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THE CHANGING STRUCTURE OF PHARMACEUTICAL PRODUCTION IN SOUTH AFRICA

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THE CHANGING STRUCTURE OF PHARMACEUTICAL PRODUCTION IN SOUTH AFRICA

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A research report submitted to the Faculty of Commerce, Law and Management, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Business Administration

Johannesburg, 2010

ABSTRACT

The structure of the South African pharmaceutical manufacturing industry has undergone changes in the last 10 to 20 years.

The purpose of this research is to investigate the changing structure of pharmaceutical production in South Africa. This includes establishing the global and local contributing factors to the changing structure and evaluating the possible implications of the changing structure on the South African pharmaceutical industry and the response of the pharmaceutical industry to these implications. Generally, these factors have resulted in a decline in the number of pharmaceutical manufacturers in South Africa and in particular manufacturing operations owned by multinational companies (MNCs).

Simultaneously, within this period the global demand for generic medicines has increased due to their ability to improve access to affordable medicines. As a result, the supply of medicines in South Africa is being increasingly met by mostly imported generic medicines and to a lesser extent locally manufactured generic medicines. These changes together with a turbulent and sometimes uncertain regulatory environment has led to interesting dynamics and changes within the structure of the pharmaceutical manufacturing industry in South Africa.

Qualitative data was collected through in-depth interviews conducted with stakeholders within the local manufacturing industry using pre-determined questions that served as a guideline for a detailed discussion.

The key findings have been that, despite an apparent decline in the number of pharmaceutical producers in South Africa in recent years, interesting trends appear to be emerging that may be indicative of a sustainable local pharmaceutical manufacturing capacity. This sustainability, however, does appear to rely mainly on government intervention and the successful strategies of the largest generic medicine producers locally. The future viability of the industry largely depends on the ability of the local industry and the government to cooperate and work collectively in achieving their individual mutually beneficial objectives.

DECLARATION

I, Carel te Water Naudé, declare that this research report is my own work except as indicated in the references and acknowledgements. It is submitted in partial fulfilment of the requirements for the degree of Master of Business Administration in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in this or any other university.

(Carel te Water Naudé)

Signed at ……

On the …….. day of …… 2010

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CHAPTER 1: INTRODUCTION

In South Africa's years of isolation from the international market prior to 1994, the local pharmaceutical industry was able to develop in terms of skills and infrastructure. Within this period, however, the provision of healthcare was not uniformly and equitably distributed amongst all members of the population (FRIDGE, 1999; Maloney and Segal, 2007).

After the first democratic elections in 1994 the new government began to address this disparity by implementing policies and regulations to increase the affordability and accessibility of medicines for all sectors of the population (Maloney and Segal, 2007). In essence this has been successful, as expenditure on medicines globally and in South Africa has decreased dramatically (CMS, 2007; McIntyre and Thiede, 2007; Taylor, 2007). A consequence, however, is that in the last decade there has been a decline in the number of pharmaceutical production facilities in South Africa, as highlighted by large-scale industry reports (FRIDGE, 1999; Maloney and Segal, 2007). The changing structure of local pharmaceutical production needs to be understood in terms of its strategic importance in ensuring the continued supply of affordable medicines in South Africa.

1.1 Purpose of the Study

The purpose of this research is to explore the recent changing structure of pharmaceutical production within the South African pharmaceutical industry. The research focuses first on the recent trends in the global pharmaceutical industry. The focus then shifts to recent events within the local pharmaceutical industry and how they impact on local pharmaceutical production. The study also provides information on how the local pharmaceutical industry has responded to factors from both the international and South African pharmaceutical industries and how these factors have impacted on local pharmaceutical production.

As part of the research methodology literature review was carried out and three main research questions were established from the literature reviewed and used to generate open-ended questions asked in interviews with stakeholders within the local pharmaceutical production industry. The interviewees' responses in conjunction with the literature review serves to provide insight into how the structure of local pharmaceutical production has changed in recent years. In this research, "production" would mainly imply pharmaceutical manufacturing, which includes the purchasing of raw materials (including active pharmaceutical ingredients (APIs)), their pharmaceutical processing and production, the packaging of finished medicines, quality control (QC), the release of the medicines by quality assurance (QA) functions and the storage and control of medicines (FRIDGE, 1999).

1.2 Context of the Study

The pharmaceutical industry is praised for being foremost in the world in discovering new chemical entities (NCEs) leading to the development of medicines (Henderson, 2002). The industry can also be praised for the generosity it exhibits in its philanthropic activities and the preservation of manufacturing standards (Henry and Lexchin, 2002). At the same time the performance of pharmaceutical industry is criticised for being too financially successful and profitable (Scherer, 1993; Henderson, 2002; Henry and Lexchin, 2002; Scherer, 2004; Reinhardt, 2007; Sloan and Hsieh, 2007b).

This focus on profits leads to a shift away from discovering and developing innovative medicines (Henry and Lexchin, 2002). A pharmaceutical company has a commercial duty to deliver an acceptable profit and return on investment (ROI) to shareholders and a social duty to the community to provide medicines. This makes the pharmaceutical industry accountable to shareholders and to the community (Angell, 2000; Reinhardt, 2007).

The industry therefore has the obligation to provide good quality drugs (and reliable information on them) to the community and society at large, at affordable prices (Angell, 2000; Graham Dukes, 2002). Lastly, Graham Dukes (2002) states that, although innovation and quality in the pharmaceutical

industry have been maintained, research priorities, drug prices and drug information are being questioned.

In modern society the pharmaceutical industry could also be viewed as having a dual role, in that as a growing industry its output contributes directly to gross domestic product (GDP). This output (i.e. medicine) also serves as an input in the production, maintenance and improvement of the population's health, thereby fulfilling its dual role (Sloan and Hsieh, 2007b).

This sets the context of this research, as the profitability of the industry could conflict with the responsibility it has as a provider of affordable quality medicines in the interest of public health.

1.3 Research Problem and Sub-problems

In this section the research problem statement and sub-problems are provided.

1.3.1 *Problem statement*

The purpose of this research is to investigate the changing structure of pharmaceutical production in South Africa. This includes establishing the global and local contributing factors to the changing structure and evaluating the possible implications of the changing structure on the South African pharmaceutical industry and the response of the pharmaceutical industry to these implications.

1.3.2 *Sub-problems*

1. Establish the global contributing factors to the changing structure of pharmaceutical production in South Africa.
2. Establish the local contributing factors to the changing structure of pharmaceutical production in South Africa.
3. Evaluate the implications of the changing structure of pharmaceutical production in South Africa and the local pharmaceutical industry's response.

1.4 Significance of the Study

Organisations and the employees within the pharmaceutical industry could find value in this research, as it attempts to clarify how the South African pharmaceutical production industry has undergone a change in structure in the last two decades and the reasons for this change. The research also aids members of the pharmaceutical industry by highlighting the global and local factors that contribute to changes within the local pharmaceutical production industry in South Africa.

Through this, employers and employees may gain an overview of the factors that impact on the local manufacturing operations to which they are affiliated

and how the changing structure of local pharmaceutical production may impact the future nature and viability of the industry. The study also provides a simplified overview of general issues that impact the local pharmaceutical industry from the points of view of the respondents interviewed in the research.

Lastly, the research could also aid in developing future strategies for employers and employees in dealing with the implications of the changing structure of pharmaceutical manufacturing. For those who participate in the industry it could serve to create a clearer understanding of the industry, and the nature of their current and possible future roles within the industry.

1.5 Delimitations and Limitations

This section provides a brief discussion of the delimitations and limitations of the research.

1.5.1 *Delimitations*

The research focuses on South African pharmaceutical manufacturing of patented medicines and generic medicines in particular and does not include other functions performed by this industry, for example research and development (R&D), drug registration, clinical trials and pharmaceutical marketing. Forms of manufacturing other than pharmaceutical medicinal preparations, for example manufacturers of health and dietary supplements, will not be included as these industries are influenced by other factors that have not been included in the scope of the literature review or the research problem.

The companies, industry organisations and government departments included in the research represent stakeholders that participate or have influence over pharmaceutical production in South Africa.

