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The effect of dossier farming on medicine registration in South Africa.

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DECLARATION

I, **MMAMASWA FLUCIA MOLOKWANE**, hereby declare that the contents of the mini thesis titled "**The effect of dossier farming on medicine registration in South Africa**" is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of full complete referencing.

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ABSTRACT

The effect of dossier farming on medicine registration in South Africa

INTRODUCTION

In this study, the researcher wanted to determine the effect of dossier farming in medicine registration in South Africa by comparing the number of generic registrations of products tendered for the government for the molecules enalapril, amlodipine and losartan, before and after innovator patent expiration and quantified the extent it is practiced and how it affected medicine registration backlog.

METHODOLOGY

This study was conducted retrospectively using a quantitative descriptive design. Data was collected using a standardised structured data collection sheet, which includes the list and names of registered generics of amlodipine, losartan and enalapril registered before and after the expiry of patent as well as the year of registration. Companies whose products were registered before 2000 were called to confirm the year of registration.

RESULTS

Dossier farming though it was the beginning of its inception after approval of pro-generic legislation in the year 2001; it lured many companies to think this would be profitable. Submission of many dossiers at the Health Authority then clogged up the system and it is one of the major causes of the backlog at SAHPRA.

CONCLUSION

Dossier farming stretched the limited capacity at the regulatory authorities which lead to more delays in the medicine registration outputs, largely contributing to the massive backlog which SAHPRA was later known for. Over 50 % of the dossiers registered for all three molecules investigated were from applicants who practiced dossier farming. This kind of increase in submissions will require a substantial increase in the resources from any Health Authority Regulator.

From the study, it is noted that the South Africa's Health Authority still have a great deal of work to do to be on par with first world countries in ensuring that pharmaceutical companies are profitable while increasing the access to essential medicines to patients by promoting generic entrance into the market but without saturating the market with dossier farming. Our study has limited number of sample size and further research with larger sample size would be required in the subsequent studies.

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GLOSSARY:

Term:	Definition:
Clone	An application submitted by the applicant of the innovator or generic product as a copy of its own product under a different proprietary name at any stage during the product life cycle (of the registered product).
NCE	New Chemical Entity - a compound which, previously, hasn't been described in scientific literature.
NDA	New Drug Application - Is a document submitted by drug companies/applicants to the Health Authorities when seeking approval of new drugs.
Variation	A variation is a change to the terms of a marketing authorisation of a medicine in a dossier of an approved product/medicine.

ACRONYMS:

Term:	Definition:
BRICS	Brazil, Russia, India, China and South Africa
CIPC	Companies and Intellectual Property Commission in South Africa
MCC	Medicines Control Council, now called SAHPRA
NCE	New Chemical Entity
NDA	New Drug Application
SADC	The Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SAPRAA	Southern African Pharmaceutical Regulatory Affairs Association
ZAZIBONA	ZaZiBoNa collaborative medicines registration initiative established in 2013 by four countries, Zambia, Zimbabwe, Botswana, and Namibia, with technical support from the WHO Prequalification Team but now include South Africa and other countries in SADC.

CHAPTER 1:

INTRODUCTION

1.1 RATIONALE OF THE STUDY

One of the goals for the South African National Drug Policy is to ensure and increase access to safe, affordable and quality medicines (National Department of Health, 1996). In 2001, Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F, passed and approved pro-generic legislation in South Africa. This legislation promoted and eased the entry of generics into the South African market. It was introduced mainly to promote competition, in addition to affordability and accessibility of the medicines. This Act did not prevent or state how many generics the health authority should register per molecule.

In dealing with access to medicines, a "nine months" expedited evaluation review system also called fast track was introduced in 2003 by Medicines Control Council (MCC), now called SAHPRA. Fast track approvals were supposed to speed up registration of both New Chemical Entity (NCEs) and Essential Medicines Listed generics to satisfy and fulfil South Africa's critical healthcare provision needs. More generics were then submitted and registered in this process (Leng, Pollock and Sanders, 2016). This created a backlog of registration of medicines due to pharmaceutical companies seeing this process as an opportunity to have their products registered and launched in a short space of time. While most generic medicines meeting the Essential Drug List (EDL) criteria were submitted for fast track registration, a few branded new molecules would also be submitted but get trapped in the backlog (Leng, Pollock and Sanders, 2016). This legislation made it attractive for local companies and marketers to register generic medicines in the country. In addition, small companies saw it as an opportunity to register cheap imported generics for tendering with the Department of Health for public hospitals and clinics (Leng, Sanders, and Pollock, 2015). Treatment of rare diseases using NCEs has also become a huge difficulty because of the time it takes to approve these special medicines in the country. It takes about six months in Europe and the USA to approve these medicines compared to an average of more than five years in South Africa (Belseck, 2018) It is also noted that African Medicines Regulatory Authorities have minimal skills and capacity to evaluate the dossiers effectively (Narsai, Williams and Mantel-Teeuwisse, 2012).

Patent exclusive rights are limited to a global standard period of about 20 years from the date of application. The pharmaceutical medical research culture emphasizes and practice early innovation disclosure long before the product is marketed (Lehman, 2003). Pragmatically, for example, it has

been observed that this backlog of registration of medicines creates a situation where if a company has a new chemical entity patent for 20 years, and it gets registered in five to seven years, then the company only has about 13 years to exclusively market their product. This prompted the researcher to investigate the effect of dossier farming in registration of pharmaceuticals.

1.2 AIM

The study aim was to determine the effect of dossier farming on the medicine registration process. Dossier farming (multiple-dossier) is described as a practice of registration of several dossiers of the same product by the same company using different proprietary names (Leng, Sanders, and Pollock, 2015). Three common therapeutic class of medicines in solid dosage forms to treat hypertension were chosen.

1.3 OBJECTIVES

The objectives of the research were to:

- To compare the number of generic registrations for enalapril, amlodipine and losartan, before and after patent expiration.
- To quantify the extent to which dossier farming is practiced and the effect it has on the medicine registration backlog.

1.4 Significance of the Study

This study seeks to determine to what extent dossier farming has contributed to the medicine registration backlog experienced within SAHPRA. Currently there are more generics registered in a shorter period of time than originator molecules (Leng, Sanders, and Pollock, 2015). This does however not necessarily benefit South Africa as a whole, as there may be many companies already offering certain generics at very competitive prices. This study also seeks to investigate whether the occurrence of dossier farming is not due to the tender system in use within the South African health care system.

1.5 Summary

Chapter 1 concludes the necessity to investigate the occurrence of dossier farming within the healthcare setting.

CHAPTER 2
LITERATURE REVIEW

2.1 MEDICINE REGISTRATION IN BRICS COUNTRIES - BRAZIL, RUSSIA, INDIA, CHINA AND SOUTH AFRICA

SOUTH AFRICA:

South Africa is one of the largest economies in Africa and is a member of the Brazil, Russia, India, China and South Africa (BRICS) countries (Africa Ranking, 2018). In addition, South Africa is a member of the ZAZIBONA as well as SADC. The Medicines and Related Substances Amendment Act, No. 72 of 2008 (of Act 101 of 1965) was passed into law by the South African president on 24 December 2015 (NDOH, Act 101 of 1965, 2015). This amendment made provision for the establishment of a new regulatory authority called The South African Health Products Regulatory Authority (SAHPRA). The new National Medicines Regulatory Authority will be able to employ experts to evaluate product applications on a full-time basis. This will strengthen its capacity, which will reduce and deal with the current backlog of registration applications, and gradually improve turnaround times (Department of Health, 2017). SAHPRA has a mandate to regulate all medicine registration, complementary medicines, clinical trials, active pharmaceutical ingredients, medical devices and in vitro diagnostic devices (NDoH, 2018). The organisation was launched February 2018.

According to SAHPRA's communication (SAHPRA, 2018) SAHPRA inherited a backlog of about 16 000 applications from Medical Control Council (MCC). This include both new applications (8000 applications) and variation applications (8 000 applications). Applications go as far back as 1992 and only 50 % of these applications are at least 5 years old.

BRAZIL:

Product registration in Brazil by National Sanitary Surveillance Agency (ANVISA) is a lengthy task. Companies can apply for registration of medicinal products if they have manufacturing local operations based in Brazil. The government of Brazil support registration of generic products by discounting the registration fees for generics (Mohak, Charmy and Manan, 2017). ANVISA's Raphael Sanches Pereira (General Manager), mentioned at the Regulatory Affairs Professional Society that there were more than 800 new and generic applications backlogged and that it would be eliminated by January 2019 (RAPS, 2018).

