Evaluating the impact of Single Exit Pricing (SEP) on medicine product withdrawal from the private health care market in South Africa.

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DECLARATION

In fulfilment of the requirements of the degree of Masters in Pharmacy in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Kasturie Naidoo declare that:

i. The research reported in this dissertation, except where referenced, is my original work.
ii. This dissertation has not been submitted for any degree or examination at any other university.
iii. This dissertation does not contain other person's data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
iv. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
    a. their words have been re-written but the general information attributed to them has been referenced:
    b. where their exact words have been used, their writing has been placed inside quotation marks, and referenced.
v. Where reference to a publication for which I am a principal author, I have referenced the "In Press" publication.

Student Signature_____

Date_____

I dedicate this dissertation to my mom, Mano Naidoo and my twin sister, Kamanie Moodley.

My mom has been a carer, teacher, inspiration and pillar of strength to me as I journeyed through various milestones and phases during my life. Her humble beginnings instilled in me a sense of grounding and realness in my roots. Her hard work to educate herself against all odds and become a teacher in languages inspired me to reach for my goals and dreams too. Her resilience in times of hardship and challenges gave me an unshakable sense of the strength a woman possesses. I have been woven into the tapestry of the woman I am today because of her consistent presence and unconditional love for me. I love you mom!

My twin sister Kamanie has always been a source of inspiration to me. She is a living example of a woman of grit and grace rolled up into a fierce ball of strength and also so much love. She spent many hours of conversations on the phone with me encouraging me to persevere through this paper. I am so grateful and I love you Kam.

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ACRONYMS AND ABBREVIATIONS

ATC – Anatomical Therapeutic Chemical Classification System

DHBs – District Health Boards

EU – European Union

GDP – Gross Domestic Product

MPC – Medicines Pricing Committee

NDOH – National Department of Health

NDP – National Drug Policy

OECD – Organisation for Economic Co-operation and Development

PBAC – Pharmaceutical Benefit Advisory Committee

PBS – Pharmaceutical Benefit Scheme

PHARMAC – Pharmaceutical Management Agency

PPP int - International dollars using purchasing power parity

RD – Royal Decrees

SEP – Single Exit Price

SKU – Stock Keeping Units

TGA – Therapeutic Goods Administration

VAT – Value added tax

WHO – World Health Organisation

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ABSTRACT / SUMMARY

Introduction

The introduction of medicine pricing policies in South Africa in the form of Single Exit Pricing (SEP), provided a mechanism to improve medicine price transparency and reduce both medicine price and inflation. However regulating medicine prices may have had further unforeseen effects on the availability of medicine. This research presents the impact of medicine price controls in the form of SEP on medicine product discontinuations from the private health care market in South Africa

Aim

The aim of this study is to evaluate the impact of SEP legislation on the availability of medicines in the private health sector market in South Africa, in terms of withdrawal of medicines from the market and rationale for withdrawal.

Methods

A descriptive, quantitative analysis of all registered medicines on the South African market by Stock Keeping Units (SKUs) to establish medicine products withdrawn from the market by SKU during a 14 year period from 2001 to 2014.

Results

A total number of 152 manufacturers discontinued 3691 SKUs between 2001 and 2014. The mean number of discontinuations per generic manufacturer was 22.34 (sd= 58.11), while innovator manufacturers discontinued a mean of 27.61 (sd= 41.89). The 2002 saw the largest number of SKUs being commercially withdrawn n=603,

followed by 2003 (n=463) and 2004 (n=407). There was a negative correlation between number of discontinued SKUs per year and SEP increase; with a Pearson's correlation coefficient (r) = -0.414 (p=0.14).

Discussion

Medicine pricing policies may have a dual impact in the market. Policies are typically aimed to make medicines more affordable to the patient; however pricing policies may have a negative effect on medicine availability. The results show that the SEP and transparent pricing policy may have had an impact on SKU withdrawal from the market. Lower prices and control of annual increases on medicines may have led to SKUs exiting the market.

Conclusion

The result of reduced product availability in the market and its impact to the cost and quality of healthcare to the patient needs to be regularly monitored and evaluated to ascertain if direct price regulations are achieving the intended outcomes as well as evaluate other intended or unintended effects in pharmaceutical market dynamics.

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CHAPTER I

INTRODUCTION

BACKGROUND

The 27th April 1994, was a historical day that began a democratic era for South Africans, with the first non-racial, democratic elections being held. The preceding decades of apartheid (translated into separate-ness) rule in South Africa, featured a notably fragmented health service, within both the public and private health sector (Coovadia , et al., 2009).

South Africa's apartheid era saw not only disparities in the public and private health sectors, but also racial, socio-economic, and rural-urban differentials in health outcomes (Harris, et al., 2011). In 1990, the private sector was responsible for 80% of South Africa's total medicine expenditure, but only accounted for 30-40% of the total medicine volumes (South African National Department of Health, 1996).

In 1994, the new democratically elected government, faced the the problems of disparities, lack of equity in access to essential medicines, rising medicine prices and cost-ineffective procurement and logistics practices (South African National Department of Health, 1996). The National Department of Health (NDOH) decided to tackle these problems systematically through the development and implementation of the National Drug Policy (NDP). The NDP would be consonant with and an integral part of the new National Health Policy, which was aimed at equity in the provision of health care for all (South African National Department of Health, 1996).

The economic objectives of the National Drug Policy were:

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- To lower the cost of medicines in both the private and public sectors;
- To promote the cost-effective and rational use of medicines;
- To establish a complementary partnership between government bodies and private providers in the pharmaceutical sector;
- To optimize the use of scarce resources through cooperation with international and regional agencies.

As part of these economic objectives the NDOH established the Medicine Pricing Committee (MPC). The committee was tasked with rationalizing the pricing structure in South Africa (South African National Department of Health, 2004). Their objectives were:

- To monitor and regulate medicine prices;
- To develop a transparent pricing structure;
- To develop a non-discriminatory pricing system;
- To replace wholesale and retail percentage mark-up system with a pricing system based on a fixed professional fee;
- To regulate medicine price increases.

The total transparency in pricing structure and non-discriminatory pricing system for medicines was legislated as “Regulations relating to a transparent pricing system for medicines and scheduled substances” (South African National Department of Health, 2004). This new regulation introduced Single Exit Pricing (SEP) to improve medicine price transparency and reduce both medicine price and inflation.

SEP was defined as “the ex-manufacturer price determined by the manufacturer or importer of a medicine or scheduled substance in terms of Regulation 22G of the Medicines and Related Substances Control Act 101 of 1965, combined with the

logistics fee and Value Added Tax (VAT) and is the price of the lowest unit of the medicine or scheduled substance within a pack multiplied by the number of units in the pack" (South African National Department of Health, 2004).

Medicine pricing policies, with the aim of regulating prices may have various effects on the availability of medicines. It may increase or decrease or have a negligible effect on availability of medicines to the patient. Pricing regulations may increase the vulnerability of the pharmaceutical market to medicine shortages. For example, the manufacturer of the medicine may decrease its price to a point where it is no longer financially sustainable to produce the medicine, causing those to disappear from the market (De Weerdt, et al., 2015).

In this study, commercial withdrawal is defined as:

1. The entire medicine brand is voluntarily withdrawn from the market by the manufacturer and no longer available.

2. One or more pack sizes/ Stock Keeping Units (SKUs) of a medicine are voluntarily withdrawn by the manufacturer, whilst one or more other pack sizes/ SKUs remain on the market.
   An SKU is defined as a product and service identification code for a store or product, often displayed as a machine-readable bar code that helps track the item for inventory.

PROBLEM STATEMENT

Subsequent to the legislation of Single Exit Pricing (SEP) in 2004, very little information has been published on the impact on availability of medicines in the private market in South Africa. Has there been an increase or decrease or negligible change to availability of medicines in the market? How has the rate and type of medicines withdrawal from the private market been influenced by the regulated pricing system?

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Pretorius (2011) looked at the impact of the implementation of single exit pricing for pharmaceuticals in South Africa, in terms of the impact on cost saving to the patient and how SEP affected the business of retail pharmacies. She found that a total reduction of 22 % of medicines prices was realised through the introduction of SEP in South Africa but also confirmed that a consistent pricing benefit was not realised by consumers. Further it was concluded in this paper that with a reduction in overall gross profit generated by pharmacies, the pressure in the business environment was evident (Pretorius, 2011).

Bangalee and Suleman (2015), evaluated the impact of the capped logistics fee on pharmaceuticals and found that there is a need for greater transparency of the mark ups along the distribution chain (Bangalee & Suleman , 2015). Gray (2009) looked at medicine pricing interventions, which gave an overview of the pricing controls that were implemented since the mandate was made via the NDP in 1996. He concludes the South African experience has demonstrated that clear legal drafting is a key element in the implementation of any intervention (Gray, 2009). Further Gray says that while (in 2009) there were still unimplemented elements of a transparent pricing system, he did see that it was possible to implement a traditional reference pricing system underpinned by rigorous pharmacoeconomic evaluation , given the engagement of all stakeholders in the medicines policy space (Gray, 2009).

PURPOSE OF THE RESEARCH

This research looks at the types and quantity of medicines that have been withdrawn from the market during the period of price regulation in South Africa. The medicines are sorted and anaylsed by ATC (Anatomical therapeutic chemical classification system) class, innovator and generic medicine. The outcome and recommendations of this research will be relevant to health care policy makers, the Medicines Pricing Committee and pharmaceutical companies in South Africa and other low and middle income countries looking to implement pricing policies for medicines.

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OVERALL AIM

The aim of this study is to evaluate the impact of SEP legislation on the availability of medicines in the private health sector market in South Africa, in terms of withdrawal of medicines from the market and rationale for withdrawal.

SPECIFIC OBJECTIVES

- To describe the change in availability, specifically with regard to withdrawal of medicines, in the private sector after the implementation of SEP, in terms of :
    - Originator and generic manufacturers
    - ATC classification

- To make recommendations with regard to further research or policy areas.

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CHAPTER II

LITERATURE REVIEW

Access to essential medicines is a fundamental human right (Vogler & Kilpatrick, 2015). The ultimate public health goal of pharmaceutical policy is to improve a population's health and wellbeing. This is best attained by low-priced medicines which consumers can afford. Publicly funded medicine benefit programs are also important in ensuring equitable access to medicines and the sustainability of such programs depends on the negotiation of affordable prices (World Health Organization, 2012).

According to the WHO HAI Project on Medicine Prices and Availability (Ball, 2011), a reliable mechanism for monitoring the prices and sales of medicines in the appropriate sector or market is essential to be able to judge the effects of pricing regulations, both intended and unintended. The report confirms that direct product price control is one of the oldest and still more widespread forms of pharmaceutical cost-containment and that this can be achieved through legislation, as in South Africa.

The WHO/HAI Project on Medicine Prices and Availability: Regulation of Mark-ups in the Pharmaceutical Supply Chain (Ball, 2011), included South Africa as one of its case study countries. This working paper found that a 5-year analysis of sales data had shown that sales of generic medicines (by volume) exceeded those of originator brands for the first time in 2007. This was stated to probably be a result of policies and laws promoting generic prescribing and substitution rather than pricing regulation. The working paper further noted that there was reportedly no difference between medicine prices in rural and urban areas, because of SEP implementation. The prices of medicines reduced by an average of 19% (25%-30% for generics and 12% for originator brands) (Ball, 2011).

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Naude and Luiz in 2013 cited that the respondents who participated in their survey, commented that price controls in South Africa have had the effect of reducing the profit margins on medicines that are sold locally (Naudé & Luiz, 2013). They further elaborate that this has resulted in increased pressure on suppliers to increase their economies of scale in order to reduce the cost per unit produced. Importantly they observe that some companies stop the production of certain products, as it no longer remains economically viable to produce them locally. In some cases, one of these local companies has also moved some of its manufacturing facilities to India in order to reduce costs and compete locally on price (Naudé & Luiz, 2013).

The principal aim of drug pricing policies is to keep medicines accessible, however the creation of lower priced markets for pharmaceuticals have led a lower level of new medicines introductions and the market withdrawal of some products (Birgli AG, 2013; De Weerdt, et al., 2015). An example of this was Greece, where 203 products were withdrawn from the market in 2012 for which 23 had no generic equivalent. According to De Weerdt et al, 2015, this was seen after the Greek market reduced medicine prices to reduce healthcare expenses, resulting in prices that were 20 % lower than other EU countries (De Weerdt, et al., 2015).

The decision to remove a medicine from the market is not taken lightly, as the impact of the commercial withdrawal of a medicine is far-reaching. In addition to the manufacturers and health authorities, health care professionals and most importantly patients are also affected (Clarke, et al., 2006). While there are ample data from high income countries on implementation and impact of medicine pricing policies, the data on the implementation and effects thereof in low and middle income countries is far less. This research aimed to discuss the possible impact of the implementation SEP on the availability of medicines in the private health sector.

The WHO Guidelines on country pharmaceutical pricing policies provides recommendations on the different modalities of pricing policies. The pharmaceutical policy interventions outlined are (World Health Organization, 2015):

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- Regulation of mark-ups in the pharmaceutical supply and distribution chain;
- Tax exemptions/reductions for pharmaceutical products;
- Application of cost-plus pricing formulae for pharmaceutical price setting;
- Use of external reference pricing;
- Promotion of use of generic medicines;
- Use of health technology assessment.

In an effort to improve access, medicine pricing policies and regulations are implemented in many countries the world over. Both developed and developing economies strive to improve patient access to essential medicines via differing levels of price control and healthcare policies. Countries can implement pharmaceutical price control by either allowing free pricing of medicines, where the pharmaceutical manufacturer may set a price freely; or apply medicine pricing regulations. These pricing regulations are guided by pricing methodologies and assessments (Vogler, 2012).