1.5.2 *Limitations*

The limitations of this research are that, although the sample includes a selection of manufacturers, industry associations, a representative from the Department of Health (DOH), and a representative from the Department of

Trade and Industry (DTI) in Gauteng, it does not include all the manufacturers and stakeholders in the industry.

The inclusion of industry associations could provide responses that could be representative of the companies that belong to these associations. This would, to an extent, overcome the limitations of not including all the pharmaceutical manufacturers.

An additional limitation is that the industry organisations that were interviewed represent mostly multinational companies (MNCs) that are suppliers of patented innovative medicines. No individuals directly affiliated to the National Association of Pharmaceutical Manufacturers (NAPM), which represents generic medicine manufacturers, were interviewed. This possible limitation was overcome by interviewing respondents from the three largest local generic manufacturers, of which two of these manufacturers are members of NAPM.

The responses from in-depth interviews with manufacturers (and those who make use of contract manufacturing) and other industry stakeholders were analysed from the perspective of what was highlighted in the literature review. This would have possible shortcomings, as the research questions were established from what was uncovered in the literature review and might, therefore, to an extent, limit the possible responses from the interview. The open-ended nature of some of the questions was designed to reduce this limitation. The responses to these open-ended questions could provide further insight into the factors that contribute to the changing structure in local pharmaceutical manufacturing.

1.6 Abbreviations used in this Document

Table 1: Definition of abbreviations

Abbreviation	Definition
AIDS	Acquired Immune Deficiency Syndrome
ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
ARV	Antiretroviral
AsgiSA	Accelerated and Shared Growth Initiative for South Africa
BEE	Black Economic Empowerment
cGMP	Current Good Manufacturing Process/Practice
CRAMS	Contract Research and Manufacturing Services
DOH	Department of Health
DTI	Department of Trade and Industry
DST	Department of Science and Technology
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
FMF	Free Market Foundation
GDP	Gross domestic product
GMP	Good Manufacturing Process/Practice
GNP	Gross national product
HIV	Human Immunodeficiency Virus
HMOs	Health Maintenance Organisations
IPRs	Intellectual Property Rights
IPAP	Industrial Policy Action Plan

Abbreviation	Meaning
M&A	Mergers and Acquisitions
MCC	Medicines Control Council
MCOs	Managed Care Organisations
MSF	Médicins Sans Frontières
NAPM	National Association of Pharmaceutical Manufacturers
NCE	New Chemical Entity or New Compound Entity
NEDLAC	National Economic Development and Labour Council
NGO	Non-Governmental Organisation
NIH	National Institutions of Health
NIPF	National Industrial Policy Framework
NME	New Molecular Entity
ODA	The Orphan Drug Act
OTC	Over the Counter
PhRMA	Pharmaceutical Research Manufacturers Association
PIASA	Pharmaceutical Industry Association of South Africa
PIC/S	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as “PIC/S”)
R&D	Research and Development
SEP	Single Exit Price
SME	Small and Medium Enterprises
TRIPS	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WTO	World Trade Organization

1.7 Assumptions

The following assumptions have been made regarding the research:

- global trends in the pharmaceutical industry have an impact on local trends;
- the literature review along with a semi-structured Interview with the chief executive officer (CEO) of Merck (Pty) Ltd has provided adequate preliminary input to set up a detailed questionnaire to explore the changing structure of pharmaceutical production in South Africa;
- stakeholders within the pharmaceutical industry will all respond differently to macro changes within the industry. It is also assumed that their responses will depend on their size, the nature of their operations, the sub-sector(s) of the industry in which they operate and the market(s) that they serve;
- the respondents will be able to provide answers to the research questions in an exploratory manner owing to their relevant knowledge and particular area of expertise within the local pharmaceutical industry; and
- if any of the assumptions transpire to be false, the collected information will only serve to elucidate the research questions from the respondents' perspective and cannot be assumed to be true for the entire local pharmaceutical industry.

CHAPTER 2: LITERATURE REVIEW

The literature was reviewed with the following aims in mind:

2.1 Establish the global contributing factors to the changing structure of pharmaceutical production in South Africa

2.2 Establish the local contributing factors to the changing structure of pharmaceutical production in South Africa

2.3 Evaluate the implications of the changing structure of pharmaceutical production in South Africa and the local pharmaceutical industry's response

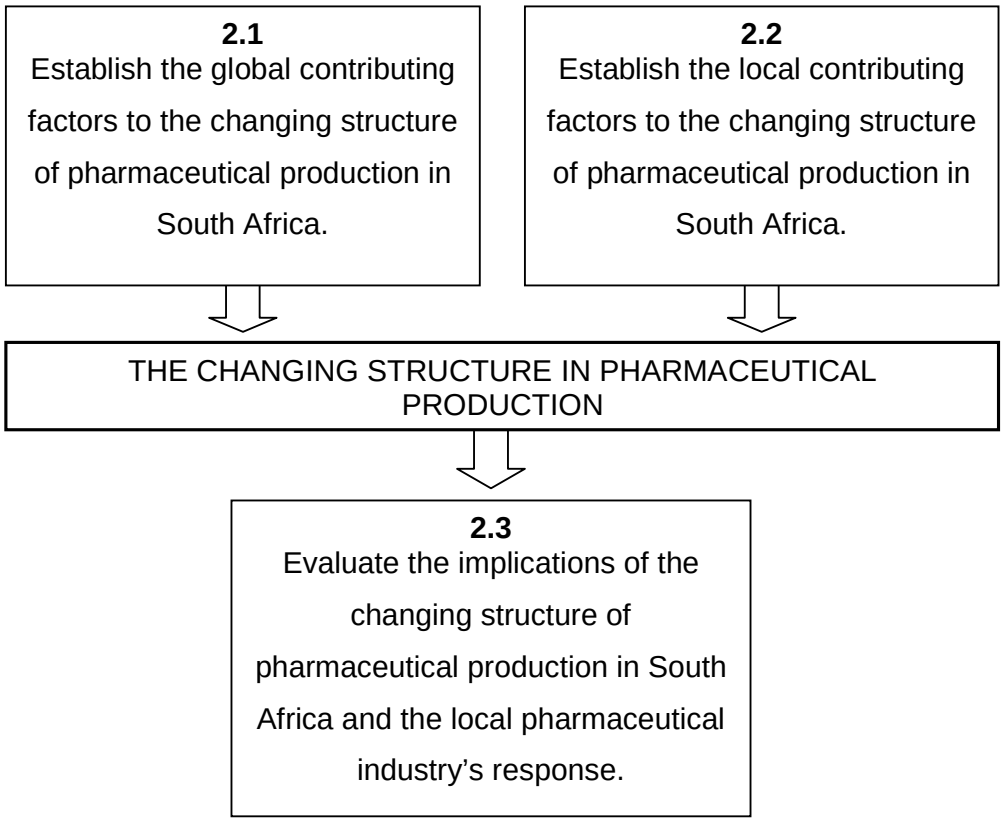


Figure 1: A graphical representation of the literature review topics

2.1 The Global Contributing Factors to the Changing Structure of Pharmaceutical Production in South Africa

The assumption has been made that global trends, dynamics and factors in the global pharmaceutical industry have an impact on the local pharmaceutical production industry. The global trends, dynamics and factors are therefore explored in this literature review before exploring the local trends, the implications that these trends have on the local pharmaceutical industry and this industry's response to these trends.

2.1.1 *Trends, changes and profitability in the global pharmaceutical industry*

Since economic studies on the United States (U.S.) pharmaceutical industry first arose through the Kefauver committee in 1959 the issues that are still being addressed within this industry concern the pricing, profitability, competition, product safety and research and development (R&D) expenditure of the industry (Henderson, 2002; Scherer, 2004). It is therefore valuable, in light of these economic concerns, to look at the changing structure of the global pharmaceutical industry.

In investigating the pharmaceutical industry, Cockburn (2004) has found that this industry's global structure, up until the mid 1970s, was characterised by the presence of large dominant pharmaceutical companies. These companies were responsible for discovering commercial drugs and in addition were able to integrate and coordinate all their research and development (R&D), clinical development, regulatory affairs, manufacturing and marketing functions (Cockburn, 2004). The companies were therefore more self-reliant, independent and integrated than they have become.