CHINA:

In 2013, China's State Food and Drug Administration (CFDA) announced the implementation of improving drug review and approval process and the plan provided incentives for the R&D of innovative clinical drugs and the reduction in the approval process (RAPS, 2013). The first reform targeted the intellectual property rights and an expedited drug review process and the second focused on developing a revised national strategy for generic drugs that were in short supply and did not have branded competitor or are used for rare disease treatment (RAPS, 2013).

In February 2017, it was reported that CFDA had pharmaceutical and clinical trial backlogs. Serious backlog was for novel agents and a large number of generic drugs. This backlog was created mainly by a large number of untrained staff at the organisation. In 2015, CFDA had more than 21 000 applications on backlog. Most of these applications were for generic applications. CFDA requires clinical trial approval first for each product before a drug application can be submitted for approval. These include generic drug applications. (Brennan, 2017). The Chinese government then set a timeline for backlog applications received before the end of 2016 to deliver approval decisions within a specified time limit by 2018 (Zhou *et al,* 2017). By 2017, measures were taken to hire and train 300 technical evaluators to clear the backlog applications (Jain, Mollet and Szucs, 2017).

INDIA:

The Central Drug Standard Control Organization (CDSCO) is the key authority for new drug approvals in India. India produces pharmaceutical drugs that supply 50 % of global demand for various vaccines. It also supplies 40 % USA generic demand and 25 % of all medicine in the United Kingdom (IBEF, 2018). The pharmaceutical industry in India has come a long way from being a non-existent to become a global leader of pharmaceutical manufacturing companies (Swain *et al*, 2014). The Hatch-Waxman Act enacted of 1984 allowed generic drugs to be approved without repeating clinical trials required for new innovative drugs. This legislation allowed accessibility to medicines of lower cost while encouraging new innovative branded drugs. This created a lot of legal patent loopholes (Swain *et al*, 2014).

RUSSIA

Russia is the 5th largest export market for the European pharmaceutical industry, following US, Switzerland, Japan and China, which covers a total of 4.3 % of total EU pharmaceutical exports. The Russian Government progressively practice protectionist policies with a strong focus on

localisation, in support of domestic manufacturing. In 2016, the Federal Law on Circulation of Medicines shortened the overall Regulatory Data Protection (RDP) period from 6 years to 4 years, thus allowing generics to apply for market authorization 4 years after the original medicine has been registered and after 3 years for a biosimilar product (EFPIA, 2018).

There is no system in place to make provision for patent holders with the opportunity to settle patent disputes before launching a follow-on generic, which eventually also participate in state procurement tenders. Very few new drug registration applications have been filed by foreign companies in 2016 and 2017. In 2017, only 35 registration approvals took place. This is due to a local Russian GMP certificate requirement required in changing every safety information of the product information (EFPIA, 2018).

2.2 GENERICS VERSUS BRANDED MEDICINAL PRODUCTS

Therapeutically equivalent drugs (generics) contain the same amount of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route (MRSA, Act 101 of 1965). In South Africa, these generics are marketed only after patent expiration and are normally cheaper than the branded original medicines (Dylst and Simoens, 2011). Generic medicines increase accessibility and affordability in global healthcare systems. They also allow rapid access to essential medicines at more affordable prices (Kaplan *et al*, 2016).

Original products are NCEs that receive marketing authorisation first in the country (Gray *et al,* 2016). Innovative pharmaceutical companies continuously research and develop molecules that improve health and quality of life of patients (Dylst and Simoens, 2011). Innovators of these molecules apply for protection, which is 20 years from granting the patent. This period gives exclusive rights to market the product and also encourages investment in research and development of new molecules to find treatments for other diseases (Dylst and Simoens, 2011). Innovative company's recovered revenues are invested back for more inventions and innovations of new molecules to treat and manage the disease burden in the world. The value of R&D used to develop, register and market innovative products compared to the period available to market and recover revenues in South Africa is much shorter for innovative companies. Pharmaceutical innovations brought about new medicines, has saved and improved innumerable lives. Yet these innovative companies cannot utilise the full length of their patent in South Africa due to the current backlog (PWC, 2014).

2.3 MEDICINE PATENTS IN SOUTH AFRICA

Patents are created to encourage investment in research and development of finding new solutions to problems or situations. A patent is an exemption given for a certain period to companies for a product, a process or an idea that delivers or shows a new way of implementing or accomplishing and finding a solution to a problem. It excludes (prohibits) other players from copying your product. In South Africa, a patent is awarded for up to 20 years (CIPC, n.d). Product registration is not linked to patent status, but product launch is subject to existing patent validity (Tahir, 2007). Innovative pharmaceutical manufacturers depend on patents to protect their intellectual property. Sir Andrew Witty, CEO of GSK said in 2016 that Intellectual property protection is a vital part of healthcare innovation, providing necessary incentives for investment in research to create new treatments which can help people around the world (GSK, 2016).

Generics are generally less expensive than original drugs because their manufactures and marketers do not incur expenses of research and development on pre-clinical and clinical data; which can amount to lots of millions of rands (Leng, Pollock, and Sanders; 2016). The process of drug discovery, research and development is a slow and expensive process. It was found that worldwide, access to medicines and vaccines to treat and prevent non-communicable diseases is unacceptably low (Hogerzeil *et al*, 2013).

Largely, when a new original drug finally gets registered and launched, the company has already spent a significant amount of money. On account of the backlog created, a few years of exclusive marketing of the product is already lost.

2.4 ACCESS TO ESSENTIAL AND AFFORDABLE MEDICINES

Essential medicines are defined as those medicines that satisfy the priority health care needs of the population. These essential medicines are selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness (WHO, nd). In South Africa, the National Department of Health has developed different levels of Standard Treatment Guideline (STGs) and Essential medicines List (EML) which is Primary Health Care, Hospital level (Adults and Paediatrics) and Tertiary and Quaternary level. The STGs and EML ensure that cost-effective treatment options are available to citizens of the country. Emerging developments in medicine and scientific advances provided the basis for the review of the STG and EML.

The recommendations regarding therapeutic interventions were guided by available, relevant clinical evidence. In addition, the costs and incremental effectiveness of alternative medicines were

considered, which ensures that the selections of medicines are affordable and sustainable within a publicly finance health system (STG, 2018).

There has been an increase in the number of generics being registered in the previous dispensation called MCC which were perceived to be cheaper than the originator; to assist alleviation of challenges of lack of access of affordable medicines.

2.5 DOSSIER FARMING AND THE MEDICINE REGISTRATION BACKLOG

Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F, did not prevent or state how many generics the regulatory authority should register per molecule. This Act somewhat encouraged "dossier farming" within the industry. The South African Health Products Regulatory Authority's (SAHPRA) guideline titled "Multiple submissions of the same application for registration with different proprietary names" defines duplicate or multiple applications as two or more applications submitted simultaneously by the same applicant, which are identical in every aspect except for the proposed proprietary name(s) and include duplicate or multiple applications of innovator and generic products.

Dossier farming created a backlog at the Regulator. According to the Industry Task Group (ITG) meeting minutes of 27 November 2017 (SAHPRA, 2017), the regulator was allocating registration applications submitted September 2012 to be evaluated for registration. This suggests that the backlog at SAHPRA was over 5 years. Prof Rees (Chairperson of SAHPRA) at the Southern African Pharmaceutical Regulatory Affairs Association (SAPRAA) meeting of 13 April 2018, verbally reported that the Regulator has over 3000 submitted applications awaiting evaluation (SAHPRA, 2018). This has been observed in an article by Leng and colleagues (2015) where it was mentioned that since 2005, the number of applications submitted more than doubled whereas the number of certificates remained approximately the same. Since the introduction of the pro-generic legislation in 2001, with an attempt to promote and ease the entry of generics into the South African market to increase competition and affordable medicines.

The pro-generic legislation allowed for fast-track of applications of medicines appearing on the EML. This increased the backlog as the energy was now focussed on registration of EML generic products through the fast-track process. Fast track approvals were supposed to speed up registration of both New Chemical Entity (NCEs) and Essential Medicine. However, this created a backlog of registration of EML generic medicines due to pharmaceutical companies seeing this process as an opportunity to have their products registered and launched in a short space of time.

While EML generic medicines were submitted for fast track registration, a few branded new molecules would also be submitted but get trapped in the backlog (Leng, Pollock and Sanders, 2016). In addition, it was noted that some companies submitted more than one application of the same dossier but under a different trade name via the expedited review. This process created further backlog and delays in registration of medicines of new chemical entities. Unfortunately, the Act did not prevent or state how many generics the regulatory authority should register per molecule. Due to this provision of the Act, innovative pharmaceutical companies are unable to enjoy the patent exclusivity period benefits and to recover revenues spent for their research and development (R&D).