MEDICINE PRICING POLICIES IN THE EUROPEAN UNION (EU)

In European countries, prices of medicines that are reimbursed i.e paid by the public funder either in full or to a specific percentage, are regulated (Vogler & Kilpatrick, 2015). Prices are regulated by EU member states utilising a range of methods and tools to varying degrees (Vogler & Kilpatrick, 2015; Kanavos, et al., 2011). A notable feature of price control is the reimbursement status, where reimbursable medicines tend to be subject to price control and manufacturers of non-reimbursable medicines are allowed to set their own prices (Vogler, 2012).

External price referencing or international price comparison is commonly employed in many EU countries to set the prices of patented medicines (Vogler, 2012;

De Weerdt, et al., 2015). This pricing policy refers to the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country (Vogler & Zimmerman, 2013)

Some EU countries require generic medicines and 'follower products' to be priced at a prescribed percentage lower than the innovator medicine, a policy referred to as 'generic price linkage' (Vogler, 2012). Internal reference pricing is another frequently used methodology to set prices of these generic medicines. This methodology uses prices of medicines in the same ATC5 level (identical molecule) or same ATC4 level (similar medicines) or with a therapeutically equivalent treatment in a country. This comparison is done to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement of the product in a given country (Vogler & Zimmerman, 2013).

Countries such as Denmark and Germany use a free pricing policy, that allows pharmaceutical companies to determine prices of their own medicines (Vogler & Zimmerman, 2013; De Weerdt, et al., 2015). However, both countries exercise indirect price control on medicines. This indirect price control is specifically used to control the prices of medicines that are reimbursed via each country's reimbursement policies (De Weerdt, et al., 2015).

Poland addressed medicine pricing policy in May 2011, when they rationalized their reimbursement policy, to reduce spending by their National Health Fund. This Reimbursement Act introduced fixed medicine prices, as well as fixed wholesale and retail margins on medicines (Kawalec, et al., 2016). The adoption of this act, led to the price of generic and innovator medicines being 43% and 59%, respectively, lower than other EU countries (Birgli AG, 2013)

Impact of pharmaceutical pricing policies on medicine availability in the EU

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The number of new products introduced to the market decreased in lower priced markets. In some markets these products were delisted completely. For example in Greece, 203 products were withdrawn from the market in 2012 for which 25 had no generic equivalent (Birgli AG, 2013).

In countries where generics had inflexible pricing and innovative medicines have a steep downward price pressure, it becomes important for manufacturers to streamline production and supply chain to reduce stock on hand inventories and cost. A decrease in inventories and flexibility of the supply chain increases its susceptibility to any sudden variance in the market (Birgli AG, 2013).

In Poland the annual savings achieved since the implementation of the Reimbursement Act made it possible to include new medicines into the reimbursement list of the funder and improve access to innovator medicines. At the same time, the decrease in prices of reimbursed medicines that the Act also regulated, led to an uncontrolled outflow of some of these medicines abroad and shortages in Poland (Birgli AG, 2013).

There is much published literature of EU medicine pricing policies successfully reducing the cost of medicines for both health funders and patients. On the other hand, these pricing policies led to unforeseen factors such as parallel export of medicines from lower priced markets, stricter supply chain with regard to keeping smaller inventories and reducing costs and some manufacturers removing medicines or not introducing them to lower priced markets also led to medicine shortages (Birgli AG, 2013; De Weerdt, et al., 2015).

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MEDICINE PRICING POLICIES IN REFERENCE COUNTRIES

During the development of the transparent pricing system in South Africa which is implemented and the international benchmarking methodology, which is currently being considered, the National Department of Health (NDoH) referenced four countries: Australia, New Zealand, Canada and Spain as benchmark country comparators along with South Africa (Urbach, 2015).

MEDICINE PRICING POLICY IN NEW ZEALAND

New Zealand is classified as a high income country by the World Bank. The country has a per capita total expenditure on health (PPP int. $) of 2655 and a population of 4,26 million. The expenditure on health is 9,7 % of the GDP (World Health Organization, 2012).

Funding of medicines is determined by the Pharmaceutical Management Agency of New Zealand (PHARMAC) and District Health Boards (DHBs). PHARMAC determines which Community Pharmaceuticals should be subsidised and to what level. "Community Pharmaceuticals" are defined as 'Pharmaceuticals listed in Sections A to G of the Pharmaceutical Schedule that are subsidised by the Funder from the Pharmaceutical Budget for use in the community' (Foster , et al., 2011).

New Zealand allows medicine prices to be determined by negotiation (Ragupathy, et al., 2015). Each year, the Community Pharmaceutical budget is agreed between the DHBs and PHARMAC, and then set by the Minister of Health. PHARMAC works on behalf of the DHBs to negotiate pharmaceutical prices and manage spending on community medicines from the Community Pharmaceutical Budget (Foster , et al., 2011).

PHARMAC negotiates supply agreements but does not directly purchase, stock or distribute pharmaceuticals. PHARMAC is able to negotiate substantial discounts

from pharmaceutical companies (Foster , et al., 2011). Further to this manufacturers of generic medicines compete on price by tender to have sole supply status for the medicine. Medicines procured via the tender system account for half the total volume of subsidised medicines in New Zealand (Foster , et al., 2011).

PHARMAC also practices internal reference pricing, where the same subsidy is paid for pharmaceuticals that have the same or similar therapeutic effect (e.g. oral contraceptives, statins). A pharmaceutical company can choose to price a particular medicine higher than this, but the product will be only partly subsidised to the level of the reference price, with the consumer paying the remaining amount. These tendering and negotiating strategies creates savings of more than $300 million per year (Foster , et al., 2011).

Therefore, albeit prices for medicines that are funded are negotiated with manufacturers, the final manufacturer price to the pharmacy and the percentage markup added by the pharmacy is not regulated by a legislated medicine pricing policy. The difference in the price is borne by the patient. As a result, New Zealanders have universal and nationally consistent pharmaceutical coverage, with lower patient pharmaceutical co-payments than many comparable countries (Ragupathy, et al., 2015).

The impact of these strategies have been very controversial due to the lower number of new medicines being available in New Zealand compared to other countries. For example in the period 2000-2009 the New Zealand patient population had access to less than half of the new medicines reimbursed by Australia. Furthermore in New Zealand, the new medicines registration process occurred on average 9 months later and listing occurred 32,7 months later, giving a 23,7 months difference in the interval between registration and listing (Koçkaya & Wertheimer, 2018). However, there is a dearth of research on whether or not the lack of access to some innovative medicines in New Zealand, or changing patients to different medicines brands, adversely affects patient outcomes (Babar, 2015).

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The New Zealand pharmaceutical market is dominated by its public health system and the public funding system may be attractive for the pharmaceutical industry. New Zealand has a relatively small population with low purchasing power, so a single purchasing organisation is considered the best option to protect the healthcare interests of the New Zealand consumer (Koçkaya & Wertheimer, 2018).

MEDICINE PRICING POLICY IN AUSTRALIA

Australia is classified as a high income country by the World Bank. The country has a per capita total expenditure on health (PPP int. $) of 3365 and a population of 21,29 million. The expenditure on health is 10,5 % of the GDP (World Health Organization, 2012).

All prescription medicines approved by the Therapeutic Goods Administration (TGA) can be sold (on prescription) in Australia; however, most prescription medicines in Australia are supplied through the Pharmaceutical Benefits Scheme (PBS) which is subsidised by the Australian Government. Medicinces available via the PBS allows Australian patients access to medicines for a low standardised patient co-payment (Australian Government Department of Health, 2017). Once a medicine has received TGA approval, its sponsor (the manufacturer or supplier of the medicine) may seek to list their medicine on the PBS (Australian Government Department of Health, 2017).

To be listed on the PBS a medicine must receive a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) which is an independent expert body established under the National Health Act 1953. The PBAC assesses a sponsor's clinical evidence to determine the need for the medicine, the efficacy of the treatment against alternatives and the cost effectiveness of the medicine compared against alternative treatment (Australian Government Department of Health, 2017).

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The PBS lists medicines available to be dispensed to patients at a government subsidised price. The scheme is available to all Australian residents who hold a Medicare card as well as overseas visitors from countries with which Australia has a reciprocal health care agreement. A flat-fee patient co-payment exists within the Australian system, with adults currently paying AU$37.70 (US$29.39) and concession cardholders AU$6.10 (US$4.76) per prescription (Cook & Kim, 2015).

Price negotiations with the responsible manufacturer for new or changed listings are undertaken by the Pricing Section on behalf of the Minister, following a positive PBAC recommendation. A Cost Information (PB11b) form is required to be submitted by the responsible person as part of the initial application to the PBAC (Australian Government Department of Health, 2017). After a price has been negotiated, the responsible person is requested to submit a Request for Approved Ex-manufacturer Price (PB11a) form in order to formalise the price offer (Australian Government Department of Health, 2017).

Pricing methods used in Autralia include :

1. Cost plus method:

A gross margin may be granted based on the cost of manufacture. This margin can vary and is determined on a case by case basis. A margin on costs of around 30% is usually considered reasonable for new medicine listings, but higher margins may be recommended for low volume products and lower ones may be recommended for high volume products (Australian Government Department of Health, 2017).

2. Reference pricing:

Reference pricing is a Government pricing policy which applies where medicines considered to be of similar safety and efficacy for pricing purposes are linked, and recommended by the PBAC as cost-minimised. The lowest priced brand or

medicine sets a benchmark price for either the other brands of that medicine or the other medicines within the same sub-group of therapeutically related medicines (Australian Government Department of Health, 2017).

3. Weighted Pricing

For a small number of medicines with multiple indications, each indication may have an indication-specific price which relates to its cost-effectiveness for the eligible patient population. The indication-specific price is usually different (i.e. higher or lower) from the published price. In this case, it is usual practice to employ a weighted pricing methodology to fulfil the requirements of the National Health Act 1953 to have a single published list price per pharmaceutical item. This generally involves applying a weighting to each indication-specific price and then adding these prices together in order to arrive at a single weighted price (Australian Government Department of Health, 2017).

Overall, these policies have been effective in decreasing medicines prices and pharmaceutical expenditure. However, there are still higher prices of generic medicines compared to some countries such as New Zealand and the United Kingdom. The high prices for new medicines requested by the pharmaceutical industry may now represent the most pressing challenge faced by the Australian PBS and will require further development of pricing agreements (Vitry, et al., 2015).

Despite recent cost containment policies aimed at keeping low the cost of medicines in the PBS schedule, there is growing evidence that many Australian patients are struggling to afford their prescribed medicines. Australian patients have faced increased prescription medicine costs over the recent years and the expenditure on the part of patients is in the mid to upper range when compared to other comparable countries (Koçkaya & Wertheimer, 2018).

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MEDICINE PRICING POLICY IN CANADA

Canada is classified as a high income country by the World Bank. The country has a per capita total expenditure on health (PPP int. $) of 3867 and a population of 33,5 million. The expenditure on health is 9,8 % of the GDP (World Health Organization, 2012).

Medicine pricing in Canada is a divided responsibility between the federal and provincial government. The price of patented medicines is largely controlled at federal level through the Patented Medicine Prices Review Board that sets a maximum introductory price for new medicines and then limits the rate of rise (allowable increase) of those prices to the rate of inflation (Lexchin, 2015).

Generic medicine prices, on the other hand, are solely the responsibility of the provinces and territories that set the prices for these products at a certain percentage of the price of the originator product (Lexchin, 2015). Public Medicine plans set the price that they will pay for generic products by capping the formulary price at a percentage of the brand name price and specifying a maximum reimbursable cost for a medicine or group of interchangeable medicines (Lexchin, 2015).

Although superficially it would seem that Canada has been successful at controlling the price of patented medicines, a deeper examination and per capita expenditures shows that the mechanism that is used is deeply flawed and leads to Canadian prices being among the highest of all the OECD countries. Generic prices remain much higher than those of New Zealand (Lexchin, 2015).

In Canada, as well as elsewhere high medicine prices are an emotional, volatile and political issue. Solutions to this are yet to be found and could pose a hurdle to market access. Canada has a complex health system with variances from Province to Province (and Territory to Territory). These variances could possibly create barriers to market access as well (Koçkaya & Wertheimer, 2018).

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MEDICINE PRICING POLICY IN SPAIN

Spain is classified as a high income country by the World Bank. The country has a per capita total expenditure on health (PPP int. $) of 2941 with a population of 44,9 million. The expenditure on health is 7,2 % of the GDP (World Health Organization, 2012).

The start of the process of reform that led to the present Spanish health care system can be traced back to the approval of the General Health Law in 1986. The focus of the reform was the transition from a social security based system to a National Health Service (NHS), with universal coverage and financed from general taxation (Rovira & Darbà, 2001).

For pharmaceuticals, patients pay 40 % of the price of medicines prescribed by NHS doctors, with the exception of those aged over 65 and some specific groups of patients. A 10% co-payment is applied, with a maximum amount stipulated, when NHS doctors prescribe medicines to consumers identified as chronic patients. Negative lists have excluded some pharmaceuticals from public funding. The patient pays for these medicines in full. The Spanish Government used this policy for the first time in 1993 and then again in 1998 to control public pharmaceutical expenditure. These two negative lists led to the removal from public funding of 29% of the total medicines registered on the market during the said period (Puig-Junoy, 2004).