Within the realm of R&D, advanced scientific technology is required to aid the discovery, development and the production of medicines for a wide range of therapeutic applications (Cockburn, 2004).

This scientific technology up until the mid-1970s was acquired mainly through reviewing academic journals, attending conferences, or by obtaining the

expertise of highly qualified graduates from universities (Cockburn, 2004). There was therefore a greater reliance of the pharmaceutical industry on basic research to advance fundamental scientific knowledge. In this period in the U.S., basic research often benefited from government funding through National Institutions of Health (NIH), nationally owned laboratories, and grants to universities, research hospitals and research institutes (Cockburn, 2004).

Owing to legal constraints and social norms at the time, commercial or contractual relationships between “open science” and drug companies did not exist (Cockburn, 2004). Cockburn (2004) claims that there was therefore a clear distinction between upstream “open science” pursuing basic research and downstream pharmaceutical companies conducting applied research.

Henderson (2002) found that prior to the mid-1970s drug discovery was varied and unsystematic. At this stage drug discovery relied mostly on the extraction of natural compounds followed by their exposure to animals to determine the actions and efficacies of these natural compounds. This approach to drug discovery was mostly empirical and relied on trial and error rather than on theory (Comanor, 2007). Once a drug was discovered and developed these firms were then able to recapture their expenditures through receptive market conditions, drug patents, brands and regulatory entry barriers, thereby protecting them from competing products (Cockburn, 2004)

Henderson (2002) claims that the pattern of drug discovery has changed in the last 30 years owing to technological advancements, most notably in biochemistry. With technological advancements in the late 1970s, scientists started understanding the functions and mechanics of chemical receptors in the body and how they are responsible for blocking or triggering biological responses (Henderson, 2002).

By the period following 1980, biotechnology companies had entered the for-profit side of the industry and acted as an intermediate sector between academic research institutions and big pharmaceutical companies (Cockburn, 2004).

The biotechnology companies now have contractual links to both academic research institutes, in the scientific community, and the major pharmaceutical firms. These biotechnology companies are now also frequently profit orientated (Cockburn, 2004; Sloan and Hsieh, 2007b). This brings about many challenges in terms of patent rights and ownership of NCEs as well as increased competition between the pharmaceutical and biotechnology companies as to which will be the first to market NCEs produced in the field of biochemistry (Cockburn, 2004; Sloan and Hsieh, 2007b).

Comanor (2007) explains that biotechnology has had its greatest effect in the process and research methods, which lead to the development of new drugs. The actual production processes or costs of drug manufacturing have, however, remained relatively unchanged. Similarly, the processes used by the U.S. Food and Drug Administration (FDA), and other regulatory agencies worldwide, to evaluate and test medicines have also remained relatively unchanged (Comanor, 2007).

Maloney and Segal (2007) found that the global pharmaceutical market could be characterised as having two main components. The first component is a high-value/low-volume component that focuses on discovering and developing new drugs with strong market potential. Such companies, according to Maloney and Segal (2007), would be global companies that could be described as R&D or “innovator” companies (examples of MNCs include Pfizer, Merck and GlaxoSmithKline). The second component, the low-value/ high-volume component, has the aim of producing existing discovered and marketed drugs more efficiently, and these companies are grouped as “generic” companies that focus on lowering production costs (a multinational example is Sandoz, Teva and Aspen – a South African example) (Maloney and Segal, 2007).

Maloney and Segal (2007) found that with the emergence of increased competition from the biotechnology companies the traditional pharmaceutical companies believed that becoming larger would enable them to invest greater sums of money into R&D and particularly into medicines developed in the biotechnology sector. This increased R&D investment would provide them with greater research laboratory capabilities and drug pipelines, and generally

enhance their knowledge, and lead to the delivery of blockbuster drugs (Maloney and Segal, 2007).

It has recently been estimated that currently between 25 and 40 per cent of the pharmaceutical industry's sales are derived from products developed in the biotechnology sector (Comanor, 2007).

Maloney and Segal (2007) have found, when viewing pharmaceutical production and manufacturing in isolation, that there has been a restructuring in the global pharmaceutical industry since the early 1990s. This restructuring within pharmaceutical production and manufacturing has led towards the development of "centres of excellence," where companies focus their production and manufacturing activities in a select number of countries (Maloney and Segal, 2007). According to Maloney and Segal (2007), these countries are typically selected in terms of having the right combination of skills, a beneficial geographic location in the world market and the provision of government investment incentives to companies. This coupled with the global trend towards mergers and acquisitions (M&A) with other pharmaceutical companies has led to these companies becoming more cost effective and profitable (Maloney and Segal, 2007).

From the early 1970s countries in the developing world, especially India and China had focused mainly on generic drug manufacturing. These countries are now starting to form partnerships with R&D pharmaceutical companies in the developed world (Maloney and Segal, 2007). These partnerships are formed across the pharmaceutical value chain, for example R&D, drug production and clinical trials. This development has allowed pharmaceutical companies from the developed world to cut costs as the developing countries can provide the companies with:

- skilled labour;
- low-cost research facilities;
- low-cost drug development sites, especially in terms of clinical trials;

- low-cost licensed or contract manufacturing;
- low-cost distribution of drugs; and/or
- low-cost sales and marketing (Maloney and Segal, 2007).

From figures obtained from the Pharmaceutical Research Manufacturers Association (PhRMA), Weidenbaum (1993) has shown that 60.4 per cent of the drugs introduced in the American market between 1940 and 1990 had been developed by the U.S. pharmaceutical industry (see Table 2).

Table 2: New drugs introduced into the U.S. market, 1940 to 1990 Source: (Weidenbaum, 1993)

Country of Origin	Number of New Drugs	Percentage
United States	764.0	60.4
Switzerland	89.0	7.0
United Kingdom	81.5	6.4
West Germany	73.0	5.8
France	39.5	3.1
Japan	26.5	2.1
Belgium	23.0	1.8
Sweden	18.5	1.5
Denmark	17.5	1.4
Holland	15.0	1.2
Italy	13.4	1.0
Mexico	10.0	0.8
Canada	5.0	0.4
Other countries	14.0	1.1
Sources not ascertained	75.0	6.0
Total	1,265	100.0

Henderson (2002) further illustrates from data obtained by the PhRMA in the year 2000 that of the 152 drugs introduced into the world market, in the period between 1975 and 1994, 45 per cent had originated from the U.S. The United Kingdom contributed 14 per cent, Switzerland nine per cent and both Japan

and Germany were responsible for seven per cent of the number of drugs introduced worldwide in this period (Henderson, 2002).

From this we can see that the vast majority of new drugs introduced globally in the above-mentioned period originated predominantly from the U.S. and other highly industrialised and developed countries. It may therefore be concluded that this may have an impact on the relative global influence that these countries have in terms of the supply and pricing of new innovative drugs worldwide.

Table 3 provides the relative ranking of the 12 pharmaceutical companies that appear in Fortune magazine's Global 500 Rank for 2008 (Cacase, 2008). This illustrates that just over two per cent of the world's 500 highest-earning corporations are found within the pharmaceutical industry.

Table 3: Ranking of the highest-earning pharmaceutical corporations in Fortune magazine's Global 500 Rank 2008

Source: (Cacase, 2008)

Rank	Company	Global 500 Rank	Revenues ($ Millions)	Profits ($ Millions)
1	Johnson & Johnson	107	61,095	10,576
2	Pfizer	143	48,418	8,144
3	GlaxoSmithKline	151	45,447	10,431
4	Roche Group	175	40,315	8,134
5	Sanofi-Aventis	178	39,977	7,204
6	Novartis	181	39,800	11,946
7	Astrazeneca	265	29,559	5,595
8	Abott Laboratories	312	25,914	3,606
9	Merck	332	24,198	3,275
10	Wyeth	381	22,400	4,616
11	Bristol-Myers Squibb	427	19,977	2,165
12	Eli Lilly	453	18,634	2,953

In terms of revenue the pharmaceutical industry was ranked as the twelfth highest-earning industry of the 51 industries represented in the Global 500 Rank (Cacase, 2008).