2.6 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-INHIBITORS), ANGIOTENSIN II RECEPTOR BLOCKERS (ARB's) AND CALCIUM CHANNEL BLOCKERS IN SOUTH AFRICA

Angiotensin converting enzyme inhibitors (ACE-inhibitors) are a class of anti-hypertensive drugs included in the Essential Medicines List (EML). They are the first drug of choice for hypertension treatment (Seedat, Rayner and Veriava, 2014). They are taken by thousands of patients as chronic medication for control of hypertension (Sweitzer, 2003). Examples of ACE-inhibitors on the market are quinapril HCl, captopril, lisinopril, enalapril maleate, ramipril, perindopril tertbutylamin and trandolapril. Enalapril constitutes the bulk of the government supply to patients, since it is the treatment of choice for treatment of high blood pressure and congestive heart failure (NDoH, 2012).

Losartan potassium is an angiotensin II receptor antagonist that binds competitively and selectively to the AII subtype 1 (AT(1)) receptor that specifically block actions of angiotensin II, thereby lowering the blood pressure (Goa and Wagstaff, 1996). It is mainly used to treat high blood pressure. Other uses include diabetic kidney disease, heart failure, and left ventricular enlargement (STG, 2018).

Calcium-channel blockers are smooth muscle dilators that inhibit Ca2+ entry into the excitable cells. They reduce blood pressure by limiting the amount of calcium or the rate at which calcium flows into the heart muscle and arterial cell walls (Zakhari, 1986). They are also first line antihypertensive drugs (Seedat, Rayner and Veriava, 2014). Amlodipine besylate, a calcium-channel blocker, is one of the drugs investigated in this research.

2.7 Summary

Chapter 2 seeks to review all relevant literature, to better understand the context of dossier farming in South Africa. Comparing the practice to other third world countries.

CHAPTER 3
RESEARCH METHODOLOGY

3.1 METHODOLOGY AND STUDY DESIGN

3.1.1 STUDY DESIGN

Study design provides the overall structure for the procedures the researcher follows, the data the researcher collects, and the data analyses the researcher conducts (Leedy and Ormrod, 2014). This study was conducted retrospectively using a quantitative descriptive design.

3.1.2 STUDY SAMPLE

SAHPRA registers approximately 500 to 600 (Leng, Sanders, and Pollock, 2015) medicines annually. On a periodic basis, SAHPRA publishes a list of registered medicines on the website for public use. This list was used to determine and compare the number of generics of amlodipine, enalapril and losartan medicines registered. The list contains the registration number, proprietary names, and ingredients of the registered medicines. The first two numbers of the registration correlate with the year of submission of that product. A list of Registration Notification from SAHPRA will indicate when the product was registered. Lista were selected according to the inclusion and exclusion criteria listed below.

3.1.3 Inclusion Criteria:

• Generic registrations of oral, solid dosage forms of losartan, enalapril and amlodipine, before and after each drug' patent expiration up to August 2018.

3.1.4 Exclusion Criteria:

- Generic registrations of losartan, enalapril and amlodipine after August 2018.
- Combination drugs of losartan, enalapril and amlodipine with other molecules.

3.2 MATERIAL AND INSTRUMENTS

3.2.1 DATA COLLECTION INSTRUMENTS

All data was collected and collated in Excel according to the format seen within the data collection tool used (Appendix 1). The categories used to capture data include: Trade Name, Active substance, Applicant Company, Registration Number, Year of NDA submission, Year of registration and Number of years after patent expiry.

3.2.2 DATA COLLECTION AND ANALYSIS

Data was collected using a standardised structured data collection sheet (Appendix 1), which includes the list and names of registered generics of amlodipine, losartan and enalapril registered before and after the expiry of patent as well as the year of registration. Companies whose products were registered before 2000 were called to confirm the year of registration.

Stata Release 15 (StataCorp, 2017) was used for data analysis. Descriptive statistics for categorical variables were presented as frequencies and percentages, and for continuous variables were presented as mean, median, quartiles. Pearson's chi-square test was used to test for association between two categorical variables. T-test was used to compare the averages between two groups and analysis of variance (ANOVA) was used to compare the means between three groups. The interpretation of results was performed at 95 % confidence limit or 0.05 error rate.

3.2.3 VALIDITY AND RELIABILITY

Validity is defined as the degree to which the researcher has measured what he has set out to measure (Kumar, 2011). It is the concept of appropriateness and accuracy as applied to a research process. It can also be defined as the extent to which a particular measure is free from both systematic and random error and indicates validity of the measure (Diamantopoulos and Schlegelmilch, 2000:33). Validity also refers to whether or not an indicator (or set of indicators) that is devised to gauge a concept really measures that concept (Bryman & Bell, 2011). This kind of measurement is usually applied to quantitative research. There are few ways of establishing validity and are: face validity, concurrent validity, predictive validity, construct validity and convergent validity.

In our study, construct validity will be used to determine the degree to which a test assesses the underlying theoretical construct it is supposed to measure. The threat to construct validity is the experimental expectancies which may relate to researcher's own biases and assumptions affect the results of the study. The researcher can provide unconscious indications or signs about the results due to the prior knowledge of backlog and dosser farming. This potential bias can be prevented by capturing the actual numbers and names of medicines. A work supervisor will be requested to verify the contents of the results. In addition, evidence used to capture data will also be furnished to the academic supervisor.

Reliability is the degree of accuracy or precision in the measurements made by a research instrument. The lower the degree of error in an instrument, the higher the reliability (Kumar, 2011).

Reliability also refers to the consistency of the measure of a concept (Bryman & Bell, 2011). The authors define three prominent factors to consider whether the measure is reliable. These include (1) stability which talks to the measure over time which does not vary or fluctuate when a measure is administered; (2) Internal reliability which measures the consistency of the scale; (3) inter-observer consistency. The proposed method to obtain consistent results should the study be repeated. Threat to reliability is likely to be researcher error (human error) when capturing data to data collection sheet. This was address by the researcher confirming the data captured and also requesting a fellow employee to verify the correctness of the data and information captured. Like the validity, the corrected of the data collected will also be validated by the supervisor and academic supervisor. Reliability and validity are closely related because validity presumes reliability. If a measure is not reliable, it cannot be valid.

As indicated above, construct validity will be applied based on the extent to which operationalisation of a construct measure a construct as defined by theory. The tool used will ensure that there is consistency of measure as the study is designed to compare number of generics post patent as well as the effect of dossier farming. The data collected are of an objective nature adding to the reliability and validity of the tool used.

3.2.4 ETHICAL CONSIDERATIONS

The ethical approval was not required because the information used is publicly available. There was no need to obtain informed consent as there were no participants used and owing to the fact that this is a retrospective study. Other ethical consideration which might emerge is accidentally slandering a company with the results of the research.

3.2.5 BIAS

Bias was addressed by using data that was publicly available. The data collected is objective, leaving no room for the researcher to manipulate the data. All data collected was also crosschecked by supervisors.

3.3. CONCLUSION

Much thought went into the data collection process, which had to be well implemented to obtain reliable and valuable results. The methodology described in this chapter was the best and most appropriate methodology for the purpose of this study.

3.4 SUMMARY

This chapter discussed the methodology of the study. Information on the study design and study site was given. Details about sample selection and data collection instruments used in this study were described. The chapter concluded with a discussion of the reliability and bias of the study as well as the ethical considerations, which were taken into consideration throughout the study period.

Chapter 4 will include results obtained in this study and the discussion of these results.

CHAPTER 4
RESEARCH RESULTS AND DISCUSSION

4.1 INTRODUCTION

The data was collected over a period of two months (October to November 2018). This section explains the data analysis and findings of the information and the outcomes of the data collected to answer the research question of determining the effect of dossier farming in medicine registration. The outcomes and analysis answer our research objective of comparing the number of generic registrations for enalapril, amlodipine and losartan. It also quantifies the extent to which dossier farming is practiced and the effect it had on the medicine backlog. Data was analysed to describe and investigate the relationship between dossier farming in medicine registration for amlodipine, enalapril and losartan drug substances.

These molecule's registration details for generics were compared with the innovator's registration details. Information on when the drug products were registered was compared before and after patent expiry. Registration details for all three molecule's data were collected from the Notification of Registration of Medicines obtained from SAHPRA's website. Companies whose products were registered before the year 2000 were called telephonically to confirm the year of registration.