The Spanish government regulated medicine price by control over:

- The manufactures price on medicine at point of market entry and any subsequent increase;
- The wholesalers gross margin;
- The pharmacists gross margin

The Interministerial Drug Pricing Commission authorises the initial prices for medicines entitled to public reimbursement. This authorisation sets the maximum price of a medicine and any further increase is also subject to approval (Rovira & Darbà,

2001). Various Royal Decrees(RD) have also been implemented in Spain over the years such as RD4/2010 which enabled the reference price system which saw a decrease in medicine prices as well as the volume of sales. This was followed by RD.8/2010 and RD.9/2011 which provided for price reductions to medicines by a fixed percentage. In 2012, RD.16/2012 introduced a co-payment system for individuals covered by the Spanish National Health System in an effort to reduce excessive use of medication (Birgli AG, 2013).

In the Birgli AG (2013) study examing medicine shortages in Europe, the highest weighted reason for medicine shortages on the Spanish market was surveyed to be prices and regulation. There were no clear and general shortages of medicines in Spain although cases of irregular supply due to payment problems in some areas did exist (Birgli AG, 2013).

MEDICINE PRICING POLICY IN SOUTH AFRICA

South Africa is classified as a upper middle income country by the World Bank. The country has a per capita total expenditure on health (PPP int. $) of 843 and a population of 50,1 million. The expenditure on health is 8,2 % of the GDP (World Health Organization, 2012).

In December 1997 the South African government promulgated the Medicines and Related Substances Control Act Amendment Act No. 90 of 1997. Parts of this legislation was aimed, through various mechanisms, at lowering the cost of drugs to all South Africans. This amendement included the insertion of Section 22G into the Medicinces and Related Substances Act 101 of 1965. Section 22G made provision for the establishment of a Pricing Committee and the introduction of transparent pricing as follows (Republic of South Africa, 1997):

1) The Minister shall appoint such persons as he or she may deem fit to be members of a committee to be known as the pricing committee.

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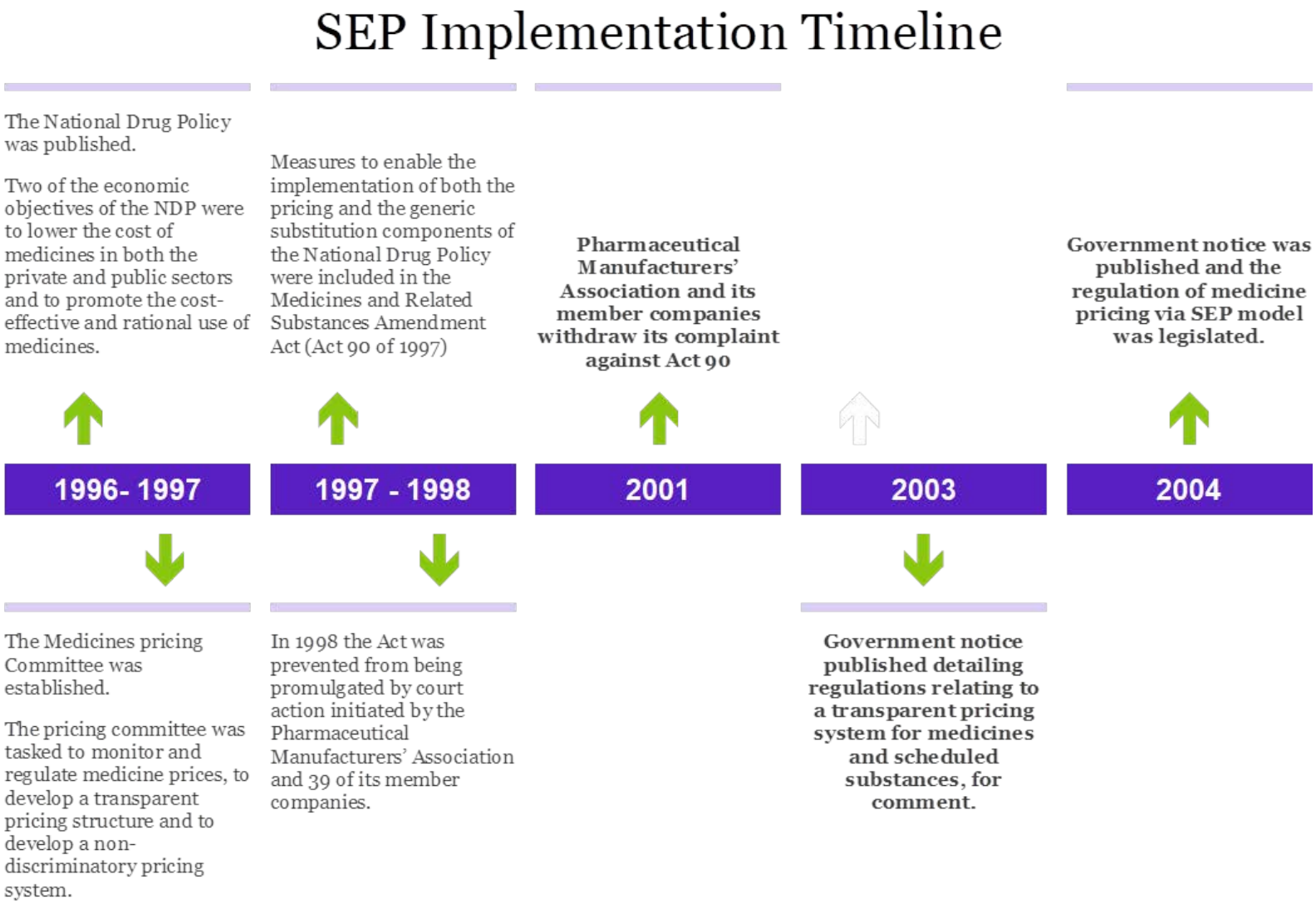
2) The Minister may, on the recommendation of the Pricing Committee make regulations
    a. on the introduction of a transparent pricing system for all medicines and scheduled substances sold in the Republic;
    b. on an appropriate dispensing fee to be charged by a pharmacist or person licensed in terms of Section 22 C (1) (a).
3) The transparent pricing system contemplated in sub-section (2) (a) shall include a single exit price which shall be the only price at which manufacturers shall sell medicines and scheduled substances to any person other than the state.

Figure 1 SEP Implementation Timeline



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The Medicine Pricing Committee was consequently appointed as an action of this amendment Act (Republic of South Africa, 1997) and this committee served to inform pricing policy. In 2004, after years of delay, "Regulations relating to a transparent pricing system for medicines and scheduled substances" was promulgated. These regulations introduced a system for a transparent medicine pricing structure and non-discriminatory pricing for medicines (South African National Department of Health, 2004)(see figure 1).

This new regulation presented Single Exit Pricing (SEP) as a mechanism to improve medicine price transparency and reduce both medicine price and inflation. The regulation defined SEP as "the manufacturer price, as determined by the manufacturer or importer of a medicine or scheduled substance combined with the logistics fee and VAT (Value Added Tax)" (South African National Department of Health, 2004). The overall aims of SEP was to improve access to medicines by reducing prices of both innovator and generic medicines and controlling medicine entry pricing and price increases and thereby improve access to medicines

The impact of medicine price controls have been extensively described in developed markets with well developed universal health coverage systems. Most EU countries, as well as South Africa's reference countries have developed national health insurance schemes and excercise price control on predominately reimbursed medicines (Vogler, 2012; Vogler & Kilpatrick, 2015; Babar, 2015).

There is little from the developing world, with similar health care systems to South Africa where a significant portion of patients are without health care insurance and with considerable out-of-pocket expenditure on medicines(Ngozwana, 2016). This is further compounded by uniqueness of direct price control practiced in South Africa, where all medicines prices (whether reimbursed or not), are controlled.

Pretorius (2011) looked at the impact of the implementation of single exit pricing for pharmaceuticals in South Africa, in terms of the impact on cost saving to the patient and how SEP affected the business of retail pharmacies. She found that a total

reduction of 22 % of medicines prices was realised through the introduction of SEP in South Africa but also confirmed that a consistent pricing benefit was not realised by consumers. Further it was concluded in this paper that with a reduction in overall gross profit generated by pharmacies, the pressure in the business environment was evident (Pretorius, 2011).

Bangalee and Suleman (2015), evaluated the impact of the capped logistics fee on pharmaceuticals and found that there is a need for greater transparency of the mark ups along the distribution chain (Bangalee & Suleman , 2015). Gray (2009) looked at medicine pricing interventions, which gave an overview of the pricing controls that were implemented since the mandate was made via the NDP in 1996. He concludes the South African experience has demonstrated that clear legal drafting is a key element in the implementation of any intervention (Gray, 2009). Further Gray says that while (in 2009) there were still unimplemented elements of a transparent pricing system, he did see that it was possible to implement a traditional reference pricing system underpinned by rigorous pharmacoeconomic evaluation , given the engagement of all stakeholders in the medicines policy space (Gray, 2009).

Further important questions that were not addressed are: How has SEP impacted the availability of medicines in the private sector? Has the pricing legislation impacted the viability of medicines on the market, such that they were discontinued? It has been 15 years since the legislation of SEP and transparent pricing process and there is a dearth of research that has been carried out to look into these questions so far.

This research addresses the need for a pre and post analysis of medicine discontinuation from the market relative to SEP implementation in 2004. When a pricing model for medicines is changed from a free market system to a regulated one, mandated by pricing regulation, it is also very important for policy makers to look at retrospective analysis of the impact of such regulation with regard to fair competition, innovation and the availability of medicines to the patient.

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CHAPTER III

METHODS

This chapter will cover the study methodology that was used to collect the data, the data source, study sample, selection and sampling time frame. It also details the type of study analysis that was employed to sort the dataset.

STUDY DESIGN

This study uses a quantitative analysis of the dataset.

TARGET POPULATION AND STUDY SAMPLE

Target Population

The targeted dataset for this study would comprise of all registered medicines on the South African market by Stock Keeping Units (SKUs).

Selection of study population

A comprehensive list of all registered medicines on the South African market by Stock Keeping Units (SKUs) was obtained from a medical data base managed by MEDPRAX. MEDPRAX are medical data specialists, who supply essential, up to date, medicine price data South African healthcare industry.

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The dataset consisted of all medicines by SKU, scheduled 1 to 8, on the private market, over the time period 2001 to 2014. The list only contains medicines that were marketed at a time point within the period described.

Study Sample

The study sample for the time period 2001 to 2014 included:

- List of medicines by SKU that was active (marketed) during the time period;
- List of medicines by SKU that was discontinued during the time period;
- All medicines by SKU was described with tradename, scheduling status, ATC code, Category, date of activity, and name of manufacturer.

Sampling frame

The time period selected for the study was from 2001 to 2014. This period was starts two years prior to the first government gazette on SEP being published in 2003, a period where pharmaceutical manufacturers had withdrawn their court action to prevent medicine price control in 2001. It was at this point the pharmaceutical industry became more cognisant of medicine price control and began effecting strategies to deal with is implementation. SEP was promulgated in 2004, and its impact was then followed for a 10 year period ending in 2014.

STATISTICAL ANALYSIS

Data was entered into Microsoft EXCEL, version 2016 in a format developed for this study. The data was analysed and summarised descriptively using frequency tables and graphs. Discontinued SKU's* was then grouped by innovator and generic companies and further by ATC** classification and summarised descriptively using

frequency tables and graphs. All statistical procedures were performed on MS Excel™ running under Microsoft Windows on a personal computer.

* An SKU is a stock keeping unit (SKU) for a product and service identification code for a store or product, often portrayed as a machine-readable bar code that helps track the item for inventory. A stock keeping unit (SKU) does not need to be assigned to physical products in inventory. Different pack sizes of a product are defined by separate SKU codes.

** ATC: Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of active ingredients of medicines according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

ETHICS

The study was granted ethical clearance by the University of KwaZulu-Natal Human and Social Sciences Research Ethics Committee (HSS/0154/013).

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CHAPTER IV

RESULTS

The total number of manufacturers identified in this study was 152. This number included all manufacturers who had at least one SKU discontinued between 2001 and 2014. The majority of the manufacturers identified, produced exclusively generic medicine (n= 96; 63.16 %), and have been classified as generic manufacturers. Manufacturers producing patent medicines accounted for 36.84% (n=56), and were classified as innovator manufacturers (see Table 1).

Table 1 Number of manufacturers identified between 2001 and 2014

Manufacturer	***n***	***%***
Generic	96	63.16
Innovator	56	36.84
Total	152	100.00

The number of SKUs discontinued during the study period was 3691. Innovator manufacturer discontinuations accounted for 41.89 % (n=1546), of all SKU discontinued, with generic manufacturers being responsible for 58.11 % (n=2145) discontinuations (see Table 2).

Table 2 Number of SKUs discontinued by designated manufacturer

Manufacturer	***n***	***%***

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Generic	2145	58.11
Innovator	1546	41.89
Total	3691	100.00

The mean number of discontinuations per generic manufacturer was 22.34 (sd = 58.11), while innovator manufacturers discontinued a mean of 27.61 (sd= 41.89). The t-test showed that there was no statistically significant difference between the means (t= -0061; p= 0.27) (see Table 3)

Table 3 Mean number of SKUs discontinued by designated manufacturer

Manufacturer	***n***	***Mean***	***sd****
Generic	96	22.34	58.11
Innovator	56	27.61	41.89
Combined	152	24.28	55.55

*sd denotes standard deviation

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GENERIC MANUFACTURERS

Ten generic manufacturers (see Table 4) were responsible for 67.41 % (n=1446) of SKUs discontinued by generic manufacturers over the study period. Aspen Pharmacare and Sandoz accounted for the majority of generic discontinuations of 26.76 % and 12.45 % respectively.