The highest return on revenue rank compares the 50 companies (in the Fortune magazine's Global 500) that have the highest returns in terms of profits as a percentage of revenue (see Table 4). Seven of the 50 companies represented on the list are in the pharmaceutical industry, indicating that the large pharmaceutical companies are amongst the most profitable companies represented in the Global 500 (Cacase, 2008).

Table 4: Ranking of the highest return on revenues in Fortune magazine's Global 500 Rank 2008

Source: (Cacase, 2008)

Highest Return on Revenues Rank	Company	Country	Global 500 Rank 2008	2007 Profits as % of Revenues
5	Novartis	Switzerland	181	30.0
26	Wyeth	United States	381	20.6
29	Roche Group	Switzerland	175	20.2
34	AstraZeneca	Britain	265	18.9
40	Sanofi-Aventis	France	178	18.0
46	Johnson & Johnson	United States	107	17.3
47	Pfizer	United States	143	16.8

However, Reinhardt (2007) states that in 2004 the U.S. pharmaceutical industry's after-tax profits of $24 billion were only 0.20 per cent of the U.S. gross national product (GNP) and only 1.3 per cent of the total spending on national health in the U.S. Despite this, critics have branded the pharmaceutical industry in terms of four "highs", when describing the manner in which they operate in developed countries.

These four “highs” are:

- high R&D costs;
- high marketing costs;
- high prices; and
- high profits (Sloan and Hsieh, 2007a).

From this section it can be seen that the pharmaceutical industry is becoming more reliant on biotechnology. Older methods of basic research appear to be less successful in producing drugs with large market potential. The continued profitability of the large multinational pharmaceutical companies in developed countries could be seen as intentional in preparation for the next (and perhaps more costly) phase of drug development through biotechnology. This era of drug development is rather new and could hold many investment risks in R&D.

This high profitability can therefore perhaps be justified by the industry, but from a social point of view it is possibly too exploitative in nature when large proportions of populations in developing countries still lack access to basic medicines.

2.1.2 *Mergers and acquisitions within the pharmaceutical industry*

Mergers and acquisitions (M&A) within the pharmaceutical industry could influence the relative structure, size and number of individual pharmaceutical companies operating worldwide. This would in turn affect the nature of the competition between competitors within the industry and the strategies employed in both developing and marketing drugs.

Takeovers, amalgamations, and M&A form a part of the corporate strategies of the world’s leading companies’ growth as is illustrated by the fact that about two-thirds of large public corporations in the U.S. have M&A in their history (Erhun, Demehin and Erhun, 2005). The following companies in the pharmaceutical industry, which have either merged or have been acquired, serve as examples of M&A trends within the pharmaceutical industry:

- Glaxo Wellcome's merger with SmithKline Beecham to form GlaxoSmithKline (GSK);
- Astra with Zeneca to form AstraZeneca;
- Rhône-Poulenc Rorer with Hoechst Marrion Roussel;
- Pfizer with Warner Lambert and Pharmacia; and
- Sanofi's merger with Aventis to form Sanofi-Aventis (Erhun et al., 2005).

Owing to the shift in supply and demand patterns within the pharmaceutical industry, the industry has had to respond to increasing pressures to develop affordable yet effective drugs. Heracleous and Murray (2001) have found that the industry has responded to these pressures by:

- Using M&As to increase the scale and scope of individual companies;
- focusing on new technologies for developing new drugs, e.g. molecular biology, biochemistry and genetics;
- exploring new techniques of drug development such as rational drug design and combinational chemistry, which increases the number of NCEs produced from several hundred a year to several thousand a year; and
- introducing pharmacoeconomics that aids in justifying certain drug treatments (even though they may be more costly) over existing alternative treatments (e.g. hospitalisation), based on the economical effectiveness of those drug treatments.

Heracleous and Murray (2001) have also found that specific reasons for M&As have been to:

- reduce R&D costs in proportion to sales;
- fill drug pipelines to mitigate profitability threats posed by generic drug competition after patent expiry; and

- reduce marketing costs which have risen because of the recent trend of marketing medicines directly to the end-users rather than just physicians.

Erhun et al. (2005) state that, in a global context, the strategy behind M&A has been to achieve critical mass and obtain intra-company synergy in operational and manufacturing functions. This would then enhance merged companies' ability to respond to increasing market pressures, regulatory and legislative processes and the changing needs of customers.

These reasons for M&A can also be seen as a response to the threat that is posed by rival companies in some instances being allowed to view patent applications prior to the patent's expiry. This enhances rival companies' ability to produce similar drugs at a much faster rate without violating the patent (Heracleous and Murray, 2001).

A less optimistic view is that the industry has also justified M&A as a means of restocking product pipelines and cutting research and marketing costs rather than providing customers with lower prices (Henry and Lexchin, 2002).

Heracleous and Murray (2001) have also found that in most pharmaceutical mergers the merged pharmaceutical company had a smaller total market share than the sum of their market shares prior to the merger. Conversely companies that did not undergo merger activity in this period experienced a growth in market share (Heracleous and Murray, 2001). It appears therefore that an individual pharmaceutical company's success depends mostly on its ability to produce an innovative drug, which would yield large sales. Innovation, however, is then not necessarily guaranteed through M&As.

2.1.3 *The pharmaceutical industry's sustainable competitive advantages*

The pharmaceutical industry has various sustainable competitive advantages that provide sustainability and growth to the industry. The previously mentioned profitability of the pharmaceutical industry (Angell, 2000; Henderson, 2002; Henry and Lexchin, 2002; Scherer, 2004) appears to be the main competitive advantage of the industry.

Yeoh and Roth (1999) have identified two additional sources of sustained competitive advantages of pharmaceutical firms: their ability to produce therapeutically differentiated drugs and new NCEs.

Roberts (1999) has found that superior financial performance of pharmaceutical firms relies on transitory monopoly positions, which are attained through the ability of these firms to be innovative and to introduce innovative drugs into the market. These innovations enable them to avoid competition whether the innovations are due to the systematic application of capabilities or chance events that enabled the firms to stumble upon an innovative drug product (Roberts, 1999). There is, however, no significant relationship between continuous profitability and the ability to avoid competition (Roberts, 1999). This implies that competition within the pharmaceutical industry is based mainly on the individual company's ability to introduce innovative drugs. Individual companies are not able to replicate the innovative capabilities (based on R&D and complex organisational routines) of their competitors easily. Ironically even if they could replicate these capabilities it would not always lead to therapeutically differentiated drugs (Yeoh and Roth, 1999).

Innovation in most pharmaceutical firms can be affected by a combination of regulation, R&D costs, scientific opportunities and knowledge dissemination factors throughout the industry (DiMiasi, 2000). In addition, DiMiasi (2000) states that individual firms have different behavioural routines that they apply when they assimilate information and develop new products and processes. These routines are developed through learning from previous successes of the company and add to the company's unique competencies. A company further supplements this learning when it compares its relative success to the success of its competitors and how they respond to changes within the industry (DiMiasi, 2000) In order not to compete on exactly the same terms and for the same markets, companies therefore also generally focus their competitive advantages on a limited number of therapeutic markets in which they have experience. This is undertaken to mitigate the risks of being late to market their drugs, in all the therapeutic markets (Yeoh and Roth, 1999).

In some cases it appears that the pharmaceutical industry's innovation is not always directed towards developing innovative drugs. The industry is also innovative in its ability to develop and obtain FDA approval for "me-too" drugs that only differ from existing drugs in minor ways but still enjoy patent protection by virtue of these differences and hence benefit through transient monopoly positions (Scherer, 1993; Angell, 2000; Scherer, 2004; Sloan and Hsieh, 2007b). According to Angell (2000), critics also believe that drug clinical trials, sponsored by the pharmaceutical industry, are designed to stress the small advantages these drugs have over similar existing treatments. These small differences are then used to justify and create a demand through marketing activities. Henderson (2002) found that many of the companies that focus on "copycat" or "me-too" drugs spend twice as much on marketing and sales than they do on R&D. After selling these drugs at about three to six times the marginal unit cost of production, the companies can then direct large amounts of profit towards creating a further demand amongst physicians through various marketing activities (Henderson, 2002).