4.2 COMPARISON OF THE NUMBER OF GENERIC REGISTRATIONS BEFORE/AFTER PATENT EXPIRY

Amongst all groups, there are 36.3 %, 30.8 %, and 32.8 % of registered molecules for amlodipine, losartan, and enalapril respectively. The innovators accounts for 5.56% across all products whereas generics accounts for 94.44 % of all products.

Table 1: Summary of number of years before/after patent expiry

Active substance	Summary of number of years before/after patent expiry		
	Mean	**Std. Dev.**	**Freq.**
Amlodipine	1.51	4.46	72
Losartan	0.47	3.25	61
Enalapril	0.29	7.58	65
Total	**0.79**	**5.42**	**198**

The mean number of years after patent expiry is 0.79 years with a standard deviation of 5.42.

Table 2: Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	59.8647213	2	29.9323606	1.02	0.3629
Within groups	5728.64538	195	29.3776686		
Total	5788.5101	197	29.3833		

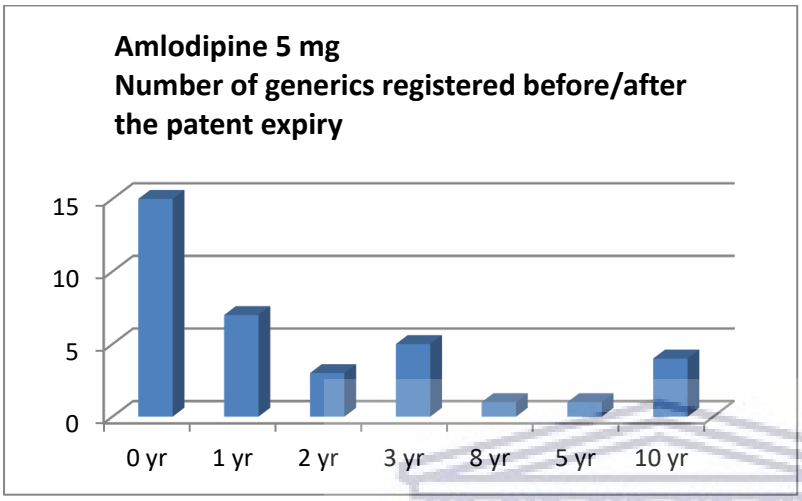
SS- Sum of squares, df- degree of freedom, MS - Mean of squares, F- F Test statistic

Analysis of variance is used to compare three or more groups for statistical significance and used for hypothesis testing. Usually, there is variation anytime that all of the data values are not identical. The Sum of squares quantifies the total variation in the observed data. In our research the variation between and within groups is 5788.51. In addition, F-statistic was used to compare the "average" variability between the groups to the "average" variability within the groups.

In the table above, the average number of years taken before/after patent expiry is not significantly different between all three active substances (p = 0.3629). There is no difference in time taken to register the products between the three molecules and within each molecule.

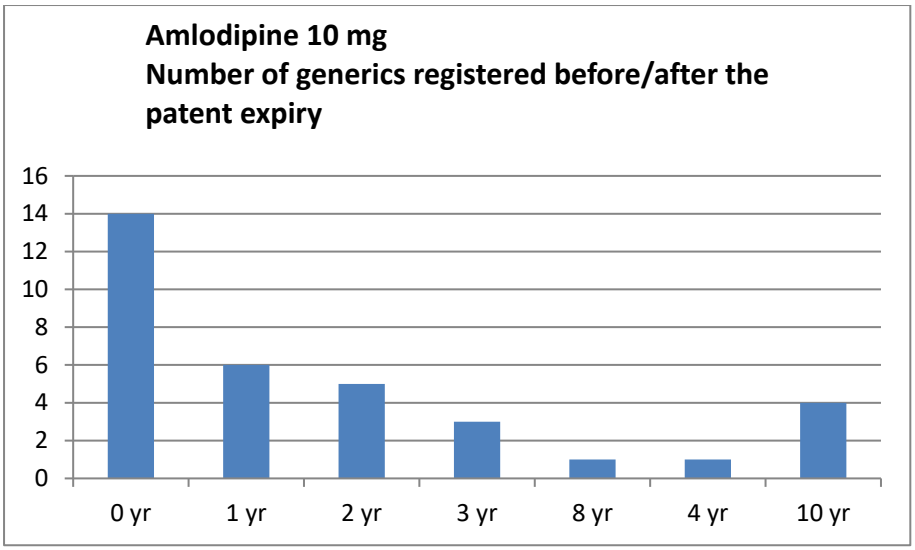
4.2.1 Amlodipine - Patent Expiry: August 2006

Graph 1: Number of amlodipine 5 mg registered



Out of the 36 generic amlodipine 5 mg dossiers registered; fifteen dossiers were registered before the expiry date of the patent for Norvasc® which expired in 2006. In the first and second year after expiry of the patent, seven and three dossiers were registered respectively. Five dossiers and only one dossier was registered on the third and eighth year after expiry of the patent. In the fifth year one dossier was registered and four dossiers on the tenth year after expiry of the Norvasc patent in 2016.

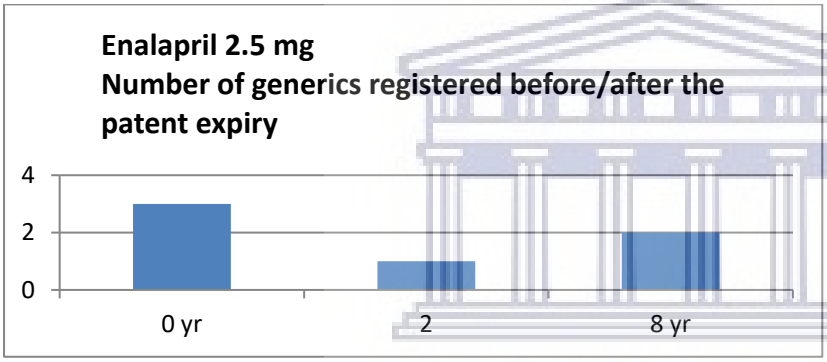
Graph 2: Number of amlodipine 10 mg registered



Out of the 34 generic amlodipine 10 mg dossiers registered; 14 dossiers were registered before the expiry date of the patent for Norvasc® which expired in 2006. In the first and second year after expiry of the patent, six and five dossiers were registered respectively. Three dossiers and only one dossier was registered on the third and eighth year respectively after expiry of the patent. In the fourth year one dossier was registered and four dossiers in 2016, on the tenth year after expiry of the Norvasc® patent.

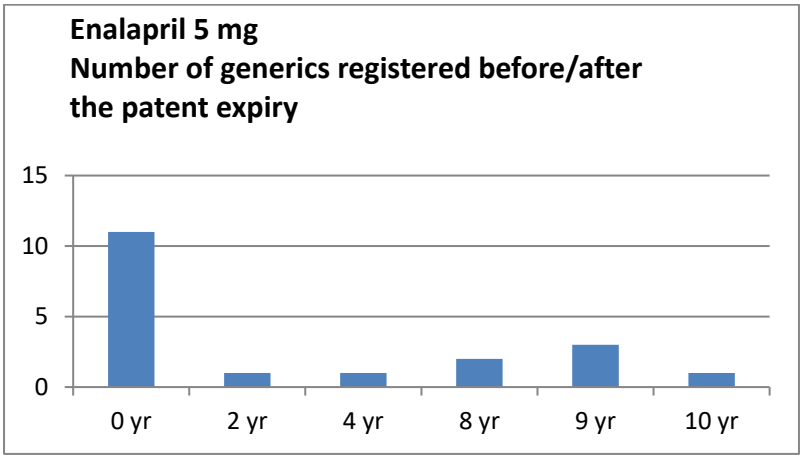
4.2.2 Enalapril - Patent Expiry: October 2006

