9M		-51%	R.4M		-81%	R.0M		-100%					2
PROSCAR 5	Finasteride	G04CB	Feb-05	R2.87M	R1.7M	1.3		-23%	R.5M		-71%	R.2M	2	-87%	R.6M	2	-67%	R.4M	2	-75%	4	1
FARESTON	Toremifene	L02BA	May-03	R2.58M	R2.1M	1.6		-21%	R.8M		-63%	R.4M		-81%	R.3M		-87%	R.2M		-90%		1
HISMANAL	Astemizole	R06AX	Apr-99	R2.41M	R2.5M	2.0		-22%	R1.1M		-58%	R.5M		-79%	R.0M		-100%					8
CILOXAN	Ciprofloxacin	J01MA	Sep-01	R2.35M	R2.1M	1.7	4	-21%	R.9M	9	-58%	R.4M	11	-79%	R2.0M	13	-5%	R1.9M	13	-11%	15	7
NOVONORM	Repaglinide	A10BX	Dec-04	R2.33M	R1.5M	1.3		-17%	R.4M		-73%	R.1M		-91%	R.7M		-59%	R.6M		-61%		1
LIVOSTIN	Levocabastine	S01GX	Jan-01	R2.27M	R2.1M	1.6		-20%	R.9M		-58%	R.4M		-80%	R.9M		-58%	R.6M		-70%		2