R&D in the pharmaceutical industry appears risky from a financial perspective, as the R&D process is very long and may have to be abandoned when the research does not yield results. Reinhardt (2007) argues that the financial risk in a pharmaceutical company's R&D is not as high as it is made out to be, as many R&D processes run concurrently and target many different drugs for a variety of diseases simultaneously. The financial risk associated with the flow of returns from investments in a pharmaceutical company has been empirically shown to be similar to the returns from investments in a well-diversified mutual fund (Reinhardt, 2007).

In summary, the main competitive advantages within the pharmaceutical industry appear to be based on the ability of an individual company to be innovative within the therapeutic market that the company has targeted. This innovation is reliant on the individual company's behavioural routines and an understanding of the competitive climate within the pharmaceutical industry. Successful innovation can also be seen in some cases through the company's ability to produce "me-too" drugs and to market existing drugs.

2.1.4 *Generic drugs*

Generic drugs can be defined as drugs that are not protected by a trademark. They are chemically identical to branded drugs but are usually much cheaper owing to the lower costs associated with the development of the generic drug when compared to branded drugs (Henderson, 2002). The introduction of generic drugs and the generic substitution of drugs have had a noticeable effect on the cost of medicines and hence the total healthcare savings (Mrazek and Mossialos, 2000; Grabowski, 2007).

When generic substitution of medicines occurs the world's drug purchases are divided into two groups: those that are price sensitive and those that are not (Scherer, 1993). Scherer (1993) also suggests that the manufacturers and marketers of pharmaceuticals in the U.S. are more likely to abandon the sale of generic drugs to the price-sensitive market than to reduce the prices of branded drugs to the price-insensitive markets.

The reason for this is essentially the increased patent protection and profitability of branded drugs. Companies producing branded drugs also sometimes also produce generic drugs known as "pseudogenerics" or "ultragenerics" (Hollis, 2003). In Canada, companies producing branded drugs have introduced "ultragenerics" to protect their market share from generic companies. These "ultragenerics" are then often distributed by other companies under licence or by another division of the same company (Hollis, 2003).

In the U.S. the Waxman-Hatch Act of 1984 (Drug Price Competition and Patent Restoration Act of 1984) (U.S., 1984) determined that, in order to obtain FDA approval for a drug to be a generic drug, the applicant only needed to prove that the active ingredient was chemically identical to the drug whose patent had expired. Prior to this Act generic drugs had to undergo the same costly clinical trial process required for branded drugs (Scherer, 1993; Grabowski, 2007). The Waxman-Hatch Act also established the accelerated drug application process known as the "Abbreviated New Drug Application" (ANDA).

This process allows generic entrants to conduct their clinical testing prior to the expiration of the original drug patent, based on the clinical data provided by the

brand name manufacturer in their original drug application (Grabowski, 2007). A 180-day exclusive marketing period was also granted to the first drug to apply for an ANDA and succeed in challenging the product in court. This was essentially undertaken to increase the rate at which and ease with which new generic drugs could enter the market and compete with branded drugs (Grabowski, 2007).

The Waxman-Hatch Act of 1984 (U.S., 1984) also provided an extended patent protection period for branded drugs to ensure that patent exclusivity of branded drugs was a minimum of 14 years. This was achieved to increase the patent protection period lost as a result of regulatory delay during the FDA approval period of the drug and to provide an incentive for continued drug innovation (Scherer, 1993; Grabowski, 2007). Scherer (1993) found that as a result many generic drugs quickly gained approval and that by 1989 more than a third of all prescriptions in the U.S. were filled with generic drugs. The implications of the Waxman-Hatch Act of 1984 (U.S., 1984) in the U.S. have been far reaching and in summary (Grabowski and Vernon, 1992) has provided four main characteristics of generic competition in the U.S. The effects of the Act are seen in the:

- large number of generic entrants soon after the expiry of patents;
- correlation between the market size of branded drugs prior to the expiration of their patents and the number of generic entrants and price competition after the patents have expired;
- increased degree of price competition with the increase in the number of new generic entrants, resulting in a diminished market share of the branded drug; and
- number of patents challenged relatively early in the product life-cycle of the branded drug, in order to benefit from the 180-day exclusivity period granted to the first drug to apply for an ANDA successfully.

Generic drugs are therefore registered, and approved for sale by regulatory authorities once the patent for the originally branded drug has expired. Henry

and Lexchin (2002) found that in some developing countries (e.g. India, China and Brazil) generic drugs are produced and sold legally while the same drugs remain patented in developed countries. In some cases these generics might be produced under the compulsory licensing provisions (a legal process that forms part of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement where governments may authorise the usage of patented technology without the agreement of the patent holder (Barton 2004)).

Owing to the affordability, safety and efficacy of generic drugs, they are often included and represent the majority of drugs on the World Health Organization's (WHO's) essential drug list as many patented drugs do not meet affordability criteria (Ford and t'Hoen, 2002). Governmental policy makers often rely on the WHO guidelines on developing national drug policies and their essential medicines list.

There is therefore an increased usage of generic medicines in order to save costs in public sector pharmaceutical expenditures, which often increase as a result of the introduction of newer expensive branded products (Mrazek and Mossialos, 2000; Grabowski, 2007).

The challenge, according to Mrazek and Mossialos (2000), is not only to increase the volume of generics supplied but also to decrease the cost of generic drugs. Even though generic drug volumes had increased significantly from the late 1980s to the late 1990s, the U.S., as the world's biggest generics market, has managed better than the United Kingdom (U.K.) and Germany (Europe's two biggest generic drug markets) in reducing the costs of generics.

The increased volumes of generics sold in these markets have been the result of financial incentive programmes aimed at physicians, pharmacists and patients to encourage the substitution and usage of generic drugs (Mrazek and Mossialos, 2000; Grabowski, 2007).

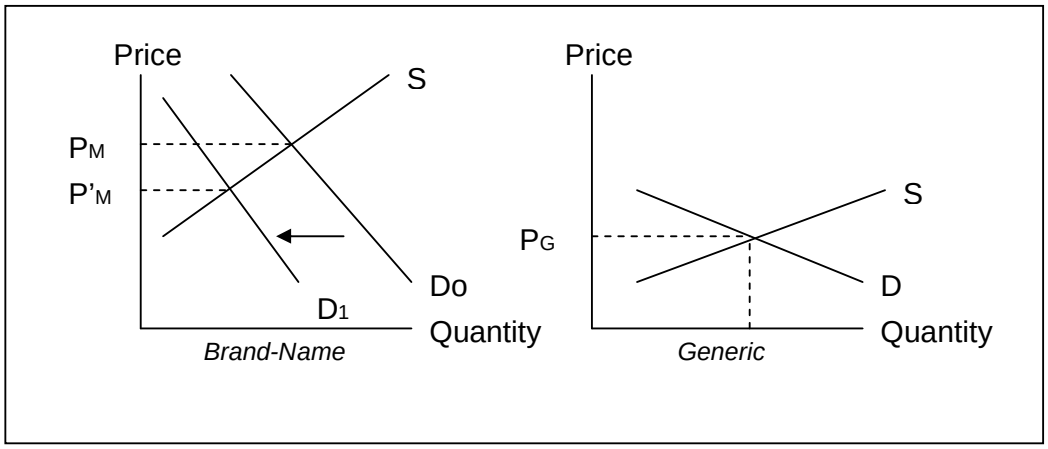


Figure 2: Graphical representation of generic competition and brand name pricing

Source: (Grabowski and Vernon, 1992)

Figure 2 provides a graphical representation of the supply and demand curves of branded drugs (on the left-hand side) and generic drugs (on the right-hand side). In the graph on the right-hand side the price of the generic drug is at P_G.

This low price is due to the lower costs associated with the development of the generic drug. The branded drug, in the graph on the left-hand side, is priced at P_M due to the higher development costs (which include R&D costs) that need to be recovered. The generic drug is viewed as a substitute product for the branded drug by virtue of its chemical similarity (Henderson, 2002).