Table 4 Number of SKUs discontinued by generic manufacturers (top 10)

Manufacturer	***n***	***%***
Aspen Pharmacare	574	26.76
Sandoz	267	12.45
Adock Ingram Ltd.	176	8.21
Mylan	120	5.59
Ranbaxy SA	71	3.31
Cipla-Medpro Pharmaceuticals	70	3.26
Thebe Medicare	48	2.24
Zydus Cadila	41	1.91
Pharmachemie	40	1.86
Be-Tabs Pharmaceuticals	39	1.82
Other (n=86)	699	32.59
Total	2145	100.00

The number of SKUs discontinued yearly by the ten generic manufacturers identified in table 4, is shown in Figure 2. These 10 generic manufacturers, collectively discontinued 1446 SKUs in the 14 year period. The most discontinuations occurred in the years 2002 (n=190), 2004 (n=166) and 2007 (n=196).

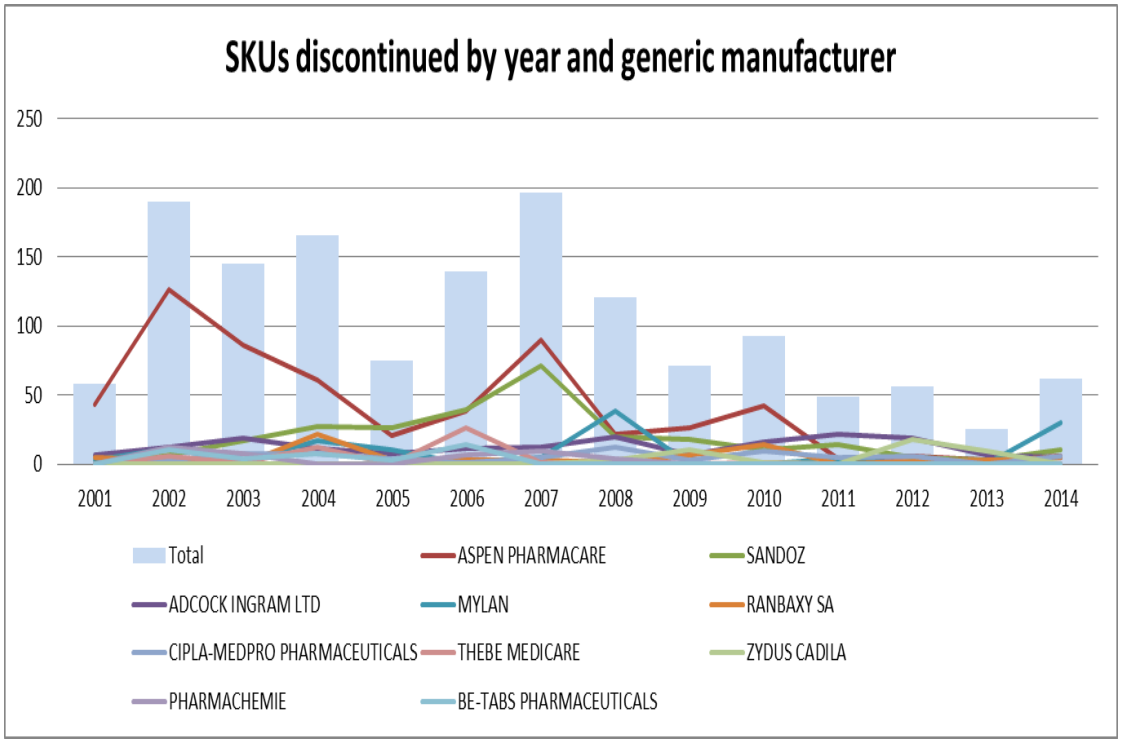

Figure 2 Graph of SKUs discontinued by year and generic manufacturer

INNOVATOR MANUFACTURERS

Ten innovator manufacturers (see Table 5) were responsible for 63.32 % (n=979) of SKUs discontinued by innovator manufacturers over the study period. MSD (Merck, Sharp & Dohme) and Sanofi Aventis accounted for the majority of innovator discontinuations with 12.03 % and 10.09 % respectively.

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Table 5 Number of SKUs discontinued by innovator manufacturers (top 10)

Manufacturer	***n***	***%***
MSD	186	12,03
Sanofi Aventis	156	10,09
Novartis	109	7,05
Pfizer Laboratories	108	6,99
Roche Products	83	5,37
Abbottt Laboratories SA	73	4,72
Glaxo Smithkline	73	4,72
Janssen Pharmaceuticals	65	4,20
Wyeth SA (Pty) Ltd	64	4,14
Astrazeneca	62	4,01
Other (n=46)	567	36,68
Total	**1546**	**100.00**

The number of SKUs discontinued yearly by the ten innovator manufacturers identified in table 5, is shown in Figure 3. These innovator manufacturers, discontinued a total of 979 SKUs in the 14 year period. The most discontinuations occurred in the years 2002 (n=148); 2003 (n=156) and 2004 (n=123).

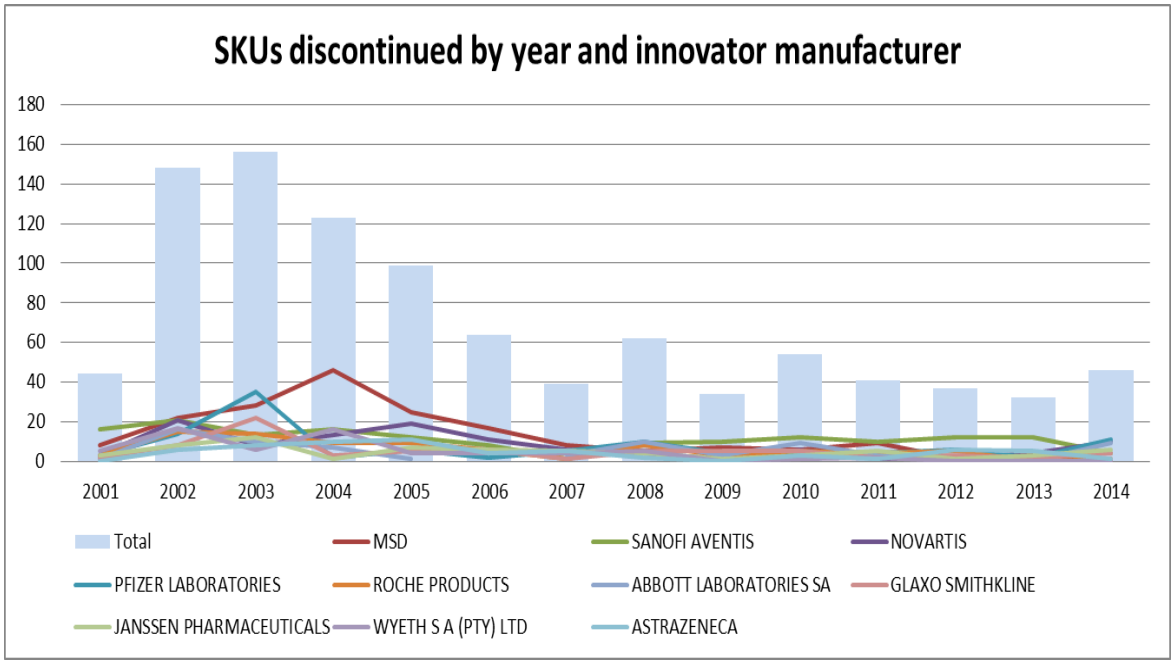

Figure 3 Graph of SKUs discontinued by year and innovator manufacturer

DISCONTINUATIONS BY DRUG CLASSIFICATION

1. Anatomical Therapeutic Chemical (ATC) Classification

The total SKUs that were discontinued (n=3691), were sorted into the Anatomical Therapeutic Chemical (ATC) Classification System (see table 6). Anti-infectives accounted for the highest number of discontinuations with 22.97 % of the total (n= 848)

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Table 6 Discontinued SKUs sorted by ATC classification system

ATC Classification	*n*	*%*
Anti-infectives for systemic use	848	22.97
Nervous system	578	15.66
Respiratory system	490	13.28
Cardiovascular system	368	9.97
Alimentary tract and metabolism	326	8.83
Musculo-skeletal system	261	7.07
Antineoplastic and immunomodulating agents	156	4.23
Dermatologicals	138	3.74
Genito-urinary system and sex hormones	123	3.33
Various	107	2.90
Sensory organs	89	2.41
Systemic hormonal preparations, excluding sex hormones and insulins	75	2.03
Blood and blood forming organs	67	1.82
Antiparasitic products, insecticides and repellents	65	1.76
Total	**3691**	**100.00**

The majority (70,71%) of SKUs discontinued fell into 5 ATC classes namely: anti-infectives for systemic use; nervous system; respiratory system; cardiovascular system and alimentary tract and metabolism medicines (see table 6). A total of 2610 discontinued SKUs fell into these classes, with the years 2002 (n=406); 2003 (n=324) and 2004 (n=309) experiencing the highest number of SKU discontinuations (see figure 4)

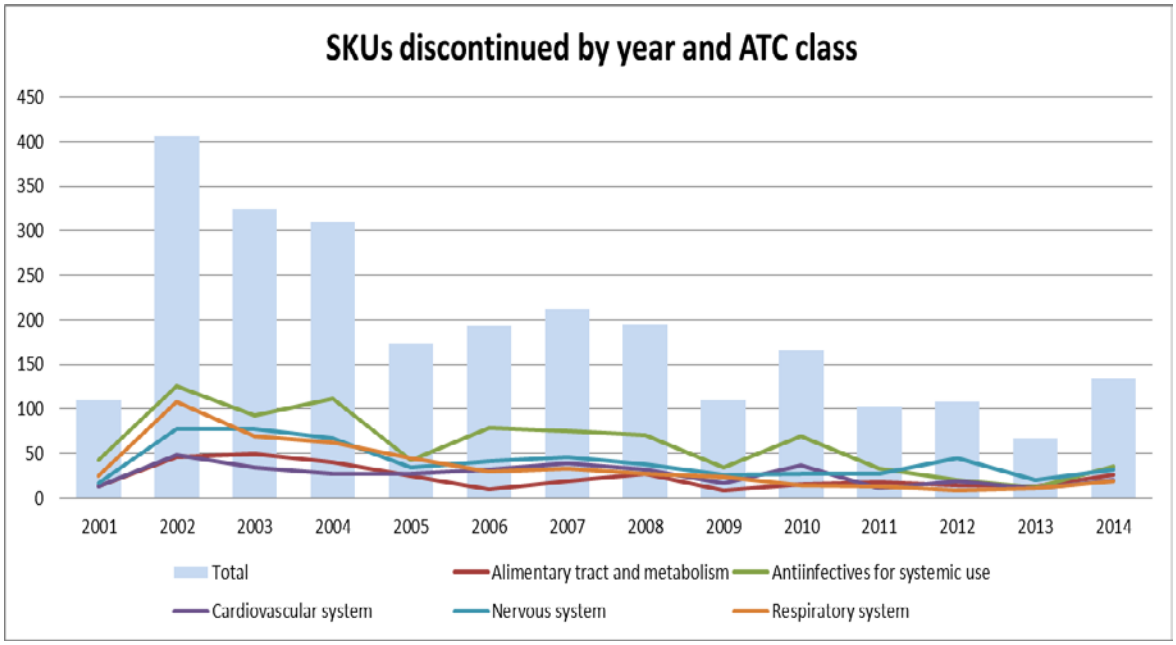

Figure 4 Graph of SKUs discontinued by year and ATC class

2. Drug Therapeutic Class

Anti-Infectives

Medicine SKUs that fell into the Anti-infectives for systemic use class, accounted for the largest number of discontinued SKUs. Generic manufacturers discontinued a consistently higher number of SKUs in this class throughout the period from 2001 to 2014 (see figure 5). The highest number of generic anti-infectives SKUs were discontinued occurred in the years 2002 (n=68); 2004 (n=79) and 2007 (n=47). The highest number of innovator anti-infectives SKUs that were discontinued occurred in 2002 (n=23) and 2003 (n=31).

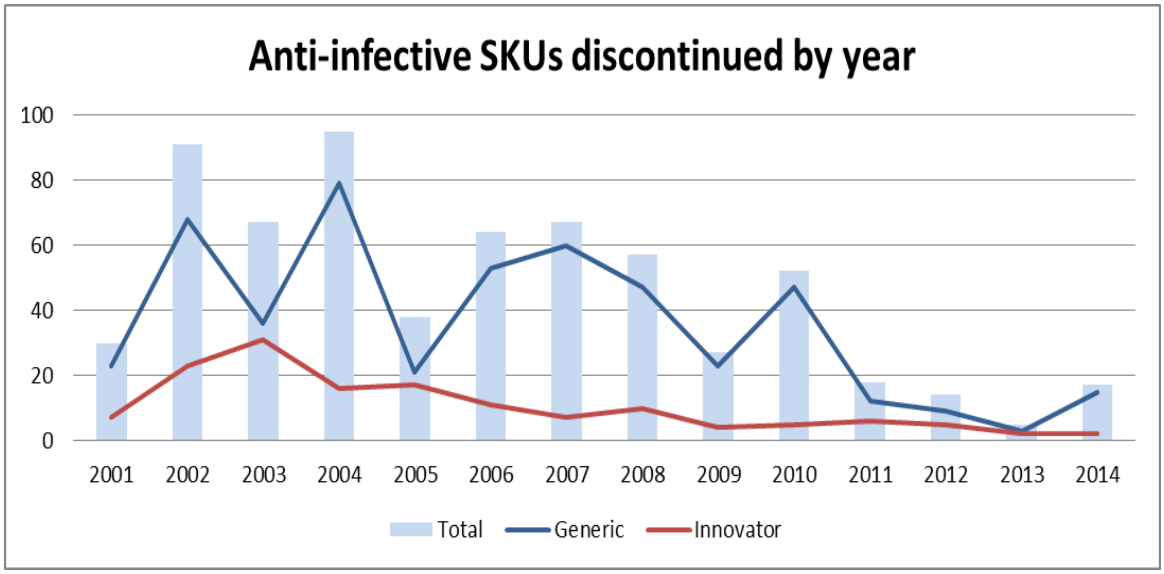

Figure 5 Graph of Anti-infective SKUs discontinued by year

The anti-infectives that were discontinued during the period 2001 to 2014 comprised of Penicillins, Cephalosporins, Sulphonamides and a few others as detailed in table 7 below. Penicillins made up the largest proportion of anti-infectives that were discontinued and comprised 31.93 % (n=205) of the ATC class.