						Year 1 After Patent Expiry			Year 2 After Patent Expiry			Year 3 After Patent Expiry			Year 4 After Patent Expiry			Year 5 After Patent Expiry				
Trade Nme	Generic Name	ATC4	Date of Patent Expiry	Sales 12 Months Preceding Expiry	Sales at Patent Expiry	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Max No. of Generics	No. of Related ATC4 s
MIRELLE	GestodeneEthinyles	G03AA	Jul-07	R2.30M	R2.0M	2.2		-16%	R1.2M		-54%	R.5M		-70%	R2.1M		-22%	R2.0M		-24%		2
MINESSE	EthinylestradiolGes	G03AA	Jul-07	R2.15M	R1.4M	.9		-36%	R.2M		-90%	R.1M		-96%	R2.0M		40%	R2.3M		62%		2
AREDIA	Pamidronic acid	M05BA	Aug-05	R2.14M	R.8M	.5		-35%	R.1M		-91%			-100%	R.5M		-42%	R.3M		-60%		4
MIVACRON	Mivacurium	M03AC	Jul-05	R2.11M	R1.9M	1.6		-16%	R.6M		-67%	R.3M		-83%	R1.3M		-29%	R1.2M		-35%		4
EXOCIN	Ofloxacin	S01AX	Aug-01	R1.97M	R2.0M	1.6	2	-20%	R.8M	3	-63%	R.4M	3	-82%	R1.9M	3	-9%	R3.1M	3	51%	3	2
DOSTINEX	Cabergoline	G02CB	Mar-01	R1.92M	R2.0M	2.1		-18%	R1.2M		-55%	R.5M		-79%	R2.3M		-9%	R2.1M		-17%	1	2
FORTUM	Ceftazidime	J01DD	May-99	R1.87M	R4.2M	3.2	1	-23%	R2.3M	1	-46%	R1.5M	1	-63%	R5.2M	1	24%	R6.7M	1	61%	2	4
CIPROBAY HC	Ciprofloxacin	J01MA	Sep-01	R1.82M	R2.2M	1.9	4	-13%	R1.0M	9	-53%	R.5M	11	-76%	R2.0M	13	-9%	R2.0M	13	-9%	15	7
ACULAR	Ketorolac	S01BC	Sep-06	R1.75M	R1.0M	1.3		-27%	R.6M		-69%	R.3M		-85%	R3.6M		107%					2
ALDARA	Imiquimod	D06BB	Nov-04	R1.73M	R1.5M	1.1		-25%	R.4M		-77%	R.1M		-94%	R2.5M		69%	R2.6M		86%		2
CIBACE	Benazepril	C09AA	Aug-02	R1.73M	R1.7M	1.3		-24%	R.5M		-69%	R.3M		-85%	R.6M		-65%	R.3M		-85%		10
ANEXATE	Flumazenil	V03AB	Sep-00	R1.67M	R1.4M	.9		-36%	R.2M		-84%	R.1M		-96%	R1.2M		-15%	R1.0M		-28%		1
ASASANTIN RETA	DipyridamoleAspirin	B01AC	Aug-07	R1.64M	R1.5M	.9		-38%	R.3M		-83%	R.1M		-95%	R1.5M		-12%	R1.0M		-30%		3
INHIBACE PLUS	CilazaprilHydrochlo	C09BA	May-03	R1.60M	R1.5M	1.2		-22%	R.4M		-75%	R.1M		-93%	R.4M		-74%	R.3M		-77%		7
NORPROLAC	Quinagolide	G02CB	Oct-02	R1.54M	R1.4M	.8		-41%	R.2M		-86%	R.0M		-97%	R1.0M		-30%	R.9M		-35%		2
CYMEVENE	Ganciclovir	J05AB	Sep-01	R1.42M	R1.0M	.7		-35%	R.1M		-90%	R.0M		-100%	R3.0M		195%	R1.6M		60%		3
URIZONE	Fosfomycin	J01XX	Jul-99	R1.41M	R1.9M	1.6		-19%	R.7M		-64%	R.4M		-81%	R2.6M		35%	R2.3M		22%		1
FENIVIR	Penciclovir	D06BB	Jan-11	R1.33M	R1.4M	.8		-43%	R.2M		-86%	R.0M		-98%								2
AROMASIN	Exemestane	L02BG	Jul-06	R1.26M	R1.5M	1.1		-25%	R.3M		-82%	R.1M		-94%	R4.0M		166%	R4.2M		180%		3
NIZOREME	Ketoconazole	D01AC	Jan-99	R1.20M	R1.5M	1.2		-20%	R.4M	1	-75%	R.1M	1	-92%	R.6M	2	-60%	R2.5M	2	86%	2	1
FUCITHALMIC	Fusidic acid	S01AA	Jan-06	R1.13M	R1.1M	.7		-37%	R.1M		-88%	R.0M		-100%	R1.0M		-6%	R.9M		-12%		1
LOMEXIN	Fenticonazole	G01AF	Apr-99	R1.09M	R2.7M	2.4		-11%	R1.3M		-53%	R.5M		-70%	R2.9M		10%	R1.6M		-41%		1
MIZOLLEN	Mizolastine	R06AX	Sep-06	R1.01M	R.7M	.4		-42%	R.0M		-94%			-100%	R.3M		-61%	R.1M		-91%		6
NAVOBAN	Tropisetron	A04AA	Dec-05	R1.00M	R.4M	.2		-62%			-100%			-100%	R.1M		-88%	R.0M		-96%		5
COMTAN	Entacapone	N04BX	Nov-07	R.96M	R.7M	.4		-43%	R.0M		-98%			-100%	R.3M		-58%	R.3M		-59%		2
BACTIDRON	Enoxacin	J01MA	Aug-99	R.96M	R.9M	.6		-40%	R.1M		-90%	R.0M		-100%	R.2M		-75%	R.0M		-95%		7
LANZOR HB	Lansoprazole	A02BC	Aug-05	R.95M	R1.0M	1.3	4	-27%	R.6M	6	-69%	R.3M	7	-85%	R.2M	7	-87%	R4.0M	8	165%	8	3
SUPREFACT	Buserelin	L02AE	Feb-00	R.92M	R.4M	.1		-83%			-100%			-100%	R1.6M		318%	R4.1M		998%		1
EXELON	Rivastigmine	N06DA	Mar-00	R.90M	R.7M	.5		-36%	R.0M		-94%			-100%	R.3M		-58%	R.2M		-70%		2
ZOMIG	Zolmitriptan	N02CC	Jun-11	R.90M	R.7M	.4		-45%	R.0M		-97%			-100%								4
NOROXIN	Norfloxacin	J01MA	Jul-01	R.83M	R.6M	.3	1	-51%	R.0M	1	-100%		2	-100%	R.0M	2	-99%		2		2	7
PERMAX	Pergolide	N04BC	Feb-99	R.81M	R2.5M	2.0		-23%	R1.0M		-59%	R.5M		-80%	R2.3M		-9%	R2.5M		-1%		3
MONOZIDE	FosinoprilHydrochlo	C09BA	Nov-01	R.80M	R1.0M	.6		-42%	R.1M		-90%	R.0M		-100%	R.6M		-40%	R.1M		-90%		7
AZOPTIC	Brinzolamide	S01EC	Apr-11	R.77M	R.6M	.5		-37%	R.1M		-89%			-100%								2
BREVIBLOC	Esmolol	C07AA	May-01	R.77M	R.6M	.5		-36%	R.1M		-90%			-100%	R.1M		-82%	R.0M				1
SENSIPAR	Cinacalcet	H05BX	Aug-12	R.66M	R1.0M	.7		-35%	R.1M		-86%	R.0M		-100%								1
PROTOPIC	Tacrolimus	L04AD	Sep-11	R.66M	R.7M	.4		-43%	R.0M		-97%			-100%							0	1
LOCERYL	Amorolfine	D01AE	Feb-10	R.60M	R1.5M	1.3		-17%	R.4M		-71%	R.2M		-86%								1
HYCAMTIN	Topotecan	L01XX	Nov-06	R.60M	R.7M	.4		-46%	R.0M		-97%			-100%	R.6M		27%					1
LEUSTATIN	Cladribine	L01BB	Jan-06	R.54M	R.4M	.1		-83%			-100%			-100%	R.2M		-43%	R.2M		-54%		1
CO-ARTEM	ArtemetherLumefar	P01BE	Jun-11	R.54M	R.6M	.3		-51%	R.0M		-100%			-100%								1
TILADE M	Nedocromil	R03BB	Apr-99	R.51M	R.5M	.2		-58%			-100%			-100%								1
NARAMIG	Naratriptan	N02CC	Aug-06	R.51M	R.5M	.2		-61%			-100%			-100%	R.4M		-17%					4
CEDAX	Ceftibuten	J01DD	Oct-04	R.45M	R.1M			-100%			-100%			-100%								4
NOVANTRONE	Mitoxantrone	L01DB	Jul-99	R.43M	R3.0M	2.5		-18%	R1.4M		-52%	R.9M		-71%	R2.9M		-6%	R2.1M		-31%	1	1
VOLTAREN OPHTI	Diclofenac	S01BC	Apr-07	R.42M	R.5M	.2	1	-63%		2	-100%		2	-100%	R.7M	2	28%	R3.5M	2	545%	2	2
ANTIZID	Nizatidine	A02BA	Sep-01	R.40M	R.3M	.1		-66%			-100%			-100%	R.0M		-94%	R.0M		-91%		2
NIZOVULES	Ketoconazole	D01AC	Jan-99	R.36M	R.4M	.2		-60%		1	-100%		1	-100%	R.1M	2	-73%	R2.5M	2	552%	2	1
MAXAQUIN	Lomefloxacin	S01AX	Sep-04	R.37M	R.1M	.0	1	-100%		1	-100%		1	-100%	R.0M	1	-75%	R.2M	1	106%	1	2
TRUSOPT	Dorzolamide	S01EC	Jun-06	R.35M	R.3M	.1		-67%			-100%			-100%	R.6M		107%					2
DIPENTUM	Olsalazine	A07EC	Dec-01	R.32M	R.4M	.1		-69%			-100%			-100%	R.2M		-46%	R.2M		-50%		1
OKACYN	Lomefloxacin	S01AX	Sep-04	R.26M	R.3M	.1	1	-67%		1	-100%		1	-100%	R.2M	1	-16%	R.2M	1	-30%	1	2
HALITAN	Halofantrine	P01BX	Sep-04	R.25M	R.1M	.0		-100%			-100%			-100%	R.1M		-23%	R.1M		-24%		1
RILUTEK	Riluzole	N07XX	Oct-12	R.25M	R.2M	.0		-80%			-100%			-100%								1
ESTRACOMBI TTS	EstrogenaNorethist	G03CA	Mar-08	R.21M	R.2M	.1		-69%			-100%			-100%								2
SEMPREX	Acrivastine	R06AX	Feb-03	R.20M	R.1M	.0		-95%			-100%			-100%								8
AZACTAM	Aztreonam	J01DF	Feb-01	R.20M	R.2M	.0		-79%			-100%			-100%	R.5M		190%	R.2M		-12%		1
ACCOLATE	Zafirlukast	R03DC	Dec-11	R.20M	R.2M	.0		-74%			-100%			-100%								2
IMODIUM PLUS	LoperamideSimeti	A07DA	Oct-10	R.16M	R1.3M	.8		-41%	R.1M		-89%	R.0M		-98%								1
CUTIVATE	Fluticasone	R03BA	Feb-01	R.10M	R.3M	.2		20%	R.1M		-17%	R.1M		-19%	R.1M		-33%	R.1M		-29%	0	1
RHINOLAST	Azelastine	S01GX	Nov-06	R.17M	R.1M	.0		-95%			-100%			-100%	R.1M		-29%					2
ETOPOPHOS	Etoposide	L01CB	Jul-06	R.16M	R.3M	.1	1	-69%		1	-100%		1	-100%		1			1		1	1
ZOMETA	Zoledronic	M05BA	Nov-07	R.11M	R1.5M	1.1		-26%	R.3M		-81%	R.1M		-94%	R0.6M		473%	R4.1M	1	172%	1	4
BARACLUDE	Entecavir	J05AF	Oct-11	R.10M	R.1M	.0		-97%			-100%			-100%								1
WELLVONE	Atovaquone	P01AX	Apr-04	R.06M	R.1M			-100%			-100%			-100%	R.1M		-30%	R.1M		-15%		1
ESTRING	Estradiol	G03CA	Jun-07	R.06M	R.0M		1	-100%		1	-100%		1	-100%	R.0M	1	-47%	R.0M	1	-45%	1	2
TASMAR	Tolcapone	N04BX	Mar-07	R.05M	R.0M			-100%			-100%			-100%	R.0M		-63%					2
GOPTEN	Trandolapril	C09AA	Dec-02	R.04M	R.0M		1	-100%		1	-100%		1	-100%		1			1		1	10
TEVETEN	Eprosartan	C09CA	Aug-12	R.04M	R.0M			-100%			-100%			-100%								7
PROTOS	Strontium	M05BX	Aug-10	R.03M	R7.5M	7.0		-6%	R4.3M		-43%	R2.9M		-61%								1
ADIFAX	Dexfenfluramine	A08AA	Dec-01	R.02M	R.0M																	2
RELENZA	Zanamivir	J05AH	Apr-11	R.01M	R.0M			-100%			-100%			-100%								1