Henderson (2002) explains that, based on economic theory, the presence of a low price substitute would cause a leftward shift in the demand curve (depicted by the shift from D_O to D_1).

The price of the branded drug would therefore decrease from P_M to P'_M. Henderson (2002) provides the example of empirical evidence (Grabowski and Vernon, 1992) that, in practice, the presence of generic substitutes does in fact cause a decrease in the price of the branded drug. Contrary to what might be expected, Scherer (1993) found that there was no significant drop in the prices of branded drugs in the U.S. when generic substitutes competed on price.

One reason given for this occurrence was that medical practitioners were insensitive to price or were risk adverse to the usage of generic drugs despite their prices being 40 to 70 per cent lower than branded drug prices (Scherer, 1993). In Canada and more particularly in the Ontario province, the price of branded drugs had not decreased when competing against cheaper generic drugs (Lexchin, 2003).

The Intercontinental Marketing Services (IMS) (the world's leading provider of market intelligence to the pharmaceutical and healthcare industries) (Aitken, 2008) released the U.S. Pharmaceutical Market Performance Review on 12 March 2008, for the year 2007, from which the following is highlighted:

- the dispensed drug prescription volume experienced a 2.8 per cent increase in 2007 (compared to eight per cent in 2006);
- the U.S. pharmaceutical market's unbranded generic drugs continued to gain market share to represent 67.3 per cent of prescribed medicines in all therapeutic markets;
- there have been fewer new innovative medicine launches than at any time in the last three decades; and
- a lack of sales' growth has been attributed to safety concerns raised by the FDA for drugs in certain therapeutic classes and product withdrawals from the market (Aitken, 2008).

Generic drug production in the U.S. is experiencing continued growth and appears to contribute significantly to the total growth of the U.S. pharmaceutical market. Aitken (2008) has commented that the U.S. pharmaceutical market is entering a new era where modest growth can be expected mostly owing to the continued impact of generic drugs (especially for lower cost treatments), lower introduction of innovative drugs, and drug safety issues in certain therapeutic markets.

2.1.5 *Elasticity of demand of medicines*

The demand for drugs in economic terms is considered to be relatively inelastic (Wonderling, Gruen and Black, 2005). The price elasticity of demand of a drug is calculated by the dividing the percentage change in the quantity of the drug demanded by the percentage change in the price of the drug (Wonderling et al., 2005). If the percentage change in the quantity of drug demanded is smaller than the percentage change in the price of that drug, the drug's demand is viewed as being relatively inelastic. Conversely, if the relative change in quantity of drug demanded is greater than the change in price, the drug's demand is viewed as being elastic (Wonderling et al., 2005).

The closeness in similarity and availability of substitutes for a drug would also affect the elasticity of the drug's demand. If the drug has no close substitutes then the demand would be more inelastic and a relative increase in price of that drug would then have a less pronounced effect on the demand for that drug (Wonderling et al., 2005). One could therefore argue that the demand for drugs with many substitutes (e.g. generic substitutes) would be more elastic than the demand for newer branded medicines for which fewer substitutes exist.

The implications of the elasticity of demand on the revenue obtained by the manufacturer of that drug also deserve attention. If the drug's demand were inelastic, a one per cent increase in the price of the drug would result in a change in quantity sold of less than one per cent. The total revenue obtained by the manufacturer would consequently increase. Conversely, if the price of a drug with an inelastic demand were to be decreased by one per cent and this were to be accompanied by a change in demand of less than one per cent, the revenue would decrease as the change in price would have less effect on the quantity demanded. The decrease in price therefore does not increase the demand for drugs that exhibit a greater inelasticity of demand (Wonderling et al., 2005).

From this it can be deduced that newer innovative and patented drugs with fewer substitutes (i.e. drugs with a relatively inelastic demand) provide beneficial financial implications for drug manufacturers. In a market

environment without price regulations, in which the manufacturer has the freedom of setting the price of a new drug, the high price would have less influence in decreasing demand and higher revenue could be realised.

2.1.6 *Pricing and pricing policies of medicines*

Before discussing the pricing policies of medicines it is useful to consider the typical cost structure of the pharmaceutical industry. According to Reinhardt (2007), the industry, in general, has high annual fixed costs, which include R&D costs. The average variable costs (AVCs) or incremental cost of a drug is the cost of producing an additional unit of output. The average total cost (ATC) per unit of output includes the fixed costs allocated to that unit of output and the AVCs that represent a relatively small portion of the average total cost (Reinhardt, 2007).

It is possible for a company with this type of cost structure to sell drugs at a price that is slightly higher than the AVC and still yield a small profit. This price will not, however, cover the ATC (Reinhardt, 2007). The difference in ATC and the price for that particular product can then be recovered from other higher priced products. This cost structure is successful as long as there is sufficient production capacity and the unit price is higher than the AVC. This, in essence, is referred to as “price discrimination” (Reinhardt, 2007).

Price discrimination could also occur when the same product is sold to different customers at different prices, while the cost of producing the product remains constant (Henderson, 2002; Reinhardt, 2007). This form of price discrimination benefits the consumer, as those consumers unable to afford a high price can obtain the product at a lower price while still benefiting the manufacturer, who gains a larger market share (Reinhardt, 2007).

Three characteristics are typical of industries that employ price discrimination practices. These characteristics are:

- low AVCs relative to fixed costs, which can provide some customers with very low prices;

- the grouping of customers in terms of their price sensitivity and bargaining power; and

- technical or legal constraints which prohibit customers from reselling the products to one another (Reinhardt, 2007).

Price discrimination, as highlighted by Reinhardt (2007), is controversial in that there is concern over its benefit to society and whether it requires government policy interventions. Government pricing regulations often exist in the pharmaceutical industry to prevent monopoly profits (possibly gained through price discrimination) and this is often remedied through price controls (Mc Pake, Kumarananyake and Normand, 2002; Scherer, 2004). These controls are implemented with the purpose of ensuring that there is a balance between technological progress in terms of pharmaceutical R&D and the affordability of drugs (Scherer, 2004).

In the case of price regulation it is useful to refer to a diagrammatical representation of price controls in general. Henderson (2002) diagrammatically explains the economic effects of regulating drug prices.

In the graph below (see Figure 3) the following is indicated: the relatively inelastic demand curve (D) of patented medicines, the marginal revenue (MR), marginal cost (MC), the average variable cost (AVC) and the average total cost (ATC).