Table 7 Anti-infectives SKUs discontinued listed by drug class

Drug Class	***n***	***%***
Penicillin	205	24.17
Cephalosporin	167	19.69
Sulphonamide	61	7.19
Tetracycline	52	6.13
Macrolide	50	5.90
Quinolone	42	4.95
Aminoglycoside	32	3.77
Other	239	28.18
Total	**848**	**100.00**

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Antiretrovirals

Antiretrovirals (ARVs) that treat HIV infections, which is one of the top four burdens of disease in South Africa, were sorted by generic and innovator manufacturers. The highest number of discontinuations was seen in 2011 for both types of manufacturers (see figure 6).

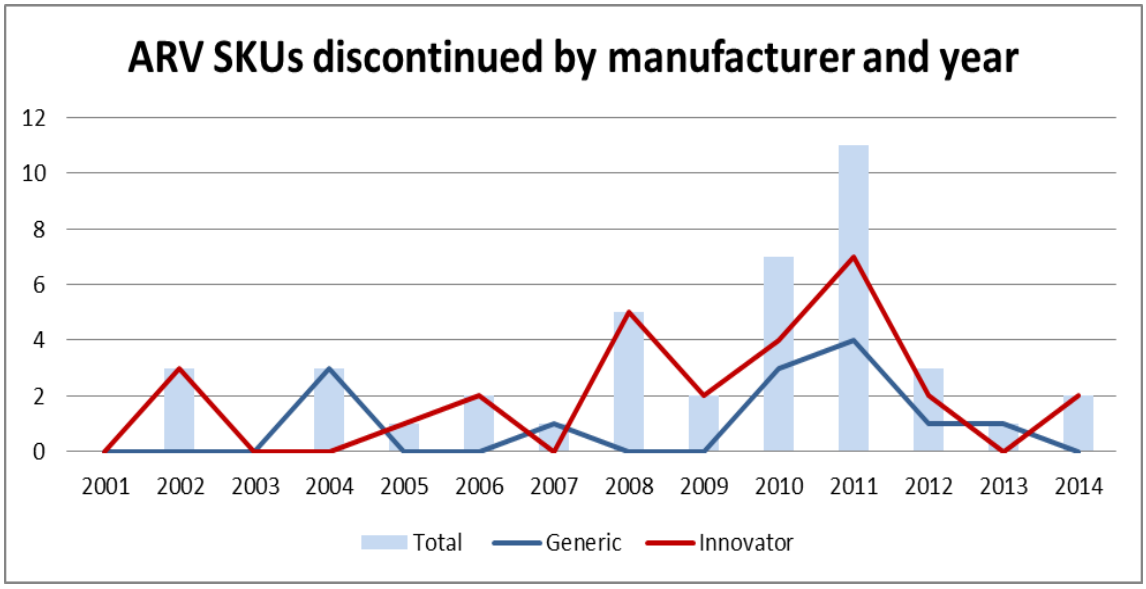

Figure 6 ARV SKUs discontinued by manufacturer and year

When looking at the total number of ARV's that were discontinued, the list is further elaborated with respect to the products that contained 1 active ingredient or a combination of 2 or more active ingredients (see Table 8 and 9). It is evident that of the total n= 41 SKUs that were discontinued, only 7 products were made up of a combination of active ingredients.

Table 8 ARV SKUs discontinued by active ingredient

Active Ingredients	*n*	*%*
Stavudine	9	21.95
Didanosine	6	14.63
Indinavir	3	7.32
Lopinavir/Ritonavir	3	7.32
Nelfinavir	3	7.32
Zalcitabine	3	7.32
Zidovudine	3	7.32
Lamivudine/Zidovudine	2	4.88
Ritonavir	2	4.88
Darunavir	1	2.44
Efavirenz	1	2.44
Lamivudine	1	2.44
Lamivudine/Stavudine/Nevirapine	1	2.44
Lamivudine/Zidovudine/Nevirapine	1	2.44
Nevirapine	1	2.44
Saquinavir	1	2.44
Total	**41**	**100**

Table 9 ARV SKUs discontinued by Single or Combination Product

Product	*n*	*%*
Single Ingredient	34	82.93
Combination Ingredients	7	17.07
Total	**41**	**100**

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Cardiovascular Medicines

Cardiovascular disease presents a high burden of non-communicable disease in South Africa. Cardiac medicines that were discontinued by SKUs were sorted by generic and innovator manufacturers. (see Figure 7). The highest number of discontinuations is evident in 2002 (n=48); 2007(n=39) and 2010 (n=37).

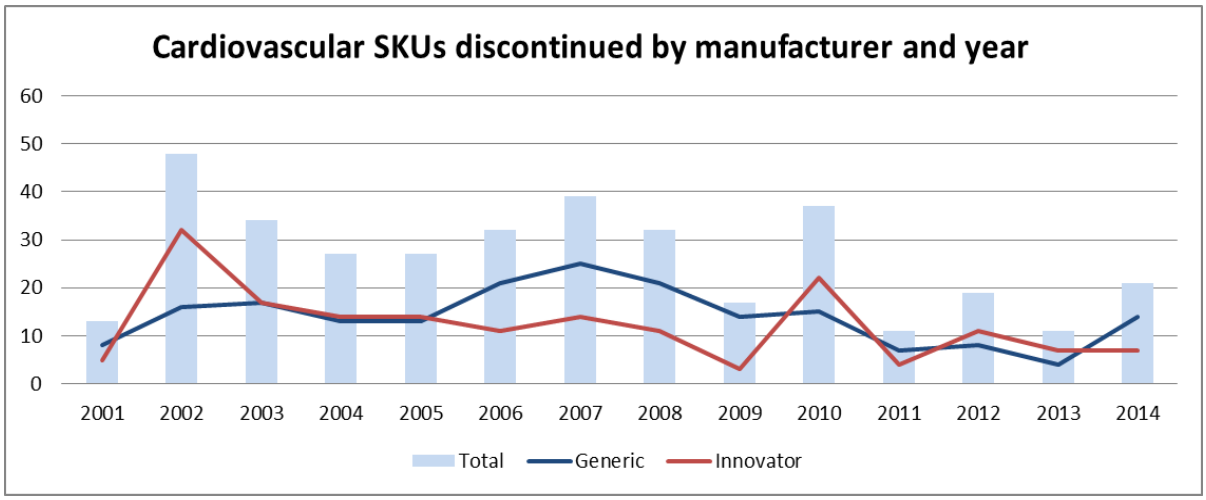

Figure 7 Graph of cardiovascular SKUs discontinued by manufacturer and year

The cardiovascular medicines that were discontinued are further elaborated according to class (see Table 10). It is evident that medicines acting on the renin-angiotensin system was the largest class of these medicines that were discontinued (n=94). This was followed by beta- blockers (n=61) and the third highest discontinued class was diuretics (n=48).

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Table 10 Cardiovascular SKUs discontinued according to therapeutic class

Cardiovascular Drug Class	*n*	*%*
Agents acting on the renin-angiotensin system	94	25.54
Beta blocking agents	61	16.58
Diuretics	48	13.04
Calcium channel blockers	46	12.50
Cardiac therapy	36	9.78
Lipid modifying agents	34	9.24
Antihypertensives	31	8.42
Peripheral vasodilators	9	2.45
Vasoprotectives	9	2.45
Total	**368**	**100**

Oncology Medicines

The total number of oncology SKUs discontinued was n= 152 (see Table 11). The oncology SKUs were further described according to the number of SKUs per oncology active ingredient (see Table 12). Thereafter, in Table 13 the SKUs are sorted according to the active ingredients that are no longer available on the market and those that are available, where n=10 SKUs which are no longer available after the product was discontinued. The discontinued SKUs that are no longer available on the market are described according to their active ingredient in table 10, where it is evident that n= 7 active ingredients (molecules) were no longer available on the market after discontinuation. These 7 molecules were therefore no longer available as treatment options for cancer patients after the products were discontinued

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Table 11 Total number of discontinued Oncology medicine SKUs

Manufacturer	***n***	***%***
Generic	76	50.00
Innovator	76	50.00
Total	152	100.00

Table 12 Active ingredient (molecule) that constitute the discontinued Oncology SKUs

Active ingredient (molecule)	***n***	***%***
Doxorubicin	10	6.58
Interferon	10	6.58
Fluorouracil	9	5.92
Cisplatin	8	5.26
Methotrexate	8	5.26
Other (n=49)	107	70.39
Total	**152**	**100**

Table 13 Oncology medicines (molecule) availability after SKU discontinuation

Manufacturer	***n***	***%***
Molecule not available	10	6.58
Molecule is available	142	93.42
Total	152	100.00

Table 14 Discontinued oncology molecules no longer available

Discontinued Active ingredient (molecule)	*n*	*%*
Molgramostim	3	30.00
Vindesine	2	20.00
Daclizumab	1	10.00
Formestane	1	10.00
Raltitrexed	1	10.00
Teniposide	1	10.00
Thalidomide	1	10.00
Total	**10**	**100.00**

TOTAL SKU DISCONTINUATIONS

For all SKUs discontinued from the market, 2002 saw the largest number of SKUs being commercially withdrawn; generic manufacturers n = 314 and innovator manufacturers n=289 (see Figures 8 and 9)

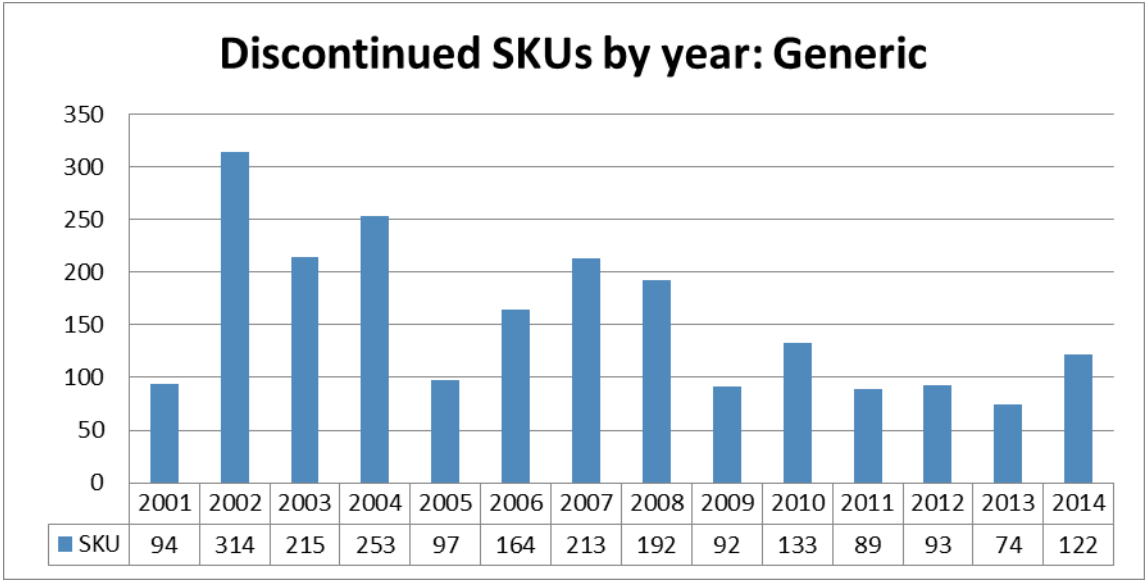

Figure 8 Total number of SKUs discontinued by generic manufacturers by year

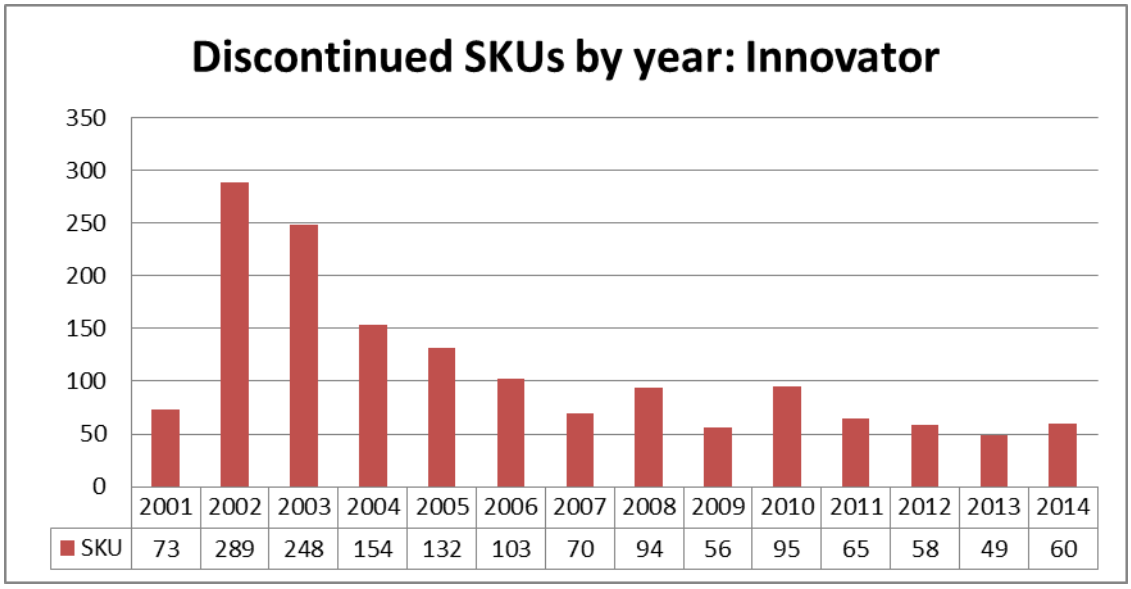

Figure 9 Total number of SKUs discontinued by innovator manufacturers by year

Of the total products discontinued in the line graph presentation the highest number of discontinuations for both generic, n= 314 and innovator, n= 289 were seen in 2002. Generic medicines also saw an increasing trend in discontinuations between 2004 and 2007 (see Figure 10).