						Year 1 After Patent Expiry			Year 2 After Patent Expiry			Year 3 After Patent Expiry			Year 4 After Patent Expiry			Year 5 After Patent Expiry				
Trade Nme	Generic Name	ATC 4	Date of Patent Expiry	Sales 12 Months Preceding Expiry	Sales at Patent Expiry	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Sales	No. of Generics	% Change From Expiry Sales	Max No. of Generics	No. of Related ATC4 s
TEVETEN PLUS	Eprosartan+hydrochl	C09CA	Aug-12	R.00M	R.0M																	7
LIVIFEM	Tibolone	G03CX	Mar-10	R.00M	R11.1M	8.2		-26%	R6.6M		-40%	R4.0M		-58%								1
ZORAC	Tazarotene	D05AX	Mar-08	R.00M	R.0M										R.1M							1
Min (All Products)					R.0M	R.0M	1	-100%	R.0M	1	-100%	R.0M	1	-100%	R.0M	1	-100%	R.0M	1	-99%	0	1
Max (All Products)					R249.7M	R.0M	13	10%	R254.1M	14	4%	R244.5M	14	-10%	R226.4M	14	497%	R148.0M	14	948%	10	10
Average (All Products)					R18.6M	R.0M	1.75	-28%	R16.1M	3.38	-50%	R14.7M	3.74	-68%	R13.8M	4.00	-13%	R11.6M	4.23	-3%	5	3
Count (All Products)					R.0M	206	87	214	R.0M	69	214	R.0M	81	214	R.0M	88	140	R.0M	94	140	112	214
SD (All Products)					R24.7M	R.0M	2.14	24%	R22.4M	3.73	17%	R20.7M	3.33	24%	R27.1M	3.40	134%	R23.2M	3.60	170%	4	3
Total for Top 20					R246.6M	R.0M	46	-	R190.6M	73	-	R164.2M	100	-	R104.6M	113	-	R67.9M	144	-	188	187
Total for All Products					R4068.7M	R.0M	155	-11.7%	R3961.1M	224	-27.2%	R3475.4M	303	-36.2%	R2476.7M	354	-49.8%	R1473.8M	398	-56.9%	533	494