Graph 3: Number of enalapril 2.5 mg registered



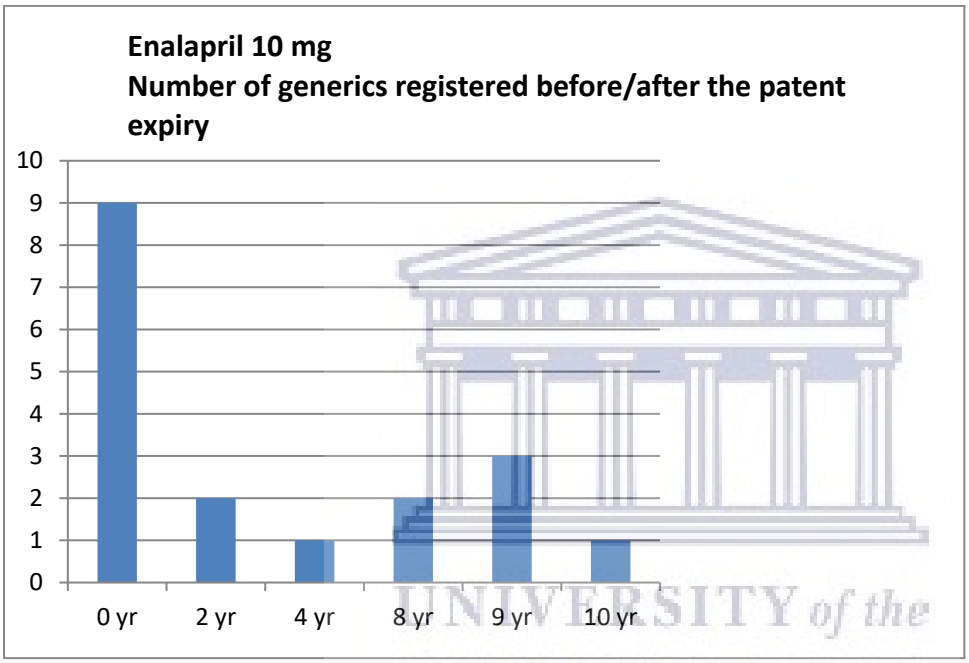
Out of the 6 generic enalapril 2.5 mg dossiers registered between the year 2000 and 2015; three dossiers were registered before the expiry date of the patent for Renitec® which expired in 2007. In the second and eighth year after expiry of the patent, one and two dossiers were registered respectively.

Graph 4: Number of enalapril 5 mg registered



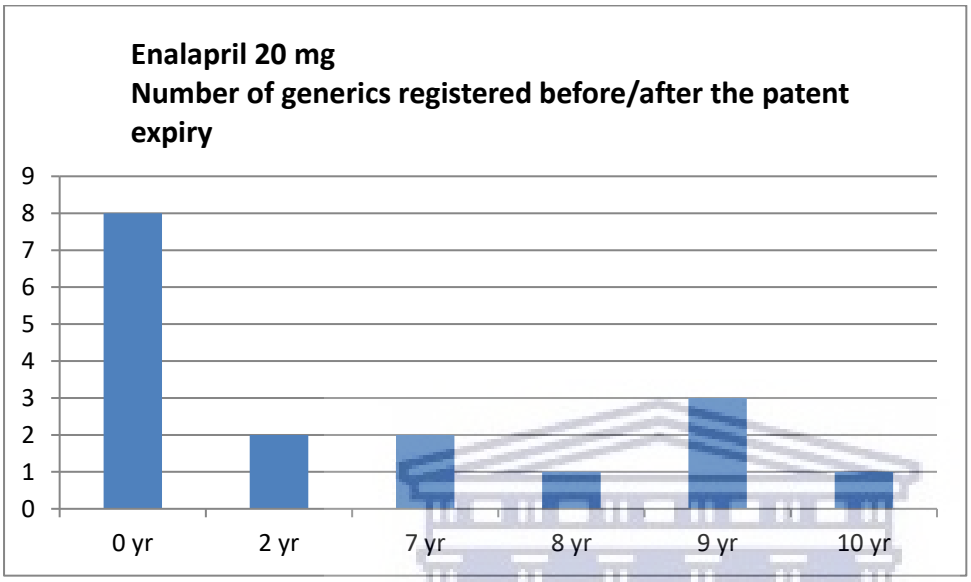
Out of the 19 generic enalapril 5 mg dossiers registered; eleven dossiers were registered before the expiry date of the patent for Renitec® which expired in 2007. In the second and fourth year after expiry of the patent, one dossier per company was registered and the eighth year two dossiers and three dossiers in the ninth year and only one dossier was registered in 2015.

Graph 5: Number of enalapril 10 mg registered



Out of the 18 generic enalapril 10 mg dossiers registered; nine dossiers were registered before the expiry date of the patent for Renitec® which expired in 2007. In the second and fourth year after expiry of the patent, two and one dossier were registered respectively per company. The eighth and ninth year registered two and three dossiers respectively and only one dossier was registered in 2015, nine years after patent expiry.

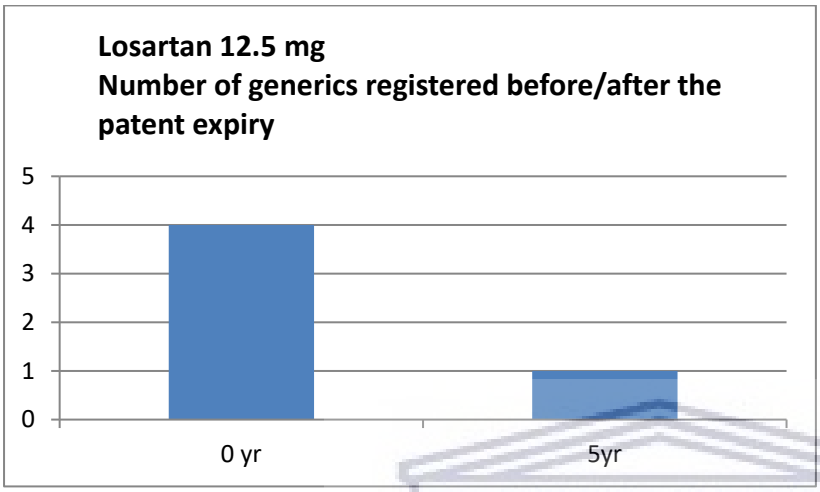
Graph 6: Number of enalapril 20 mg registered



Out of the 17 generic enalapril 20 mg dossiers registered; eight dossiers were registered before the expiry date of the patent for Renitec® which expired in 2007. Two dossiers were registered in the second and seventh year. The eighth and ninth year registered one and three dossiers respectively and only one dossier was registered in 2015.

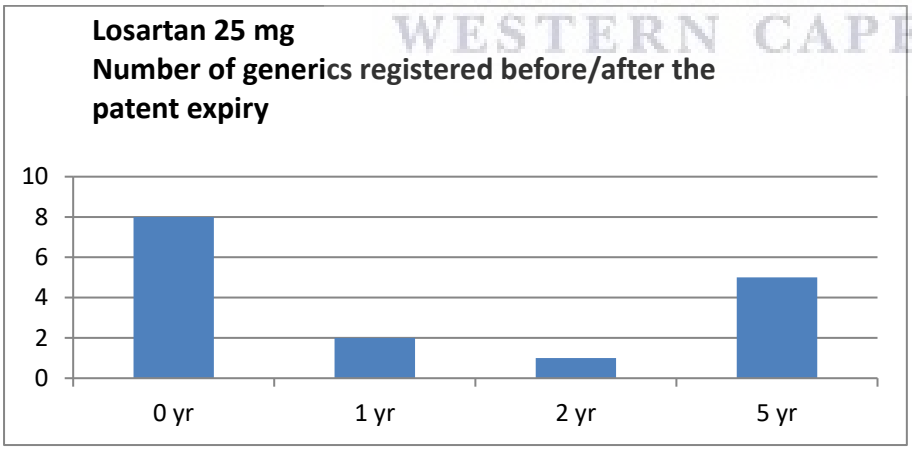
4.2.3 Losartan - Patent Expiry: August 2009

Graph 7: Number of losartan 12.5 mg registered



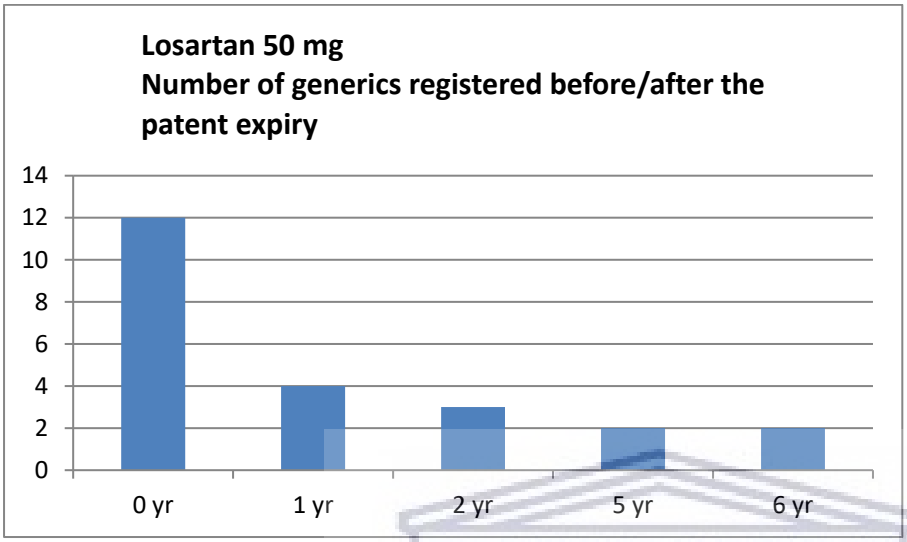
Out of the 5 generic losartan 12.5 mg dossiers registered between the year 2007 and 2014; four dossiers were registered before the expiry date of the patent for the molecule losartan in 2009. MSD as the innovator for losartan did not register a 12.5 mg strength. In the fifth year after expiry of the patent, one dossier was registered in 2014.