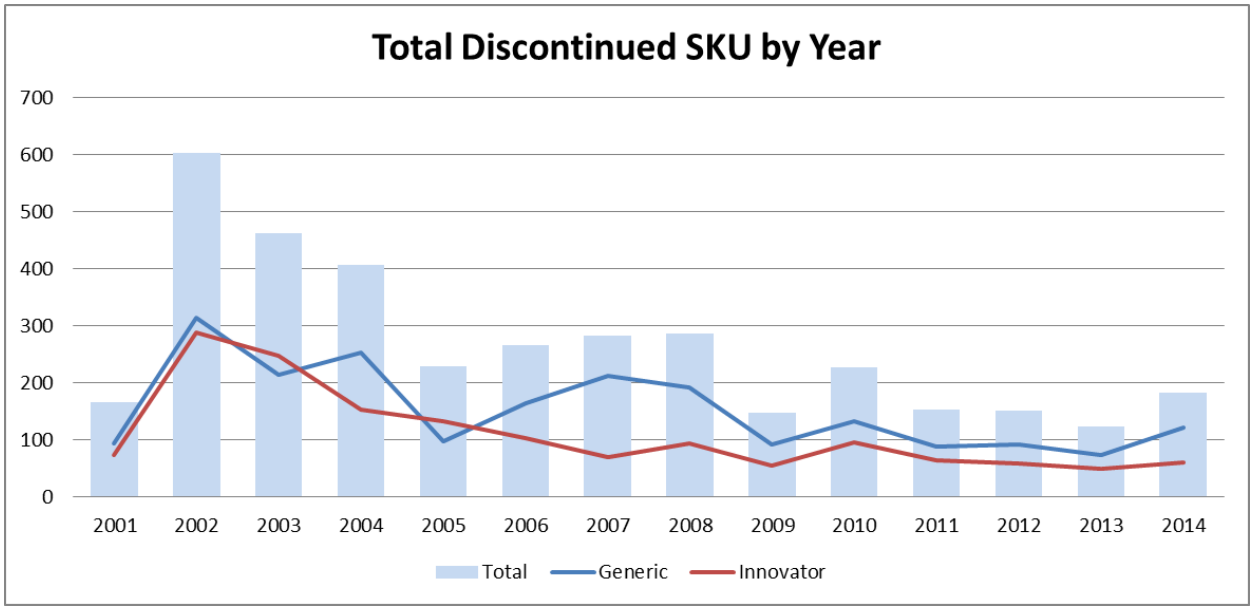

Figure 10 Total generic and innovator SKUs discontinued per year

The data obtained showed number of discontinued SKUs ranged from 123 to 603. The corresponding SEP increase per year ranged from 0 % to 13,2 %. The relationship between number of discontinued SKUs per year and SEP increase was investigated, with the number of SKUs discontinued being the dependent variable (Y).The regression line was determined to be as follows : SKUs discontinued = -14.06(SEP Increase) + 309.89 (figure 11). The regression line showed a negative relationship between number of SKU's discontinued and the SEP increase allowed, with a Pearson's correlation coefficient (r) = -0.414 (p=0.14)

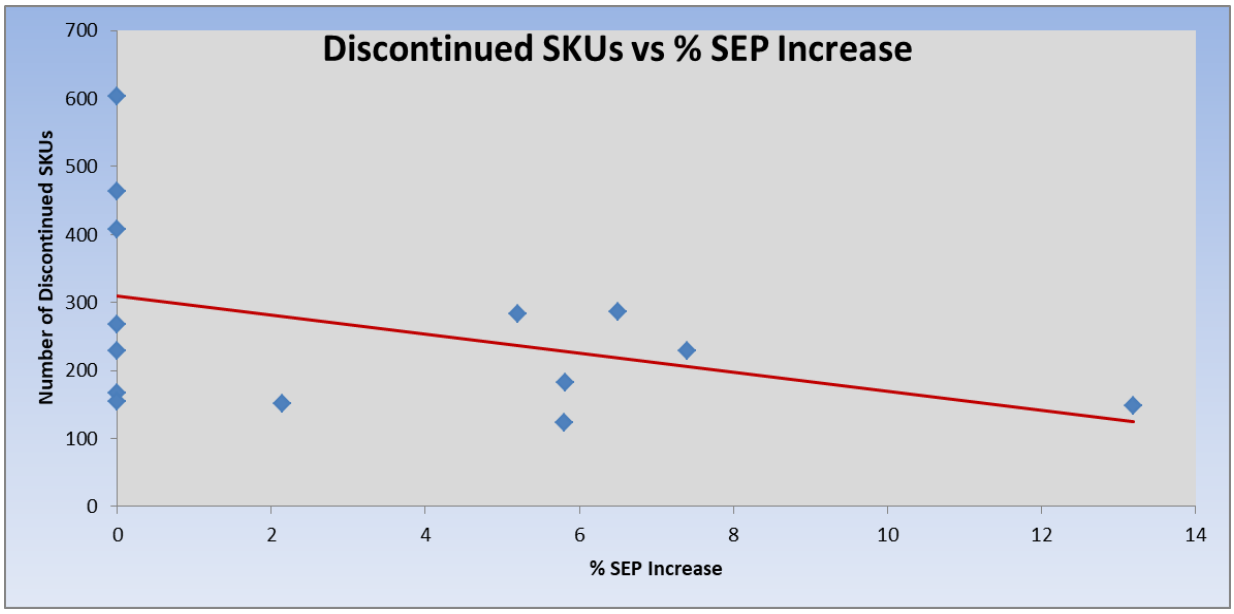

Figure 11 Scatter plot and line between the dependent variable number of SKUs discontinued and the independent variable % SEP Increase

The results of this research have been summarised as a scienticfic article to be published in an academic journal (see appendix A).

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CHAPTER V

DISCUSSION

The results from the analysis done for this research showed that generic and innovator manufacturers commercially withdrew SKUs during the study period. Three generic manufacturers were responsible for most commercially withdrawn generic SKUs. Generic manufacturers have a high vulnerability to price, thus a possible reason for the high number of generic SKU withdrawals could be due to price reductions, where it is no longer financially sustainable to produce the SKU (Bongers & Carradinha, 2009).

The years just prior to the implementation of SEP i.e. 2002-2004 saw the highest number of SKUs withdrawn. This was consistent for generics as well as innovator medicines. Pharmaceutical Manufacturers' Association and 39 of its member companies against the amendments to the Act that would enable pricing transparency and generic substitution was withdrawn in 2001 after a lengthy legal process. The sharp increase of commercial withdrawal of medicines between 2002 and 2004 could have been due to the anticipation by pharmaceutical manufacturers of the price regulation on medicines via SEP legislation. SEP was eventually promulgated in amendments to the Act in May 2003. SEP was legislated in April 2004.

A pharmaceutical manufacturer has the right to commercially withdraw a product from the market at any time. This phenomenon is seen globally, as the withdrawal is of prescription medicines is largely due to commercial reasons (Clarke, et al., 2006). The reason for these withdrawals is often economically driven e.g. the product did not have the expected margin of profit or there was a lack of money to invest in the production process to comply to different quality demands (De Weerdt, et al., 2015).

A strategy employed by pharmaceutical manufacturers to maximize profit (and a reason for commercial withdrawal), is SKU rationalisation. SKU rationalisation can be viewed as an effort by a company to maintain fewer SKUs on the market e.g. if a manufacturer previously had 3 pack-sizes of a pain medication (10's, 20's and 30's), they could withdraw the SKUs, which are the least profitable and maintain only the most profitable SKU on the market. This is especially true in the South African market as SEP is applied to a single unit dose and not pack-size; therefore reduction in cost to the manufacturer is seen in terms of packaging components; material and packaging operations.

This type of commercial withdrawal has a direct impact on the patient. SKU rationalisation means fewer pack-size options available to the patient and with only 1 SKU available; the patient is forced to purchase the pack size that remained on the market, regardless of the quantity they require thereby increasing medicine wastage. A good example of this practice is seen with oncology medicines, where these therapies are low volume but high costs. Our analysis showed that only 10 SKUs (7 molecules) withdrawn are no longer in the market i.e. there was no generic equivalent available after the product was discontinued. Whether the patient is paying out of pocket or the cost is borne by a private medical aid insurer, SKU rationalisation may ultimately lead to a possible higher wastage and higher cost of pharmaceutical care.

Another, albeit less common reason for a voluntary withdrawal of a medicine from the market is due to safety reasons. In South Africa, very few medicines were completely withdrawn from the market between 2001 and 2014 due to safety reasons.

Two anti-inflammatory medicines; Valdecoxib and Rofecoxib were withdrawn in 2004 due to evidence of them causing increased risk of heart attack and stroke. An anti-diabetic medicine; Rosiglitazone was withdrawn in 2011 and in the same year dextropropoxyphene containing products were withdrawn, both due to cardiac concerns. The small number of safety withdrawals during the study period, is consistent with finding of studies that analysed medicine withdrawal due to safety reasons (Clarke, et al., 2006).

It may also be plausible to also consider that changes to Clinical guidelines e.g there have also been changes to ARV guidelines and the introduction of fixed-dose-combinations guidelines that may have also had an impact on the discontinuation of certain products from the market.

Further to this, one should also consider that some products may have been highly genericised with many competitors for one molecule. This type of crowded market and downward pressure on price hereto may also be a reason that some SKUs were withdrawn and not primarily based on SEP policy.

Commercial withdrawal of an SKU may have a further unforeseen effects in that it may cause medicine shortages. This directly impacts healthcare providers and patients alike, and also may increase the cost of healthcare. Pricing procedures has been considered as a major cause of drug shortages, because if the price of a certain product is too low or no longer profitable, a manufacturer can decide to withdraw the product from the market. These withdrawals may result in either drug unavailability or more often drug shortages.

Anti-infective, cardiovascular and anti-retroviral medicines are three therapeutic classes associated with high usage and expenditure in the South African private health sector (Bester, et al., 2018). Our analysis revealed that anti-infective and cardiovascular drugs accounted for 9.97% and 22.97% of all SKU withdrawals, respectively. Majority of the withdrawn SKUs in the cardiovascular class was anti-hypertensives, which is concerning as hypertension has a very high prevalence (129.9/1000 lives) in South

Africa (Bester, et al., 2018). Anti-infective medicines follow a similar trend with most withdrawn SKUs being the most used antibiotics i.e. beta-lactam antibiotics (Bester, et al., 2018). Medicines in these classes are highly genericised and pricing policies may increase their vulnerability to drug shortages.

SEP was introduced in 2004 to increase the access to affordable medicines and reduce healthcare costs in general. Prior to this South Africa used to be the only country outside the U.S. that did not have some form of price control over medicines (Naudé & Luiz, 2013). As mentioned previously, the prices of medicines reduced by an average of 19% over a five year period (Ball, 2011). However these price controls had the effect of reducing the profit margins on medicines that are sold locally and possibly led to the withdrawal of products as it no longer remains economically viable to produce and market them (Naudé & Luiz, 2013).

SEP is further regulated by a fixed allowable maximum annual increase that is determined according to Regulation 8.1 of the Act, 2004 (South African National Department of Health, 2004). It states that the extent to which the single exit price of a medicine may be increased will be determined annually by the Minister of Health. The annual increase is published after consultation with the Pricing Committee, and with consideration of the average Consumer Price Index (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 and international pricing information. This process would also be cognisant of the need to ensure the availability, affordability and quality of medicines (South African National Department of Health, 2004).

SEP increases determined for the year is not predictable and which makes forecasting and budgeting activities difficult. It is therefore difficult to forecast what the costs of the companies' other activities, like marketing, should be in order to still be able to realise a profit (Naudé & Luiz, 2013). A CEO of a leading South African generic company remarked to the Business Day in January 2018, in response to the annual SEP increase of 1, 26 % that "continued pressure on the industry also leads to products being pulled from market, which means a smaller variety of quality, affordable medicines for

patients (Business Day Live, 2018). He also added that “according to IMS data for 2012-2017, as many as 700 pharmaceutical products have been pulled from the South African marketplace over the past five years and it is not far-fetched to assume that the majority were pulled due to decreasing profitability rendering the molecules unviable” (Business Day Live, 2018).