8. REFERENCES

1. Ngozwana S. Policies to control prices of medicines: does the South African experience have lessons for other African countries? In: Wamae W, Mackintosh M, Tibandebage P, Banda G, editors. Making medicines in Africa: the political economy of industrializing for local health. United Kingdom: Palgrave Macmillan; 2016. p 203-223.

2. McIntyre D, and Thiede M. 2007. Health care financing and expenditure. In Harrison S, Bhana R, and Ntuli A. (eds). *South African Health Review 2007*. Durban: Health Systems Trust.

3. National Department of Health, South Africa. 1997. White Paper on the transformation of the health system in South Africa. General Notice 667 of 1997. Available online: https://www.gov.za/sites/www.gov.za/files/17910_gen667_0.pdf. Accessed: 02 Jan 2017.

4. BMI Research, A Fitch Group Company. South Africa pharmaceuticals and healthcare report. Q4 2016.

5. National Department of Health, South Africa. 1997. National drug policy for South Africa. Available Online: http://apps.who.int/medicinedocs/documents/s17744en/s17744en.pdf.
Accessed: 05 Dec 2016.

6. Department of Trade and Industry, South Africa. Patents Act, Act No. 57 of 1978.

7. South African Government. 1996. Constitution of the Republic of South Africa, Act No. 108 of 1996.

8. Hassim A, Heywood M, and Berger J. Health and democracy: a guide to human rights, health law and policy in post-apartheid South Africa. Siberlnk. 2007.

9. National Department of Health, South Africa. Regulations relating to a transparent pricing system for medicines and scheduled substances. 2004. Government Notice No. 26304.