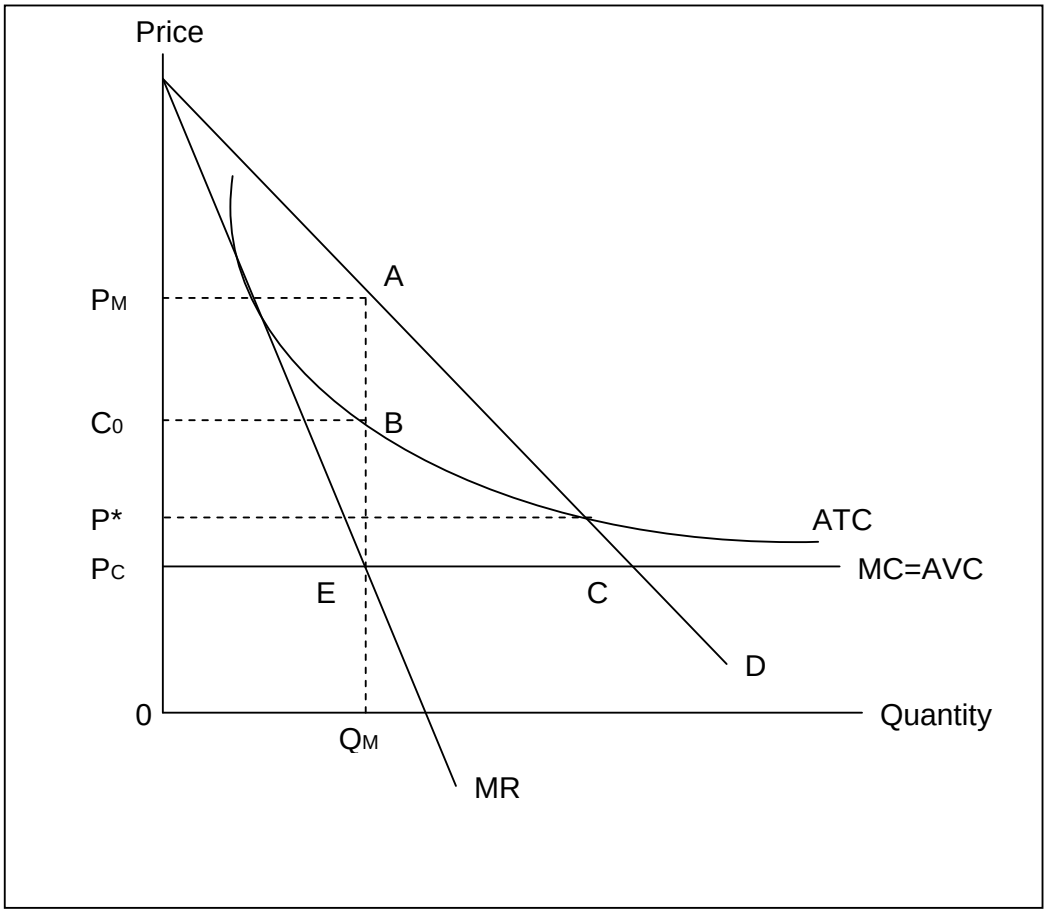


Figure 3: A graphical representation of the economics of regulating drug prices

Source: (Henderson, 2002)

The output level at which the pharmaceutical company will achieve maximum profitability occurs at point E when MR=MC. The quantity produced at this level is therefore depicted by point $Q_{M.}$ Owing to the relative inelasticity of demand, however, the customers would be willing to accept the price depicted at $P_{M.}$ At this point the pharmaceutical company can earn monopoly profits, as the resulting revenue of each unit of sale is higher than the fully allocated costs (which include the opportunity costs of capital invested as illustrated in the diagram by the rectangle P_MABC_o) (Henderson, 2002)

The triangle ACE represents an economic deadweight loss resulting from the restrictions on the quantity supplied by the pharmaceutical company in order to

guarantee the price P_M. The economic deadweight loss combines both the loss in producer and consumer surplus, which occurs when the price of the product (in this case P_M) is above the competitive equilibrium price (Henderson, 2002). In this scenario, governments often introduce price regulations, which could result in fixing the price at P_C. When this occurs the price is equal to the cost of producing one additional unit, i.e. the marginal cost. The pharmaceutical firm would then experience a loss as the average total cost of production is higher than the fixed price (P_C) (Henderson, 2002).

This loss can be recovered by adjusting the price to P*, where the price would then be equal to the average total cost (ATC) and the company would be able to earn a normal profit and only lose some efficiency. Alternatively in some forms of price control a government could subsidise a firm by the amount that it loses when the price is set at P_C (Henderson, 2002).

Although the theory behind price regulation is simple, the practical application is complex because the actual demand and costs of drugs are uncertain (Henderson, 2002). In addition the implications of price policy changes need to be fully understood before they are considered, as they are complex and can have severe implications for the supply and demand of drugs (Henderson, 2002; Scherer, 2004).

For instance, if the drug price is reduced through price regulation and the reduced price cannot be subsidised by other drug prices (also possibly due to price regulation), the production of the drug could be unviable. At the very least, such price regulation could limit the amount of profit from the sale of the drug and reduce further R&D expenditure.

Governments are often large purchasers of drugs in the pursuit of providing cost-effective healthcare. Large governments in some cases negotiate demanded drug volumes and prices with the pharmaceutical companies (Henry and Lexchin, 2002).

The reason that these prices need to be negotiated is so that the prices are low enough for the government not to exceed its national drug budget (as a proportion of its total health budget) and high enough to prevent the

pharmaceutical company from withdrawing from that market or possibly reducing investment in that country (Henry and Lexchin, 2002).

In the U.S. the distribution of drugs exists through Health Maintenance Organisations (HMOs), Managed Care Organisations (MCOs), retail and hospital pharmacies, mail order pharmacies and more recently Internet pharmacies (Heracleous and Murray, 2001). These institutions would be able to influence the demand for certain medicines. A national public health system, health insurance schemes or a physician (whose main interest is the effectiveness of the drug) also determines the demand and therefore the price of drugs (Heracleous and Murray, 2001). The price is then often not a concern of the end-user, i.e. the patient. Governments and MCOs are therefore often the main negotiators of drug prices, also because they have the greatest accumulated buying power in drug purchasing (Heracleous and Murray, 2001).

The government then often regulates or fixes the prices in order to achieve an improved access to medicines or reduce the pharmaceutical component of its healthcare expenditure. Dickson (1992) states that when fixing prices most countries use a combination of the following approaches in deciding on the price of drugs:

- the therapeutic value of a drug, which includes cost-effectiveness studies when the applicants apply for registration of new drugs;
- reference pricing where new drug prices are compared to existing drugs on the market and this may take into consideration the drug's improved therapeutic value when compared to existing drugs (e.g. in Belgium) or after negotiating with pharmaceutical companies (e.g. France);
- reference pricing where a comparison is made to the price of the same drug in other countries, which leads to smaller price differences within in the pharmaceutical market (e.g. Canada); and
- a price fixing system which takes into account the contributions of pharmaceuticals to the economy (e.g. Belgium, Spain, and the U.K.) (Dickson, 1992).

The optimal level of consumption of drugs would be that level of consumption where the perceived social benefit is equal to the social costs of drugs (Sloan and Hsieh, 2007a). Medical insurance is designed to insure against the risk of financial loss that occurs when an individual is ill. The social cost of medicines therefore often exceeds the social benefits when medical insurance covers the risk of ill health.

Sloan and Hsieh (2007a) explain that because medical insurance often covers the costs of drugs, this creates an incentive for the pharmaceutical industry to focus its R&D activities on meeting the demands of patients who have medical insurance (e.g. elderly patients with chronic diseases). In treating these diseases medical insurance is often willing to pay for the latest and often most expensive patented medicines.

This, in turn, leads to an increase in medicine expenditure that frequently results in private and public attempts to contain these costs through price controls or medicine formularies (which could include a larger proportion of cheaper generic drugs). The resultant effect is that drug demand is reduced in the short term. In the long term, however, the reduced demand in the short term reduces the rate of innovation by the pharmaceutical industry (Sloan and Hsieh, 2007a).

This has a negative effect on the innovative nature of the pharmaceutical industry and the ability to produce new drugs that could, potentially, reduce costs in other areas of healthcare provision, for example, hospitalisation and surgery. A disordered approach to pharmaceutical industry pricing in the U.S. could impair this industry's resources for investing in new products (Scherer, 1993; Mc Pake et al., 2002).

Scherer (1993) explains that, if regulation amounts to only reasonable profits, the industry's risk in investing in R&D (leading to the development of new important drugs) is higher than just expanding on existing drugs.

This could lead to variations of existing drugs rather than the development of new drugs through R&D. Scherer (1993) believes that improved information on

the expiry of drug patents would make generics more effective substitutes, as they could then be sold at lower prices soon after the expiration of the patent.

Increased competition and regulation (regarding pricing) within the U.S. pharmaceutical industry could lead to decreased revenue within this industry. This loss of revenue could, however, be compensated outside the U.S. through increased patent protection, but that would lead to higher welfare costs to governments of less developed nations (Scherer 1993).

Another issue regarding the pricing regulation of drugs is the concept of parallel importing. Within this occurrence a country with high drug prices exports drugs to a country with low prices as determined by that country's regulatory authority. A wholesaler in the country with low prices then buys the drugs and then exports them back to the country with high prices, where the drugs are then sold at a lower price (Ess, Schneeweiss and Szucs, 2003).

Most governments determine acceptable profit margins of drug wholesalers and retailers so as to limit the amount of profit taking at each level of the pharmaceutical value chain. Countries in the European Union (E.U.) are now faced with a single European pharmaceutical market, which has led to the parallel importation of cheaper drugs from other countries within the E.U. (Ess et al., 2003). Free trade of goods and pharmaceuticals across Europe would, in theory, eliminate price differentials and that the reason that this does not happen with pharmaceuticals is that drug prices are regulated, which makes parallel importation possible (Kanavos and Mossialos, 1999).