Graph 8: Number of losartan 25 mg registered



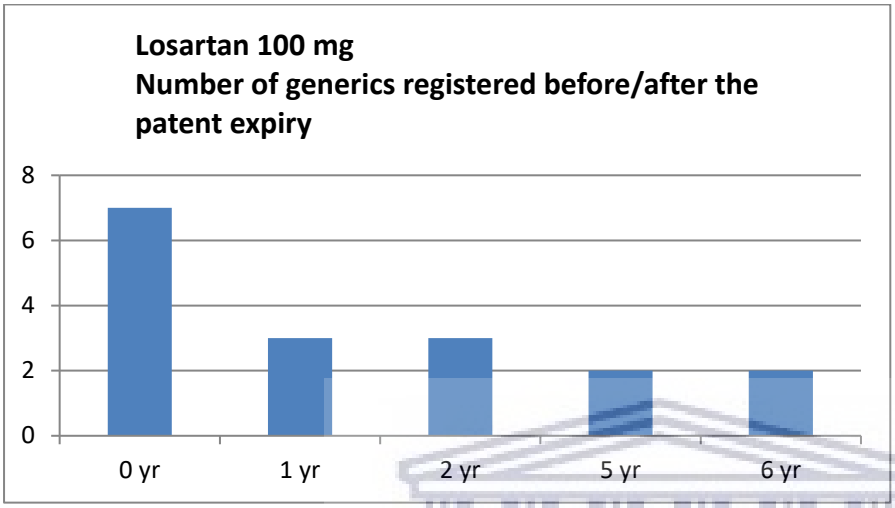
Out of the 16 generic losartan 25 mg dossiers registered between the year 2007 and 2014; eight dossiers were registered before the expiry date of the patent for the molecule losartan in 2009. MSD as the innovator for losartan did not register a 25 mg strength tablet. In the first, second and fifth year after expiry of the patent, two and one and five dossiers was registered.

Graph 9: Number of losartan 50 mg registered



Out of the 23 generic losartan 50 mg dossiers registered between the year 2007 and 2015; twelve dossiers were registered before the expiry date of the patent for Cozaar 50 in 2009. MSD is the innovator of the molecule. In the first year after expiry of the patent, four dossiers were registered, then three dossiers were registered in 2011. Two dossiers per company were registered in 2014 (5 yr) and 2015 (6yr).

Graph 10: Number of losartan 100 mg registered



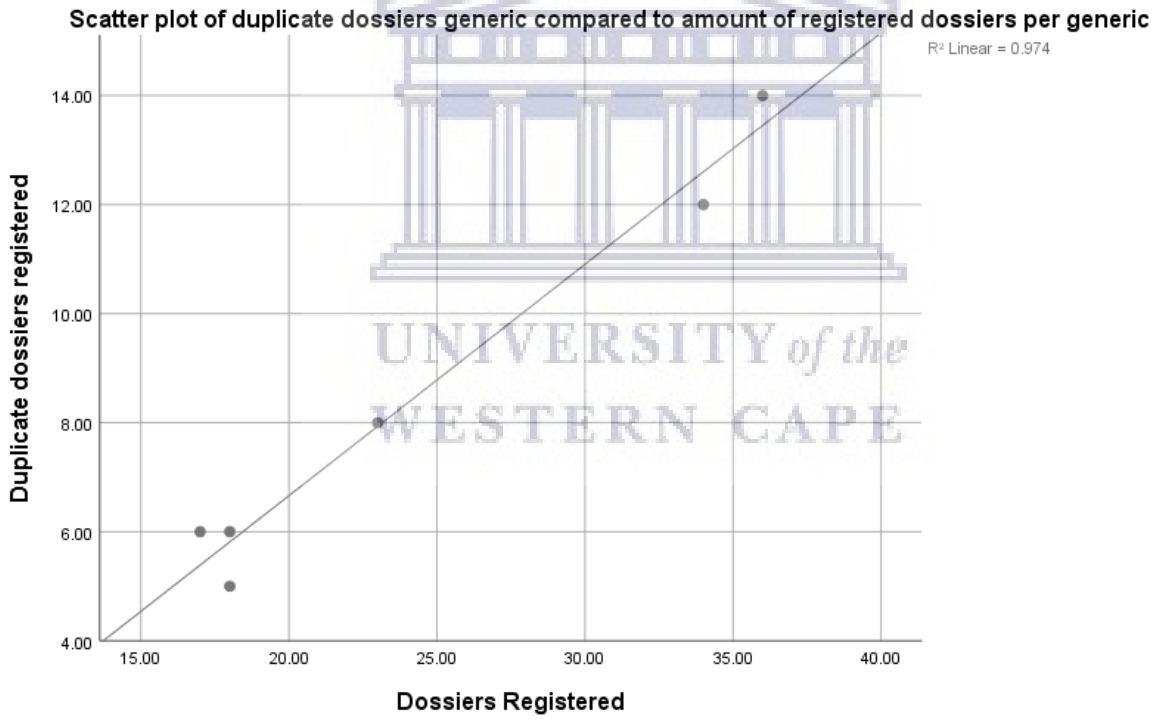
Out of the 17 generic losartan 100 mg dossiers registered between the year 2007 and 2015; seven dossiers were registered before the expiry date of the patent for Cozaar 100 which expired in 2009. In the first year after expiry of the patent, three dossiers were registered in 2010, and three dossiers in 2011. Two dossiers per company were registered in 2014 and 2015.

4.3 Dossier farming

This section demonstrates and shows how many dossiers of the same product and same strengths were registered by the same company (applicant).

Upon conducting a Pearson's correlation coefficient there was a significant correlation between the number of dossiers registered and the amount of dossier farming
Pearson correlation = 0.987 which constitutes a p-value of 0.000251.

Graph 11 Scatterplot of Total Dossiers registered vs Duplicate dossiers registered



There was not a significant any correlation between dossiers registered/farmed or tender contract quantity (quantity of generic required by government) or amount paid by government for each generic (tendered amount).

		Tablets required by government	*Total amount of dossiers registered*	*Amount of duplicate dossiers*	*Price awarded for each generic*
Tablets required by government	Pearson Correlation	1	.031	-.047	.982**
	Sig. (2-tailed)		.954	.930	.000
	N	6	6	6	6
Total amount of dossiers registered	Pearson Correlation	.031	1	.987**	-.051
	Sig. (2-tailed)	.954		.000	.923
	N	6	6	6	6
Amount of duplicate dossiers	Pearson Correlation	-.047	.987**	1	-.132
	Sig. (2-tailed)	.930	.000		.803
	N	6	6	6	6
Price awarded for each generic	Pearson Correlation	.982**	-.051	-.132	1
	Sig. (2-tailed)	.000	.923	.803	
	N	6	6	6	6

**. Correlation is significant at the 0.01 level (2-tailed).

4.3.1 AMLODIPINE DOSSIER FARMING

Table 3: Number of generic dossiers registered per company for Amlodipine

Generic name:	Company name:	Dossiers registered	Generic name:	Company name:	Dossiers registered
Amlodipine 5 mg	Pfizer	1	**Amlodipine 10 mg**	Pfizer	1
	Accord	2		Accord	2
	Aurobindo	2		Aurobindo	2
	Camox	2		Camox	2
	Dezzo	4		Dezzo	2
	Dr Reddy	3		Dr Reddy	3
	Hexal	2		Hexal	2
	Pharma Dynamics	4		Pharma Dynamics	4
	Sandoz	3		Sandoz	3

Amlodipine 5 mg

Out of the 36 generic amlodipine 5 mg dossiers registered from the year 2004 to 2016, eight companies practiced dossier farming. Two companies registered four dossiers; two companies registered three dossiers while the remaining five companies registered two dossiers each. The rest of the companies (28) registered one amlodipine 5 mg dossier. The innovator Pfizer registered a clone Lomanor. Thus out of the 36 generic amlodipine 5mg products registered 14 were duplicate dossiers entered at the same time the company had already submit a single primary dossier.