10. Council of Medical Schemes. 1998. Medical schemes act, Act No. 131 of 1998.

11. Nicolosi E, Gray A. Potential cost savings from generic medicines - protecting the prescribed minimum benefits. *South African Family Practice*. 2009;51(1):6-24.

12. Danzon PM, Ketcham JD. Reference pricing of pharmaceuticals for medicare: evidence from Germany, the Netherlands, and New Zealand. *Front Health Policy Res*. 2004;7:1-54.

13. Boyce A, and Bartlett G. The maximum medical aid price programme. A review of the concept and of its ability to reduce expenditure on medicines. *South African Medical Journal.*1990;78:147.

14. World Health Organisation. Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. WHO Library Cataloguing-in-Publication Data. Geneva, Switzerland; 2011.

15. Scott MF. Entry decisions in the generic pharmaceutical industry. *RAND Journal of Economics*. 1999;30:421-440.

16. Lofgren H. 2002. Generic Drugs: International trends and policy development in Australia. pharmaceutical industry project equity, sustainability and industry development. Working paper series, Working Paper No. 10.

17. Suh DC, Manning WG, Schondelmeyer S, and Hadsall RS. Effect of multiple-source entry on price competition after patent expiration in the pharmaceutical industry. *Health Serv Res*. 2000;35(2):529-47.

18. Satterthwaite MA. Consumer information, equilibrium industry price, and the number of sellers. *Bell Journal of Economics*. 1979;10(2):483-502.

19. Saha A, Grabowski H, Birnbaum H, Greenberg P, and Bizan O. Generic competition in the US pharmaceutical industry. *International Journal of the Economics of Business.* 2006;13(1):15-38.

20. Hudson J. Generic take-up in the pharmaceutical market following patent expiry: A multi-country study. *International Review of Law and Economics*. 2000;20(2):205-221.

21. Magazzini L, Pammolli F, Riccaboni M. Dynamic competition in pharmaceuticals: patent expiry, generic penetration, and industry structure. *The European Journal of Health Economics.* 2004(2):175.

22. Adriaen M, De Witte K, Simoens S. Pricing strategies of originator and generic medicines following patent expiry in Belgium. *Journal of Generic Medicines*. 2008;5(3):175-187.

23. Besanko D, Braeutigam RB. 2016. Microeconomics: An Integrated Approach. Dublin, Ireland. Wiley

24. Congregational Budget Office. 1997. How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry. Available from: https://www.cbo.gov/sites/default/files/105th-congress-1997-1998/reports/pharm.pdf. Accessed: 15 Dec 2016.

25. Hardon A, Hodgkin C, and Fresle D. 2004. How to investigate the use of medicines by consumers. World Health Organization, Geneva.

26. Neuman W. Social research methods: qualitative and quantitative approaches. 7th ed. Edinburgh Gate, Harlow, Essex CM20 2JE: Pearson Education Limited; 2013.

27. Department of Health, South Africa. 1965. Medicines and Related Substances Act 101 of 1965, Integrated Act 101 (2).

28. Cook A. Forecasting for the pharmaceutical industry. 1st ed. Suite 420 101 Cherry Street Burlington VT 05401-4405 USA: Gower Publishing Company; 2006.

29. World Health Organization. 2003. ATC index with DDDs and Guidelines for ATC classification and DDDs assignment. WHO Collaborating centre for drugs statistics methodology, Oslo. Available online: http://www.whocc.no. Accessed: 30 Dec 2016.

30. World Health Organization. 2011. World medical situation - pharmaceutical consumption. annex 2, classification of acute and chronic disease medicine.

31. Regnier S. What is the value of 'me-too' drugs? *Health Care Manag Sci.* 2013;16(4):300-13.

32. Aulton M, and Taylor K. Pharmaceutics. The design and manufacture of medicines. 4th ed. Lacon House 84 Theobalds Road: Churchill Livingstone; 2013.

33. Tenn S, Wendling BW. Entry threats and pricing in the generic drug industry. *Rev Econ Stat*. 2014;96(2):214-228.

34. Craig AM, Malek M. Market structure and conduct in the pharmaceutical industry. *Pharmacol Ther*. 1995;66(2):301-337.

35. Gupta H, Kumar S, Roy SK, Gaud RS. Patent protection strategies. *J Pharm Bioallied Sci*. 2010;2(1):2-7.

36. MSD. MSD/SCHERING-PLOUGH Merger.
Available from: http://www.msd.co.za/about-us/pages/merck-schering-plough-merger.aspx. Accessed: 10 Nov 2016.

37. Hitchings A, Baker E, and Khong T. Making medicines evergreen. *BMJ.* 2012;345(7886):18-20.

38. Grabowski H, Brain C, Taub A, and Guha R, editors. Pharmaceutical patent challenges and their implications for innovation and generic competition, AEA Conference, Boston, MA, USA, 2015.