The analysis of this study shows that a total of 3691 SKUs were discontinued during the period 2001 to 2014, with the highest number of withdrawals observed between 2002 and 2004, which is just prior to the implementation of SEP. The years following the implementation of SEP saw a 4.19% yearly average price increase, with the Pricing Committee publishing a 0% increase in 2004, 2005, 2006 and 2011. The first increase of 5.2% was published in 2007, almost 3 years after the pricing regulation implementation.

Bearing in mind the annual increases that were gazetted each year, it is interesting to note that from the analysis, generic medicines showed the highest number of product withdrawals during the period 2002 to 2008, with 1448 of the total of 2145 for the period. Innovator medicines withdrawals during this period were also high with 1090 of the total 1546. The highest SEP annual increase was seen in 2009 with the Pricing Committee publishing a 13.2% increase in SEP. It was this year that interestingly , saw the lowest number of generic and innovator withdrawals from the market since 2002.

There was a reduction of SKU withdrawals between 2009 and 2014 and SEP increase may not have been the only driving factor, as these reductions could have also been attributed to the strengthening of the South African Rand (ZAR) against the United States Dollar (USD). The ZAR showed great strength in recovery in 2009, trading at R8.07 to the USD after lows hovering around ZAR10 to the USD at the end of 2008. During the period 2011 to 2014, the analysis showed a decreasing number of product withdrawals for both generic and innovator medicines versus the previous decade. The lower number of SKUs discontinued over this period could have been due to a both the stable exchange rate as well as SEP price increases that was gazetted during this time.

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The data analysis showed that the yearly increase in SEP may have had a direct effect of the number of SKUs withdrawn during the study period. Using a scatter plot we performed a linear regression to assess if there was any correlation between the yearly SEP increase and the number of SKUs withdrawn. The regression line revealed a negative correlation i.e. as the yearly percentage SEP increase improved the number of SKU withdrawals decreased. This was further confirmed by the Pearson's correlation coefficient (r=-0.414), however the correlation was not statistically significant (p=0.14).

Medicine pricing policies may have a dual impact in the market. Policies are typically aimed to make medicines more affordable to the patient. However pricing policies may have a negative effect on medicine availability. The results show that the SEP and transparent pricing policy may have had an impact on SKU withdrawal from the market. Lower prices and control of annual increases on medicines may have led to SKUs exiting the market. This has a direct impact on medicine availability in the market.

LIMITATIONS:

The limitation of the study was that the dataset did not allow for analysis on the availability or lack thereof of a discontinued molecule/ generic equivalent on the market after the discontinuation of one brand. This study analysed SKU withdrawals from the market and not entire products, which means a product may have remained on the market with fewer or one SKU/s available. The number of SKU withdrawals were ~~very~~ high during the period 2002 to 2008 after SEP legislation.

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CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

SEP legislation was part of the overarching aim of the NDP to promote the availability of safe and effective medicines at transparent prices in the private market in South Africa. The effects of a regulated pricing model together with controlled price increases, and fixed professional fee and logistic fee caps within the SEP determination, could have had an impact on product availability in the market.

Direct product price control may result in an immediate cost lowering effect of medicines; however this also leads to products being withdrawn perhaps because of non-viability due to financial losses to the manufacturing companies. It is also possible that products were withdrawn due to pricing and clinical superiority of other medicines available in the same therapeutic class. Interestingly, this study showed that a larger number of innovator and generic SKUs were withdrawn from the market during the period 2002 to 2008 compared to year 2001 and the period 2009 to 2014. The rationale for the withdrawals was not explored in this study. However possible reasons for product withdrawal as cited in the discussion chapter were a combination SKU rationalisation and product brand rationalisation. Product withdrawal due to safety reasons was negligible over these years when one looked at the actual number of products that were withdrawn from the market for safety reasons during the study period. The impact to the patient in terms of cost, quality and options of medicines available remains to be further analysed.

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Recommendations:

Further to the amount of product withdrawals from the market subsequent to SEP legislation, a study that analyzes the number, timing to and trend in new product launches in the market would augment the body of evidence with regard to the market effects of SEP. This would be valuable in exploring the impact of a legislated medicine pricing model on both withdrawal and innovation.

Another relevant study would be an analysis of product registration timelines and its impact on new launch timing in South Africa compared to other countries after SEP legislation.

According to the WHO HAI Project on Medicine Prices and Availability, low prices can reduce the attractiveness of certain countries to manufacturers and importers which might result in important products not being produced and marketed in a particular country or at least, being marketed with substantial delays.

These types of analyses would provide important information on the impact of a regulated pricing model on market dynamics and also the effects on the availability of new medicines to the South African patient.

An analysis that can differentiate between the discontinuation of a molecule as a whole would be valuable. This would show some interesting insights into the real impact of discontinuations and is recommended for future studies.

The result of reduced product availability in the market and its impact to the cost and quality of healthcare to the patient needs to be regularly monitored and evaluated to ascertain if direct price regulations are achieving the intended outcomes as well as evaluate other intended or unintended effects in pharmaceutical market dynamics.

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APPENDICES

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APPENDIX A : PUBLICATION SUBMISSION

Evaluating the impact of Single Exit Pricing (SEP) on medicine product withdrawal from the private health care market in South Africa.

ABSTRACT / SUMMARY

Introduction

The introduction of medicine pricing policies in South Africa in the form of Single Exit Pricing (SEP), provided a mechanism to improve medicine price transparency and reduce both medicine price and inflation. However regulating medicine prices may have had further unforeseen effects on the availability of medicine. This research presents the impact of medicine price controls in the form of SEP on medicine product discontinuations from the private health care market in South Africa

Aim

The aim of this study is to evaluate the impact of SEP legislation on the availability of medicines in the private health sector market in South Africa, in terms of withdrawal of medicines from the market and rationale for withdrawal.

Methods

A descriptive, quantitative analysis of all registered medicines on the South African market by Stock Keeping Units (SKUs) to establish medicine product withdrawn from the market by SKU during a 14 year period from 2001 to 2014.

Results

A total number of 152 manufacturers discontinued 3691 SKUs between 2001 and 2014. The mean number of discontinuations per generic manufacturer was 22.34 (sd= 58.11), while innovator manufacturers discontinued a mean of 27.61 (sd= 41.89). The 2002 saw the largest number of SKUs being commercially withdrawn n=603, followed by 2003 (n=463) and 2004 (n=407). There was a negative correlation between number of discontinued SKUs per year and SEP increase; with a Pearson's correlation coefficient (r) = -0.414 (p=0.14).

Discussion

Medicine pricing policies may have a dual impact in the market. Policies are typically aimed to make medicines more affordable to the patient; however pricing policies may have a negative effect on medicine availability. The results show that the SEP and transparent pricing policy

may have had an impact on SKU withdrawal from the market. Lower prices and control of annual increases on medicines may have led to SKUs exiting the market.

Conclusion

The result of reduced product availability in the market and its impact to the cost and quality of healthcare to the patient needs to be regularly monitored and evaluated to ascertain if direct price regulations are achieving the intended outcomes as well as evaluate other intended or unintended effects in pharmaceutical market dynamics.

Introduction

South Africa's apartheid era saw disparities in the public and private health sectors (Harris, et al., 2011). In 1990, the private sector was responsible for 80% of South Africa's total medicine expenditure (South African National Department of Health, 1996). In 1994, the newly democratically elected government, faced with the problems of, amongst others, the lack of equity in access to essential medicines and rising medicine prices, decided to tackle these problems systematically through the development and implementation of the National Drug Policy (NDP) (South African National Department of Health, 1996).

In December 1997, the South African government promulgated the legislation aimed at lowering the cost of medicines to all South Africans (Republic of South Africa, 1997). This legislation made provision of for the establishment of the Medicine Pricing Committee (MPC) to make recommendations on the introduction of a transparent pricing system for all medicines sold in South Africa (Republic of South Africa, 1997). In 2004, "Regulations relating to a transparent pricing system for medicines and scheduled substances" was promulgated (South African National Department of Health, 2004).

This new regulation introduced Single Exit Pricing (SEP), as a mechanism to improve medicine price transparency and reduce both medicine price and inflation. The overall aims of SEP was to improve access to medicines by reducing prices of both innovator and generic medicines and controlling medicine entry pricing and price increases and thereby improve access to medicines (South African National Department of Health, 2004).

The principal aim of medicine pricing policies is to keep medicines accessible; however regulating medicine prices may have various effects on the availability of medicine (Birgli AG, 2013; De Weerdt, et al., 2015). It may increase or decrease or have a negligible effect on availability of medicines to the patient. Pricing regulations have led a lower level of new medicines introductions and the market withdrawal of some products which may increase the

vulnerability of the pharmaceutical market to medicine shortages (Birgli AG, 2013; De Weerdt, et al., 2015).

The impact of medicine price controls have been extensively described in developed markets with well-developed universal health coverage systems and who exercise price control on predominately reimbursed medicines (Vogler, 2012; Vogler & Kilpatrick, 2015; Babar, 2015). Pricing policies in the EU have successfully reduced the cost of medicines for both health funders and patients. The policies have also led to unforeseen factors such as parallel export of medicines from lower priced markets, stricter supply chain with regard to keeping smaller inventories and reducing costs and some manufacturers removing medicines or not introducing them to lower priced markets (Birgli AG, 2013; De Weerdt, et al., 2015).

There exists limited literature addressing impact of medicine price controls in the developing world, where a significant portion of patients are without health care insurance and incur considerable out-of-pocket expenditure for medicines (Ngozwana, 2016). In the South African context, this is further compounded by the uniqueness of the price controls adopted, where all medicines prices (whether reimbursed or not), are controlled.

The introduction of SEP in South Africa realised a total reduction of 22 % of medicines prices, however a consistent pricing benefit was not realised by consumers (Pretorius, 2011). Pretorius further established that with a reduction in overall gross profit generated by pharmacies, the pressure in the business environment was evident (Pretorius, 2011).

A survey conducted by Naude and Luiz in 2013 found that price controls in South Africa, reduced profit margins on medicines that are sold locally and that this has resulted in increased pressure on suppliers to increase their economies of scale in order to reduce the cost per unit produced (Naudé & Luiz, 2013). Importantly they also observed that some companies stopped the production of certain products, as it no longer remains economically viable to produce them locally (Naudé & Luiz, 2013).

This research presents the impact of medicine price controls in the form of SEP on medicine product discontinuations from the private health care market in South Africa. The pre and post analysis of medicine product discontinuation from the market relative to SEP, also addresses the impact of such regulation with regard to fair competition, innovation and the availability of medicines to the patient. For the purpose of this study medicine discontinuation will also refer to medicine withdrawal.

Aim

To evaluate the impact of SEP legislation on the availability of medicines in the private health sector market in South Africa, in terms of withdrawal of medicines from the market and rationale for withdrawal.

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Methods

A quantitative analysis of all registered medicines on the South African market by Stock Keeping Units (SKUs) to establish medicine product withdrawn from the market by SKU. A SKU is a code assigned to a product to identify the price, product options and manufacturer.

A comprehensive list of all marketed medicines on the South African market by SKUs was obtained from a medical data base managed by MEDPRAX. MEDPRAX are medical data specialists, who supply essential, up to date, medicine price data South African healthcare industry. The dataset consisted of all medicines by SKU, scheduled 1 to 8, over the time period 2001 to 2014. The dataset contained all medicines by SKU that were marketed, withdrawn or flagged for withdrawal at a time point within the period described. Scheduled 0 products were excluded as they are exempt from price controls.

Data was entered into Microsoft EXCEL, version 2016 in a format developed for this study. The data was analysed and summarised descriptively using frequency tables and graphs. Discontinued SKU's* was then grouped by innovator and generic companies and further by Anatomical Therapeutic Chemical (ATC) classification and summarised descriptively using frequency tables and graphs. All statistical procedures were performed on MS Excel™ running under Microsoft Windows on a personal computer.

Results

A total number of 152 manufacturers discontinued at least one SKU between 2001 and 2014. Majority of the manufacturers identified, produced exclusively generic medicine (n= 96; 63.16 %), and have been classified as generic manufacturers. Manufacturers producing patent medicines accounted for 36.84% (n=56), and were classified as innovator manufacturers (see table 1).

The total number of SKUs discontinued during the study period was 3691. Innovator manufacturer discontinuations accounted for 41.89 % (n=1546), of all SKU discontinued, with generic manufacturers being responsible for 2145 (58.11%) discontinuations (see table1).

The analysis showed number of discontinued SKUs ranged from 123 to 603. The mean number of discontinuations per generic manufacturer was 22.34 (sd= 58.11), while innovator manufacturers discontinued a mean of 27.61 (sd= 41.89). The t-test showed that there was no statistically significant difference between the means (t= -0061; p= 0.27) (see table 1).

The 2002 saw the largest number of SKUs being commercially withdrawn n=603, followed by 2003 (n=463) and 2004 (n=407).Generic manufacturers consistently discontinued more SKUs each year except in 2003 and 2005 (see figure 1)

70.71% of total SKUs discontinued fell into 5 ATC classes (see table 2). Three of these classes namely: anti-infectives for systemic use; respiratory system and cardiovascular system represent drugs treating a high burden of communicable and non-communicable disease in South Africa (n=848; n=490 and n=368 respectively). Following the trend of total discontinuations, 2002; 2003; 2004 experienced the highest number of discontinuations.

The relationship between number of discontinued SKUs per year and SEP increase was investigated, with the number of SKUs discontinued being the dependent variable (Y).The regression line was determined to be as follows : SKUs discontinued = -14.06(SEP Increase) + 309.89 (figure 2). The regression line showed a negative relationship, with a Pearson's correlation coefficient (r) = -0.414 (p=0.14).