Amlodipine 10 mg

Out of the 34 generic amlodipine 10 mg dossiers registered from the year 2004 to 2016, eight companies practiced dossier farming. One company registered four dossiers; two companies registered three dossiers while the remaining five companies registered two dossiers each. The rest of the companies (26) registered one amlodipine 5 mg dossier. The innovator Pfizer registered a clone Lomanor. Thus 12 out of 34 dossiers were duplicate dossiers.

4.3.2 ENALAPRIL DOSSIER FARMING

Table 4: Number of generic dossiers registered per company for Enalapril

Generic name:	Company name:	Dossiers registered	Generic name:	Company name:	Dossiers registered
Enalapril 10 mg	Aspen Pharma	2	**Enalapril 20 mg**	Aspen Pharma	2
	Biotech Lab	2		Biotech Lab	2
	Arrow Pharma	2		Arrow Pharma	2
	Austell	3		Austell	3
				Cipla	2

Enalapril 10 mg

Out of the 18 generic enalapril 10 mg dossiers registered from the year 2000 to 2015, four companies practiced dossier farming. One company registered three dossiers and three companies registered two dossiers each. The rest of the companies (14) registered one enalapril 10 mg dossier each. 5 out of 18 dossiers were duplicate dossiers.

Enalapril 20 mg

Out of the 18 generic enalapril 20 mg dossiers registered from the year 2000 to 2015, four companies practiced dossier farming. One company registered three dossiers and four companies registered two dossiers each. The rest of the companies (13) registered one enalapril 20 mg dossier each. Thus 6 out of the 18 dossiers were duplicate dossiers.

4.3.3 LOSARTAN DOSSIER FARMING

Table 5: Number of generic dossiers registered per company for Losartan

Generic name:	Company name:	Dossiers registered	Generic name:	Company name:	Dossiers registered
Losartan 50 mg	Hexal	2	**Losartan 100 mg**	MSD	1
	Cipla	2		Cipla	3
	Pharma Dynamics	2		Austell	2
	Austell	3		Specpharm	2
	Specpharm	2		Ranbaxy	2
	Ranbaxy	2		Aurobindo	2
	Aurobindo	2			

Losartan 50 mg

Out of the 23 generic losartan 50 mg dossiers registered from the year 2001 to 2016, seven companies practiced dossier farming. One company registered three dossiers and six companies registered two dossiers each. The rest of the companies (16) registered one losartan 50 mg dossier each. 8 out of 23 registered losartan 50 mg forms were duplicate dossiers.

Losartan 100 mg

Out of the 17 generic losartan 100 mg dossiers registered from the year 2001 to 2015, six companies practiced dossier farming. One company registered three dossiers and five companies registered two dossiers each. The rest of the companies (12) registered one losartan 50 mg dossier each. MSD, the innovator registered a clone Fortzaar®. Six out of 17 losartan 100 mg dossiers approved were duplicate dossiers.

4.4 AMLODIPINE DISCUSSION

Amlodipine is indicated for the treatment of mild to moderate hypertension. It is also indicated for the treatment of angina pectoris (Norvasc package insert, 2001). It is the 1st line treatment for hypertensive urgency both in hospitals and primary healthcare treatment (STG, 2018). It constituted 29 % of the three molecules discussed here for the country by Department of Health for the period August 2016 to July 2018. The amount for both amlodipine 5 mg and 10 mg tendered was R134 743 426.00 (NDOH, 2018A).

Out of the 36 generic amlodipine 5 mg and 34 of amlodipine 10 mg dossiers registered between 2004 and 2016; fifteen and fourteen dossiers were registered respectively before the expiry date of the patent for the innovator Norvasc® in 2006. Generic companies can register their products with the Health Authority and only launch them after patent expiry. This indicates how generic companies prepared themselves to market immediately after patent expiry. In South Africa, a product can be registered but not launched before patent expiry. Graph 1 and 2 indicate that there were more products registered for amlodipine to launch immediately after patent expiry. There were fifteen amlodipine 5 mg and fourteen amlodipine 10 mg dossiers registered to launch at the same time or period. Of interest is that the innovator Pfizer, also registered Lomanor®, a clone in 2005 – a clone is an application submitted by the innovator as a copy of its own product under a different proprietary name at any stage during the product life cycle (SAHPRA, 2015). Lomanar® was registered a year before patent expiry. This has been seen as a strategy for molecule owners (innovators) to protect and still gain out of their inventions.

In the first and second year after expiry of the patent, seven amlodipine 5 mg and three amlodipine 10 mg dossiers were registered respectively. Five dossiers and only one dossier were registered on the third and eighth year after expiry of the patent. In the fifth year one dossier was registered and four dossiers on the tenth year after expiry of the Norvasc patent in 2016.

Even though there are 36 amlodipine 5 mg and 34 amlodipine 10 mg generics registered, many of these generics were submitted by eight applicants. These applicants constitute 61 % of dossier farming on these two strengths for amlodipine. Sandoz and Hexal companies belong to a Novartis company. Combined, they registered five generics each of amlodipine

5 mg and 10 mg. Two companies, Dezzo and Pharma Dynamics, registered four generics each of amlodipine 5 mg and amlodipine 10 mg. This can only indicate that some of these dossiers can be sold to companies in demand of already registered dossiers to be able to compete in the private and public tender market.

4.5 ENALAPRIL DISCUSSION

Enalapril is indicated to treat all grades of essential hypertension, symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction (Pharmapress package insert, 1999). It is used for the treatment in both children and adult subjects with congestive cardiac failure. It is the 1st line treatment for hypertension with diabetes in both hospitals and primary healthcare treatment (STG, 2018). Enalapril constituted 70 % of the three medicines in this research required for the country by Department of Health for the period August 2016 to July 2018. The amount for both enalapril 10 mg and 20 mg tendered was R324 293 584.00 (NDOH, 2018A).

Out of the 18 generic enalapril 10 mg and 17 of enalapril 20 mg dossiers registered between 2000 and 2015; there were nine enalapril 10 mg dossiers and eight enalapril 20 mg dossiers available for launch before patent expiry of the innovator Renitec® in 2007. This is 50 % of the enalapril dossiers finally registered. This also indicates how generic companies prepare themselves to market immediately after patent expiry. In South Africa, a product can be registered but not launched before patent expiry. Graph 3 to 6 for enalapril 2.5 mg, 5 mg, 10 mg and 20 mg indicate that there were more products registered for enalapril to launch immediately after patent expiry.

It is important to note that only six generics were registered for enalapril 2.5 mg and only one company (Arrow Pharma) practiced dossier farming in registering two dossiers. Enalapril 2.5 mg and 5 mg were not requested for tendering between August 2016 and July 2018. Of the 18 generics registered for enalapril 10 mg and 18 dossiers also registered for enalapril 20 mg, dossier farming was practiced by four applicants for enalapril 10 mg, which accounts to 50 % and 61 % dossier farming for enalapril 20 mg. One company (Austell Laboratories), received the tender for both enalapril 10 mg and 20 mg. This company registered three dossiers for each strength and the other applicants registered two dossiers each.

4.6 LORSATAN DISCUSSION

Losartan is mainly used to treat high blood pressure. Other uses include diabetic kidney disease, heart failure, and left ventricular enlargement (STG, 2018). It constituted 1 % of all the three molecules researched and required for tendering the country by Department of Health for the period August 2016 to July 2018. The amount for both losartan 50 mg and 100 mg tendered was R4 931 608.00 (NDOH, 2018A).

Out of the 23 generic losartan 50 mg and 18 losartan 100 mg dossiers registered between 2007 and 2015; twelve and seven dossiers were registered respectively before the expiry date of the patent for the innovator Cozaar® in 2009. This also indicates how generic companies prepare themselves to market immediately after patent expiry. In South Africa, a product can be registered but not launched before patent expiry. Graph 7 to 10 for losartan 12.5 mg, 25 mg, 50 mg and 100 mg indicate that there were more products registered for losartan to launch immediately after patent expiry. Twelve generics for losartan 50 mg and seven generics registered for losartan 100 mg before patent expiry.

Losartan 12.5 mg, 25 mg, 50 mg and 100 mg had five, thirteen, twenty three, and seventeen generics registered respectively. Of importance to note is that the innovator (MSD) also registered a clone, Fortzaar® 100. This clone was registered in 2001. This is eight years before the original patent expiry. Innovator companies use this clone strategy to protect their intellectual property and continue gaining revenues before and after patent expiry.