39. Grabowski H. Patents, innovation and access to new pharmaceuticals. *Journal of International Economic Law*. 2002;5(4):849-860.

40. Hitchings A, Baker E, Khong T. Making medicines evergreen. *BMJ*. 2012;345(7886):18-20.

41. Kanavos P. Measuring performance in off-patent drug markets: a methodological framework and empirical evidence from twelve EU member states. *Health Policy*. 2014;118(2):229-241.

42. Leng H, Sanders D, and Pollock A. Pro-generics policies and the backlog in medicines registration in South Africa: implications for access to essential and affordable medicines. *GABI*. 2015;4(2):58-63.

43. Kashyap U, Gupta V, and Raghunandan H. Comparison of drug approval process in United States & Europe. *J Pharm Sci & Res*. 2013;5(6):131.

44. Mossialos E, Mrazek M, and Walley T. (editors). Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. United Kingdom: Open University Press; 2004.

45. Farmer REA, and Winter RA. The role of options in the resolution of agency problems: a comment. *J Finance*. 1986;41(5):1157-1170.

46. Congress Budget Office. 1998. How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry. Available from: https://www.cbo.gov/sites/default/files/105th-congress-1997-1998/reports/pharm.pdf. Accessed: 06 Jan 2017.

47. Appelt S. Authorized generic entry prior to patent expiry: reassessing incentives for independent generic entry. *Rev Econ Stat*. 2015;97(3):654-666.

48. Pharmaceutical Task Group. 2015. Pharmaceutical task group's response to third party submissions concerning the pharmaceutical sector. Available from: http://www.compcom.co.za/wp-content/uploads/2015/05/PTG-Submission-Response-to-Stakeholders1.pdf. Accessed: 14 Feb 2017.

49. United Nations. 2016. High-level meeting on antimicrobial resistance. Available from: http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/. Accessed: 01 Apr 2017.

50. National Department of Health. Antimicrobial stewardship: the South African perspective. Accessed: 27 Apr 2017. Available online: http://www.who.int/phi/implementation/Precious_Matsoso_MoH_South_Africa.pdf?ua=1

51. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, and Bradshaw D. The burden of noncommunicable diseases in South Africa. *Lancet*. 2009;934(47):374.

52. Sinclair A. Key Factors Affecting Brand Erosion at Patent Expiry. *Innovations in Pharmaceutical Technology*. 2007; 23.

53. Shargel L, and Kanfer I. (editors) Generic drug product development: bioequivalence issues. New York: CRC Press; 2008.

54. World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. 2006; 937.

55. The generic pharmaceutical market in South Africa: at the crossroads? *Journal of Generic Medicines*. 2009;6(2):137-144.

56. Bootman J.L., Townsend R.J., McGhan W.F. Principles of pharmacoeconomics. 1st ed. Cincinnati, USA: Harvey Whitney Books Company; 1996.

57. Medecins Sans Frontieres. Fatal imbalance: the crisis in research and development for drugs for neglected diseases. Available from: https://www.msfaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_FatalImbalance_CrisisInR&D_ENG_2001.pdf. Accessed: 28 Mar 2017.

58. Pouris A, and Pouris A. Patents and economic development in South Africa: managing intellectual property rights. *S Afr J Sci*. 2011;107(11):24-33.

59. Farrell J, and Shapiro C. How strong are weak patents? *Am Econ Rev*. 2008;98(4):1347-69.

60. Doctors Without Borders. Oral Contraceptives: Yasmin®, Yaz® and Ruby® Available from: http://www.fixthepatentlaws.org/wp-content/uploads/2014/10/YasminFinal_3.pdf. Accessed: 28 Feb 2017.

61. Gabble R, Kohler JC. "To patent or not to patent? the case of Novartis' cancer drug glivec in India". *Globalization & Health*. 2014;10(1):1-12.

62. McGee S. The economic and pricing impact of authorized generic medicines in South Africa. *International Journal of Pharmaceutical & Healthcare Marketing*. 2015;9(1):20.

63. Veltrop JD, and Landmon CA. The impact of a brand generic launch on the recovery of patent damages. *IPL Newsletter*. 2005;23(4):1.

64. DiMasi JA, Faden LB. Competitiveness in follow-on drug R&D: a race or imitation? *Nature Reviews Drug Discovery*. 2011;10(1):23-27.

65. Henry D, and Searles A. Pharmaceutical pricing policy. In: Management Sciences for Health (MSH). Managing access to medicines and health technologies. Arlington, VA: Management Sciences for Health; 2013. p. 9.2 – 9.20.