Discussion

The results from the analysis done for this research showed that both generic and innovator manufacturers commercially withdrew SKUs during the study period. Amongst the generic manufacturers, three were responsible for withdrawing the most SKUs. Generic manufacturers have a high vulnerability to price, thus a possible reason for the high number of generic SKU withdrawals could be due to price reductions, where it is no longer financially sustainable to produce the SKU (Bongers & Carradinha, 2009).

The years just prior to the implementation of SEP i.e. 2002-2004 saw the highest number of SKUs withdrawn. This was consistent for generics as well as innovator medicines. It was in 2001 that an industry body, the Pharmaceutical Manufacturer's Association, withdrew its long standing legal battle against the implementation of amendments to legislation that would enable pricing transparency including SEP. SEP was finally legislated in April 2004 (South African National Department of Health, 2004). The high number of SKU withdrawals between 2002 and 2004 could have been due to a reaction by pharmaceutical manufacturers anticipating the imminent medicine price regulation via SEP legislation.

A pharmaceutical manufacturer has the right to commercially withdraw a product from the market at any time. This phenomenon is seen globally, as the withdrawal is of prescription medicines is largely due to commercial reasons (Clarke, et al., 2006). The reason for these withdrawals is often economically driven e.g. the product did not have the expected margin of profit or there was a lack of money to invest in the production process to comply to different quality demands (De Weerdt, et al., 2015).

A strategy employed by pharmaceutical manufacturers to maximize profit (and a reason for commercial withdrawal), is SKU rationalisation. SKU rationalisation can be viewed as an effort by a company to maintain fewer SKUs, of the same product, such that they only market the most profitable SKU. This is especially true in the South African market as SEP is applied to a

single unit dose and not pack-size; therefore reduction in cost to the manufacturer is seen in terms of packaging components; material and packaging operations.

This type of commercial withdrawal has a direct impact on the patient. SKU rationalisation means fewer pack-size options available to the patient regardless of the quantity they require thereby increasing medicine wastage. Whether the patient is paying out of pocket or the cost is borne by a private medical aid insurer, SKU rationalisation may ultimately lead to a possible higher wastage and higher cost of pharmaceutical care.

Commercial withdrawal of an SKU may have further unforeseen effects in that it may cause medicine shortages. This directly impacts healthcare providers and patients alike, and also may increase the cost of healthcare. Pricing procedures has been considered as a major cause of drug shortages, because if the price of a certain product is too low or no longer profitable, a manufacturer can decide to withdraw the product from the market. These withdrawals may result in either drug unavailability or more often drug shortages (De Weerdt, et al., 2015).

Anti-infective, cardiovascular and anti-retroviral medicines are three therapeutic classes associated with high usage and expenditure in the South African private health sector (Bester, et al., 2018). Our analysis revealed that anti-infective and cardiovascular drugs accounted for 22.97% and 9.97% of all SKU withdrawals, respectively. Majority of the withdrawn SKUs in the cardiovascular class was anti-hypertensives, which is concerning as hypertension has a very high prevalence (129.9/1000 lives) in South Africa (Bester, et al., 2018). Anti-infective medicines follow a similar trend with most withdrawn SKUs being the most used antibiotics i.e. beta-lactam antibiotics (Bester, et al., 2018). Medicines in these classes are highly genericised and pricing policies may increase their vulnerability to drug shortages.

SEP was introduced to increase the access to affordable medicines and reduce healthcare costs; however these price controls had the effect of also reducing the profit margins on medicines that are sold locally and may have possibly led to the withdrawal of products which became no longer economically viable to either produce or market (Naudé & Luiz, 2013).

SEP is further regulated by a fixed allowable maximum annual increase. The annual increase is published after consultation with the MPC, and with consideration of the average Consumer Price Index (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 and international pricing information (South African National Department of Health, 2004).

The unpredictability of the annual SEP increases has created difficulties in effectively forecasting and budgeting, which leads to companies being unable to effectively calculate what costs of other activities, like marketing, should be in order to still be able to realise a profit (Naudé & Luiz, 2013). A CEO of a leading South African generic company remarked to the Business Day in January 2018, in response to the annual SEP increase of 1, 26 % that "continued pressure on the industry also leads to products being pulled from market, which means a smaller variety of quality, affordable medicines for patients (Business Day Live, 2018). He also added that "according to IMS data for 2012-2017, as many as 700 pharmaceutical

products have been pulled from the South African marketplace over the past five years and it is not far-fetched to assume that the majority were pulled due to decreasing profitability rendering the molecules unviable" (Business Day Live, 2018).

The analysis of this study showed that a total of 3691 SKUs were discontinued during the period 2001 to 2014, with the highest number of withdrawals observed between 2002 and 2004, which is just prior to the implementation of SEP. The years following the implementation of SEP saw a 4.19% yearly average price increase, with the MPC publishing a 0% increase in 2004, 2005, 2006 and 2011. The first increase of 5.2% was published in 2007, almost 3 years after the pricing regulation implementation.

Bearing in mind the annual increases that were gazetted each year, it is interesting to note that from our analysis, generic medicines showed the highest number of product withdrawals during the period 2002 to 2008, with 1448 of the total of 2145 for the period. Innovator medicines withdrawals during this period were also high with 1090 of the total 1546. The highest SEP annual increase was seen in 2009 with the MPC publishing a 13.2% increase in SEP. It was this year that interestingly saw the lowest number of generic and innovator withdrawals from the market since 2002.

In addition to SEP increases, the reduction of SKU withdrawals between 2009 and 2014 may have also been driven by the strengthening of the South African Rand (ZAR) against the United States Dollar (USD). The ZAR showed great strength in recovery in 2009, trading at ZAR8.07 to the USD after lows hovering around ZAR10 to the USD at the end of 2008. The lower number of SKUs discontinued over this period could have been due to a both the stable exchange rate as well as SEP price increases that was gazetted during this time.

Our analysis also showed that the yearly increase in SEP may have had a direct effect of the number of SKUs withdrawn during the study period. Using a scatter plot we performed a linear regression to assess if there was any correlation between the yearly SEP increase and the number of SKUs withdrawn. The regression line revealed a negative correlation i.e. as the yearly percentage SEP increase improved the number of SKU withdrawals decreased. This was further confirmed by the Pearson's correlation coefficient ($r=-0.414$), however the correlation was not statistically significant ($p=0.14$).

Medicine pricing policies may have a dual impact in the market. Policies are typically aimed to make medicines more affordable to the patient; however pricing policies may have a negative effect on medicine availability. The results show that the SEP and transparent pricing policy may have had an impact on SKU withdrawal from the market. Lower prices and control of annual increases on medicines may have led to SKUs exiting the market.

A limitation of the study was that the dataset did not allow for analysis on the availability or lack thereof of a discontinued molecule/ generic equivalent on the market after the discontinuation of one brand. This study analysed SKU withdrawals from the market and not entire products, which means a product may have remained on the market with fewer or one

SKU/s available. The impact to the patient in terms of cost, quality and options of medicines available remains to be further analysed.

Conclusion

Direct product price control may result in an immediate cost lowering effect of medicines; however this also leads to products being withdrawn perhaps because of non-viability due to financial losses to the manufacturing companies.

According to the WHO HAI Project on Medicine Prices and Availability, low prices can reduce the attractiveness of certain countries to manufacturers and importers which might result in important products not being produced and marketed in a particular country or at least, being marketed with substantial delays.

The result of reduced product availability in the market and its impact to the cost and quality of healthcare to the patient needs to be regularly monitored and evaluated to ascertain if direct price regulations are achieving the intended outcomes as well as evaluate other intended or unintended effects in pharmaceutical market dynamics.

Analysis of the number, timing to and trend in new product launches in the market would augment the body of evidence with regard to the market effects of SEP. This would be valuable in exploring the impact of a legislated medicine pricing model on both withdrawal and also on the effects on the availability of new medicines to the South African patient.

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Tables and Figures

Table 15 Number of SKUs discontinued by designated manufacturer

Manufacturer	*n*	*Number of SKUs Discontinued*	*Mean*	*sd**
Generic	96	2145	22.34	58.11
Innovator	56	1546	27.61	41.89
Combined	152	3691	24.28	55.55

*sd denotes standard deviation

Table 16 Discontinued SKUs sorted by ATC classification system

ATC Classification	*n*	*%*
Anti-infectives for systemic use	848	22.97
Nervous system	578	15.66
Respiratory system	490	13.28
Cardiovascular system	368	9.97
Alimentary tract and metabolism	326	8.83
Musculo-skeletal system	261	7.07
Antineoplastic and immunomodulating agents	156	4.23
Dermatologicals	138	3.74
Genito-urinary system and sex hormones	123	3.33
Various	107	2.90
Sensory organs	89	2.41
Systemic hormonal preparations, excluding sex hormones and insulins	75	2.03
Blood and blood forming organs	67	1.82
Antiparasitic products, insecticides and repellents	65	1.76
Total	**3691**	**100.00**

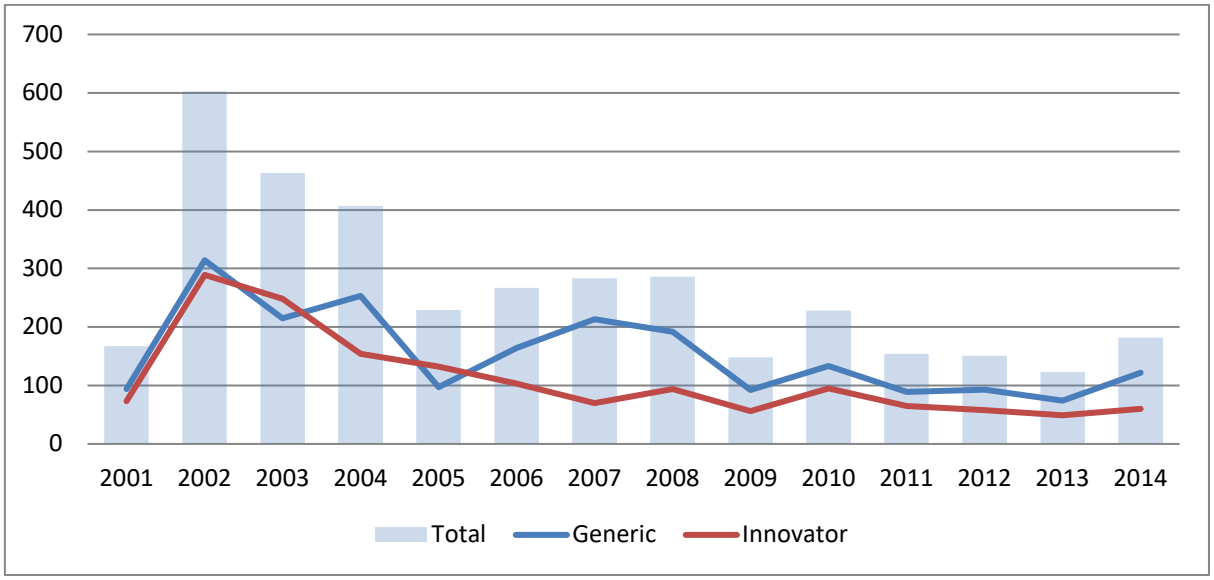

Figure 12 Total Generic and Innovator SKUs discontinued per year

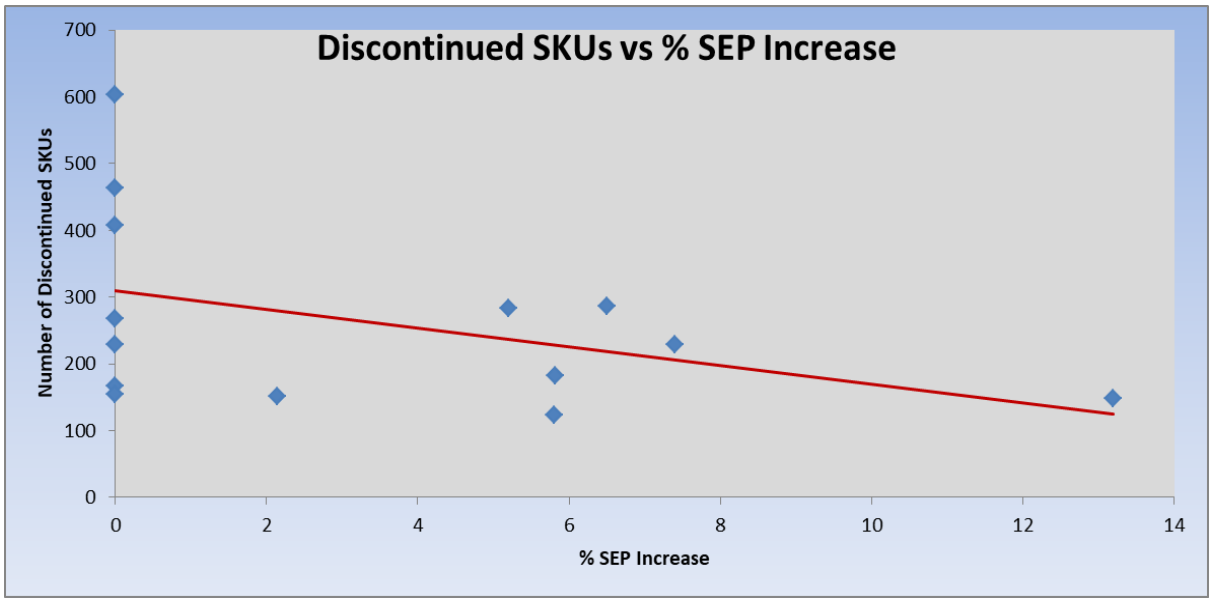

Figure 13 Scatter plot and line between the dependent variable number of SKUs discontinued and the independent variable % SEP Increase