Out of the 23 generic losartan 50 mg dossiers registered from the year 2001 to 2015, seven companies practiced dossier farming. This constitutes 65 % of the losartan registered. This is indicated on Table 5. One company registered three dossiers and six companies registered two dossiers each. The rest of the sixteen companies registered one losartan 50 mg dossier each. Out of the 17 generic losartan 100 mg dossiers registered from the year 2001 to 2015, six companies practiced dossier farming. This is 70 % of the losartan 100 mg registered. One company registered three dossiers and five companies registered two dossiers each. The rest of the twelve companies registered one Losartan 50 mg dossier each.

In the year 2001, MSD, the innovator registered a clone Fortzaar® 50. This is eight years before the original patent expiry. Innovator companies use this clone strategy to protect their intellectual property and continue gaining revenues before and after patent expiry.

Monopoly by innovative companies ends when the patent expires. Generics normally enter the market on a much lower price than the innovator price. Availability of these products is also an advantage that even when one company cannot produce the required units, tenders can be divided into different companies. There are only two companies who can supply injectable contraceptives (NDOH, 2017).

CHAPTER 5
RESULTS AND DISCUSSION

5.1 INTRODUCTION

According to SAHPRA's communication (SAHPRA, 2018) SAHPRA inherited a backlog of about 8000 new applications from Medical Control Council (MCC) in February 2018. Ninety percent (90 %) of these applications are for generic applications. Sixteen percent (16 %) of these applications contain 15 active substances averaging only 20 applicants. This indicate that out of the 8000 new application backlog at SAHPRA, 1152 applications were submitted for 15 active drug substances by only 20 applicants. This averages 3.84 applications of dossier farming per active substance per applicant. These further indicate that these 20 generic applicants submitted on average 4 dossiers of the same active substance.

This backlog amounts to public health crisis and an obstacle for patients to receive new innovative products and an obstruction to the pharmaceutical industry growth. With all three molecules researched i.e. amlodipine, enalapril and losartan; there were over 10 generics registered for the strengths tendered by the government.

Out of these three tendered products researched, enalapril 10 mg and 20 mg had the highest percentage of 69.87 % and losartan 50 mg and 100 mg had the lowest 1.09 %. The tendering amount of the three molecules was worth R463 968 618.00 (NDOH, 2018A). It is of interest to note that Dezzo and Austell Laboratories are the two companies awarded most tenders for all three molecules. Dezzo was awarded tenders for both amlodipine 5 mg and Enalapril 10 mg worth R25 777 061.00 (NDOH, 2018A). This constituted 5.6% of all the three molecules on tender. Austell Laboratories was awarded tenders for amlodipine 5 mg, amlodipine 10 mg, enalapril 10 mg, enalapril 20 mg and all tenders for losartan 50 mg and 100 mg. This tenders were worth R35 495 657.00 (NDOH, 2018A) which constituted 7.7 % of three molecules on tender. Out of all these companies tendering, Dezzo was found to have practiced dossier farming on 4 dossiers with amlodipine 10 mg. Having more dossiers of the same molecule registered implies that a company has more chance of receiving tenders, if submitted using different trade names to compete on the same tenders.

5.2 SUMMARY OF RESULTS

Companies tend to start the registration procedure through SAHPRA well in advance of the patent expiration date. This is likely because only marketing and distribution are delayed until the patent expires. Thus if the company registered the generic well in advance, the company has to wait and only launch after innovator patent expiry.

Having generics has benefited the country and the patients of South Africa. Competition is encouraged and profits are shared within companies. Having too many generics in the country can saturate the market. It was proven that only 54 % of all registered generic brands investigated by Leng, Pollock and Sanders were marketed (Leng, Pollock and Sanders, 2016).

It is realised from the above research that dossier farming though it was the beginning of its inception after approval of pro-generic legislation in the year 2001; it lured many companies to think this would be profitable. This study found a significant link between the amount of dossiers registered and the amount of duplicate dossiers (dossier farming). This means that, the more dossiers are registered per generic, the more likely there will be duplicates within the waiting list.

There was not significant correlation between the amount of units (generic pack sizes) and the number of registered dossiers. The total amount of dossiers registered according to the inclusion criteria was 146 of which 51 dossiers were duplicate dossiers. This translated to roughly a third of all generic registrations being duplicate dossiers.

CHAPTER 6

STUDY LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

6.1 LIMITATIONS:

The study had a small sample size. The medications included were only representative of chronic conditions. Dossier farming practices in enalapril, losartan and amlodipine might not be reflected in all applications submitted to SAHPRA. The amount of applications were not available, only those medicines that were successfully registered.

6.2 DISCUSSION:

Companies tend to start the registration procedure through SAHPRA well in advance of the patent expiration date. This is likely because only marketing and distribution delayed until the patent expires. Thus if the company registered the generic well in advance, there are no hindrances to start promoting and selling their generics immediately after patent expiry.

Having generics has benefited the country and the patients of South Africa. Competition is encouraged and profits are shared within companies. Having too many generics in the country can saturate the market. It was proven that only 54 % of all registered generic brands investigated by Leng, Pollock and Sanders were marketed (Leng, Pollock and Sanders, 2016).

It is realised from the above research that dossier farming although it was the beginning of its inception after approval of pro-generic legislation in the year 2001; it lured many companies to think this would be profitable. This study found a significant link between the amount of dossiers registered and the amount of duplicate dossiers (dossier farming). This means that, the more dossiers are registered per generic, the more likely there will be duplicates within the waiting list of dossiers still to be registered.

There was no significant correlation between the number of units (generic pack sizes) tendered for and the amount of dossiers registered. The total amount of dossiers registered according to the inclusion criteria was 146 of which 51 dossiers were duplicate dossiers. This translated to roughly a third of all generic registrations being duplicate dossiers.

6.3 RECOMMENDATIONS:

Based on the findings, the researcher further recommends the following, that:

a) After patent protection has expired only a determined number of years be allowed for submission of the generic registration. The timelines to be monitored closely and no exceptions to be allowed molecule.

b) No one company must submit more than one identical molecule. During this period no one company or applicants should be allowed to submit more than one generic molecule.

c) Similar dossiers to be evaluated by the same evaluator. The submitted dossiers should be allocated such that one evaluator would receive similar dossiers. This will eliminate time wasted by responding to similar queries at different time slots.

d) Extension time given to applicants should not hamper the current evaluation process. Should the evaluator reach the end of the queue of the evaluation he will only then receive the opportunity to attend to the other submission which were submitted late. These will again require some evaluation of some sort to verify that the query was responded adequately. These processes will eliminate dead times in the evaluation process thereby improving on the service delivery.

e) Service Level Agreements be concluded with progress monitor by the authority. This will be a contract between the authorities and the evaluators. The capacity of each individual will then be established so as not to overload the individual, but the constant flow of information will be to the advantage of the Authority.

f) Capacity building to be given via internships pharmacy student from various universities. The authority can engage the universities around the country and alert them on the issue of the backlog. They could request that the student do their internships with the Authority thereby building experience which can and maybe used at a later stage when the students have

qualified and in different role to their professions. The authority can tap into this experience and capacitate their activities.

g) Building internal expertise by offering competitive salary packages and start working on development and succession plan. The aim being that the regulator should get to a point where all required expertise are full time employees of the regulator. But this will not necessarily stop them from consulting externally.

h) The fast track process be monitored and offered to molecules on Government essential drug list. This process should not be ignored as it serves the country at large despite the backlog created by the dossier farming. The authority needs to review this process incorporating the abovementioned proposals.

i) Have Memorandum of Understanding (MoU) with regulators that they align themselves with {European Medicines Agency (EMA), Medicines & Healthcare products Regulatory Agency (MHRA), Swizz Medic, The Pharmaceuticals and Medical Devices Agency (Japan), U.S. Food and Drug Administration (FDA)}, where they can have access to product registration reports. This will enable them to shorten review timelines.

6.4 FINAL CONCLUSION

Dossier farming stretched the limited capacity at the regulatory authorities which lead to more delays in the medicine registration outputs, largely contributing to the massive backlog which SAHPRA was later known for. Over 50 % of the dossiers registered for all three molecules investigated were from applicants who practiced dossier farming. This kind of increase in submissions will require a substantial increase in the resources from any Health Authority Regulator.

From the study, it is noted that the South Africa's Health Authority still have a great deal of work to do to be on par with first world countries in ensuring that pharmaceutical companies are profitable while increasing the access to essential medicines to patients by promoting generic entrance into the market but without saturating the market with dossier farming. Our study has limited number of sample size and further research with larger sample size would be required in the subsequent studies.

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Appendix 1

Data collection Tool:

Trade Name:	Active substance:	Applicant:	Registration Number:	Year of NDA submission:	Year of registration:	No. of years after patent expiry