66. Kong Y. Competition between brand-name and generics-analysis on pricing of brand-name pharmaceutical. *Health Econ*. 2009;18(5):591-606.

67. Mediscor. 2007. Mediscor medicines review 2007. Available online: https://www.dropbox.com/s/ck1t1yuvnbq72ig/Mediscor%20Medicine%20Review%202007.pdf?dl=0. Accessed: 28 Jan 2018.

68. Medicines Control Council. 2014. Scheduling of medicines. Available online: http://www.mccza.com/documents/a56714ff2.36_Scheduling_of_Medicines_Jun14_v1.pdf. Accessed: 24 Feb 2017.

69. Pharmaceutical Society of South Africa. Changes to schedules of the medicines and related substances act. *South African Pharmaceutical Journal*. 2013;79(03):37-39.

70. Marketing Code Authority. 2014. South African marketing code. Available online: http://www.marketingcode.co.za/images/SACodeMarketingPractice.pdf. Accessed: 22 Jan 2016.

71. Taylor B, Taylor A, Burns D, Rust JD, and Grobler P. Prescribed minimum benefits - quagmire or foundation for social health reform? *South African Medical Journal*. 2007;97(6):446-50.

72. Lee C, Chen M, and Sun E. Member states' pact and industry co-movements in the BRICS markets. *Appl Econ*. 2017;49(4):313-34.

73. Lobo L. The Brazilian generic market. *Journal of Generic Medicines*. 2009;6(3):345.

74. Ecorys Research and Consulting. 2009. Competitiveness of the EU market and industry for pharmaceuticals. Available from: http://www.pedz.uni-mannheim.de/daten/edz-h/gdb/09/vol_2_markets_innovation_regulation_en.pdf. Accessed: 28 Aug 2013.

75. South African Government. 2015. President Jacob Zuma: state of the nation address. Available online: http://www.gov.za/president-jacob-zuma-state-nation-address-2015. Accessed: 13 Oct 2016.

76. Ngozwana, S. Will a state owned pharmaceutical manufacturing company solve the shortage of medicines? Available from: http://sapcconference.za.org/NPC_PDF/Monday/1.%20Monday%20I%2010h45%20-%2011h15%20I%20Ngozwana%20I%20Will%20a%20state%20owned%20pharmaceutical%20manufacturing%20company%20sole%20the%20shortage%20of%20medicines%20I%20.pdf. Accessed: 29 Dec 2016.

77. Congress of South African Trade Unions. 2013. COSATU's comments on the presidential review committee's report on state owned entities. Available from: http://www.politicsweb.co.za/documents/prc-report-on-soes-cosatus-comment. Accessed: 25 Sep 2014.

78. Reiffen D, and Ward MR. Generic drug industry dynamics. *Rev Econ Stat*. 2005;87(1):37-49.

79. Frank RG, and Salkever DS. Generic entry and the pricing of pharmaceuticals. *Journal of Economics and Management Strategy*. 1997; 6(1): 75-90.

80. Evans JR. Statistics, data analysis, and modeling. Upper Saddle River: NJ 07458; 2014.

81. Department of Health. 2015. National health insurance for South Africa, towards universal health coverage. Version 40. Available online: https://www.health-e.org.za/wp-content/uploads/2015/12/National-Health-Insurance-for-South-Africa-White-Paper.pdf. Accessed: 09 Apr 2016.

82. Council for Medical Schemes. 2015. Annual Report 2015/2016. Available from: https://www.medicalschemes.com/files/Annual%20Reports/CMS%20Annual%20Report%202015-2016.pdf. Accessed: 09 Apr 2016.

83. Gray A, Matsebula T. Drug pricing in South Africa-policy and praxis. *Journal of Pharmaceutical Finance, Economics and Policy.* 2003;12(2):95-121.

84. Mossialos E, Mrazek M, and Walley T. (editors). Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. United Kingdom: Open University Press; 2004.

85. Pharasi B, Miot J. Medicines selection and procurement in South Africa. In: Padarath A, and English R (editors). South African Health Review 2012/13, Edition 2102/2013. Durban: Health Systems Trust; 2013. p. 177-185.

86. World Health Organization. 2001. How to develop and implement a national drug policy. Marketing and Dissemination, CH 1211 Geneva 27, Switzerland.

87. Van Norman GA. Drugs and devices: Comparison of European and U.S. approval processes. *JACC: Basic to Translational Science*. 2016 8;1(5):399-412.

88. Stiefel MC, Perla RJ, Zell BL. A healthy bottom line: healthy life expectancy as an outcome measure for health improvement efforts. *Milbank Quarterly*. 2010;88(1):30-53.

89. Bor J, Rosen S, Chimbindi N, Haber N, Herbst K, Mutevedzi T, Tanser F, Pillay D, and Bärnighausen T. Mass HIV treatment and sex disparities in life expectancy: demographic surveillance in rural South Africa. *PLOS MED*. 2015;12(11):1-21.

90. Madore A, Yousif H, Rosenberg J, Desmond C, Weintraub R. 2015. Political leadership in South Africa: HIV. (Teaching case prepared for the global health delivery

project, Harvard Medical School). Available online: http://repository.hsrc.ac.za/handle/20.500.11910/9400. Accessed: 13 Nov 2016.

91. Department of Trade and Industry. 2013. Industrial Policy Action Plan 2013/14 - 2015/16. Available online: http://www.thedti.gov.za/news2013/ipap_2013-2016.pdf. Accessed: 03 Aug 2016.

92. BMI Research, A Fitch Group Company. South Africa: pharmaceuticals and healthcare report. Report No. Q4 2016. London, United Kingdom; 2016.

93. Cullinan K. South Africa moves to `test and treat'. *The South African Health News Service*. 2016.

94. South Africa: The 2010/11 to 2012/13 Industrial Policy Action Plan (IPAP). *Africa Research Bulletin: Economic, Financial & Technical Series*. 2010;47(2):18610B-C.

95. South African Government News Agency. 2015. Shortage of medical supplies to be addressed [Internet] [cited 2017 03/30]. Available online: http://www.sanews.gov.za/south-africa/shortage-medical-supplies-be-addressed. Accessed: 06 Aug 2016.

96. Gray A, and Suleman F. Pharmaceutical pricing in South Africa. Pharmaceutical prices in the 21st century. New York: Springer Publishing Company; 2015. p.251-265.

97. Urban Earth. 2013. Nersa Allows Yearly 8% Electricity Price Increase for 2013-2018. Available from: http://www.urbanearth.co.za/articles/nersa-allows-yearly-8-electricity-price-increase-2013-2018. Accessed: 19 Jun 2015.

98. Samuel C. The dark side of foreign direct investment: a South African perspective. *South African Institute of International Affairs Occasional Paper*. (167)2013.

99. World Economic Forum. The global competitiveness report 2014-2015. World Economic Forum, Geneva: The Global Competitiveness and Benchmarking Network; 2014.

100. Ilangabe lase Afrika. 2011. Human Capital Outlook Implications for Skills Development in the Pharmaceutical Sector. Available online: http://www.lmip.org.za/sites/default/files/documentfiles//Pharmarceutical%20Study.pdf. Accessed: 25 Sep 2015.

101. Gouws J. South Africa's accession to PIC/S. *Pharmaceutical Technology*. 2009; 33(8): 61-62.

102. Statistics South Africa. 2014. Producer Price Index Methods, Sources and Theory. Accessed: 13 Nov 2016. Available online: http://www.statssa.gov.za/cpi/documents/PPI_Methods_sources_and_theory_V_1.2.pdf

103. Smith R, Blouin C, Mirza Z, Drager N, and Beyer P. 2015. Trade and health: towards building a national strategy. Available online: http://apps.who.int/iris/bitstream/10665/183934/1/9789241565035_eng.pdf. Accessed: 02 Oct 2015.

104. Ministry of Health and Ministry of Industry, Federal Democratic Republic of Ethiopia. 2015. National Strategy and Plan of Action for Pharmaceutical Manufacturing Development in Ethiopia (2015–2025). Available online: http://www.who.int/phi/publications/NatStrategyPlanActionPharmManufEthiopia2015-2025.pdf?ua=1. Accessed: 25 Sep 2015.

105. Department of Health, South Africa. 2010. Medicines Procurement Reform in the Public Sector. Available online: http://ipasa.co.za/Downloads/Policy%20and%20Reports%20-%20Medicines/procurement/Medicines%20Procurement%20Task%20Team%20Report-%20Final%2029%2004%202010.pdf. Accessed: 24 Sep 2016.

106. Wasserstein J, Karst K. New law reins in "authorized generics" despite generic industry court losses, but leaves several ambiguities. *RA Focus*. 2006:8-12.

107. Arnold J. United states authorised generics: the latest challenge to the hatch-waxman act. *Building and Enforcing Intellectual Property Value*. 2007: 107-110.

108. European Commission. 2001. Directive 2001/83/EC of the European Parliament and of the Council, (2001).

109. Hollis A. The anti-competitive effects of brand-controlled 'pseudo-generics' in the Canadian pharmaceutical market. *Canadian Public Policy*. 2003;29(1):21.

110. Löfgren H. Generic medicines in Australia: Business dynamics and recent policy reform. *Southern Med Review*. 2009;2(2):24-8.

111. World Health Organisation. The world health report 2000. health systems: improving performance. Geneva, Switzerland: World Health Organization; 2000.