The question that can be considered is whether price controls actually decrease the price of medicines and in particular the total cost of healthcare services. Reekie (1998) found, through analysing pharmaceutical markets without price controls, that drug price freedom allows for competition that results in a decrease in the prices of medicines. The pharmaceutical companies within this competitive market then introduce more innovative medicines to compete for market share that then results in a reduction of the total cost of healthcare.

In addition, Reekie (1998) claims that in the context of medicines representing a diminishing proportion of healthcare, some governments still insist on price

regulation. Both prescribers and patients value innovative medicines as they lead to improved perceived and actual benefits. If these benefits and attributes (which include the price) of medicines were to be effectively communicated by the producers to the prescribers and patients, it would lead to an increase in choice. This increase in choice would then encourage innovation and competition between drug suppliers. The increased competition would then result in a decrease in price, as the price also represents a deciding factor among the other attributes of similar medicines (Reekie, 1998).

Through analysing the pricing of medicines it becomes clear that the pricing of medicines and pricing policies are quite controversial. The relative inelasticity of demand for innovative medicines allows a manufacturer in the absence of price regulations to gain a transient monopoly that allows for further innovation (through R&D), choices and benefits for consumers. This may also, in the long term, result in the decrease of the total cost of healthcare when other forms of healthcare become less necessary. Pricing regulations, conversely, appear to limit innovation, but allow for a short-term reduction of medicine prices, which increases the access to medicines and their affordability. This satisfies the social goals of the governments that implement the price controls. A delicate balance therefore exists between the social goals of governments and the economic goals of the pharmaceutical industry.

2.1.7 *The pharmaceutical industry and patent protection*

In many industrialised countries agencies exist to approve drugs before entering the market to establish their safety, efficacy and cost effectiveness (Mc Pake et al., 2002). These agencies or public authorities (such as the FDA in the U.S.) are also responsible for providing patent protection on drugs (Scherer, 2004).

Drug patents provide pharmaceutical firms with sustainable protection from competition as small differences or alterations in the molecular structure of a drug requires full clinical testing in the U.S. by the FDA (Scherer, 2004). In the U.S. pharmaceutical firms apply for patent protection shortly after conducting human clinical trials, which provide these firms with only 12 to 13 years of

patent protection and a monopoly market position once the drug is approved for sale by the FDA (Kaitin and Di Miasi, 2000; Heracleous and Murray, 2001; Scherer, 2004).

Patent protection entitles pharmaceutical firms to obtain high prices for their products (for a period of approximately 20 years) and this provides them with profits to invest in further R&D to develop new drugs (Barton, 2004). In addition, to ensure R&D investment and the development of innovative drugs for human well-being, patent protection provides the pharmaceutical industry with protection against imitators who might manufacture and market drugs at much lower costs (Reinhardt, 2007).

Another benefit of patent protection is that the public authorities that grant the approval of marketed drugs also act as an external mechanism to ensure drug efficacy, safety and internal quality control within the industry (Reinhardt, 2007). Reinhardt (2007) further adds that this is in the interest of the public and can also provide the pharmaceutical industry with protection in possible litigation over product safety.

Developing countries therefore argue that patent protection for drugs is not necessary in these markets as they only represent a small percentage of the global sales of the pharmaceutical companies that develop and market these drugs (Barton, 2004). India's 1970 patent law, for example, did not provide patent protection to drugs and the Indian government therefore chose to provide drugs, still patented in developed countries, to their public, technically, at the cost of hindering pharmaceutical firms from developing new drugs (Barton, 2004).

Developed countries (and in particular the U.S.), in response to patent violations, requested extended patent protection through the TRIPS agreement. On 1 January 1995 this TRIPS agreement was extended to all member nations of the World Trade Organzation (WTO) (Barton, 2004). The developed countries' interest in protecting patent rights is essentially to protect the potential income derived from innovative technologies and enable these

countries to retain their superior position through R&D and the resulting innovation (Barton, 2004).

Before the 1996 WTO agreements, countries like Finland, India, and Spain exempted medicines from patent protection as they believed that drugs were too important to allow pharmaceutical companies a monopoly market position for the drugs that they develop and produce (Ford and t'Hoen, 2002).

From a social perspective this makes sense, especially in the short term, as immediate healthcare can be provided at a lower cost. From a business perspective and in the long term, however, this could mean that expenditure towards innovation would be lost when other producers were able to sell at a lower price as a result of not having development costs built into their prices.

The WTO argues that ideas and knowledge are important to trade and that a drug's value is determined by the amount of invention, innovation, research, design and testing involved in the drug's development (WTO, 2008). The WTO (2008) also states that before the TRIPS agreement there was a wide variation in the extent to which the enforcement and protection of intellectual property rights occurred. The TRIPS agreement was therefore a way to order and settle disputes concerning intellectual property rights (WTO, 2008). Product and process patents, for example those that protect the manufacturing process of medicines, must according to this agreement be available to the innovator for at least 20 years. Governments can, however, refuse to issue a patent if its commercial exploitation disrupts public order or mortality. The TRIPS agreement should, therefore, also not prevent member governments of the WTO from protecting the health of their publics (WTO, 2008). The agreement also extended exemptions on pharmaceutical patent protection for developing countries until 2016.

To provide flexibility to developing countries that are unable to produce their own drugs, the TRIPS council enabled these countries to import patented drugs produced under compulsory licensing. On 30 August 2003 a waiver providing this flexibility was agreed upon (WTO, 2008)

Henry and Lexchin (2002) clarify that within the TRIPS agreement the public health of a nation and the nation's access to drugs are protected to such an extent that if a country's government declares a health emergency it may issue a compulsory licence without prior negotiation with the patent owner.

Barton (2004) explains that after initial reluctance the U.S. accepted the agreement after the chairman of the general council of the WTO concluded that the agreement would be to ensure public health and not be used as an instrument to pursue industrial or commercial gain. Non-governmental organisations (NGOs) like Médicins Sans Frontières (MSF) and Oxfam, however, disagreed, claiming that the agreement would do little to reduce the cost of essential medicines (Kapp, 2003). The U.S. was concerned that the agreement would lead to the ability of developing nations to export the low-cost products to developed markets (Kapp, 2003).

Barton (2004) elucidates that the TRIPS agreements made in 2001 and 2003 were based on a compromise that developed nations would sell drugs at lower prices (near production costs) to developing nations (e.g. the United Nation's (U.N.'s) least developed countries) and at high prices in the developed world, thereby enabling the drug firms to recover R&D spending. Barton (2004) further states that the research-based pharmaceutical industry would rather benefit the developing nations through drug donation programmes than by charging different prices.

The first sub-problem poses:

Research question 1: How do global factors contribute to the changing structure of pharmaceutical production in South Africa?

2.2 The Local Contributing Factors to the Changing Structure of Pharmaceutical Production in South Africa

2.2.1 *Evidence of the changing structure of pharmaceutical manufacturing in South Africa*

Three main studies, namely the FRIDGE, Pharmaceutical Investment Scoping Analysis and Genesis Study, have been conducted in the last decade to determine the strategic significance and growth potential of pharmaceutical manufacturing in South Africa. These studies provide a very in-depth and specific analysis of the local pharmaceutical industry and highlight the potential obstructions that inhibit the potential growth of the industry. The Pharmaceutical Investment Scoping Analysis was mostly concerned with the feasibility of API production locally and will therefore not be discussed in the context of this research.

The Fund for Research into Industrial Development Growth and Equity (FRIDGE), in conjunction with the Chamber of the National Economic Development and Labour Council (NEDLAC), in 1999 conducted a study into pharmaceutical manufacturing in South Africa. The FRIDGE study (FRIDGE, 1999) investigated trends and developments in both the global and local pharmaceutical industries and then took a sample survey of locally based manufacturers. The study investigated growth and development opportunities that were identified for local pharmaceutical manufacturing.

The Genesis Study (Maloney and Segal, 2007) was conducted six years after the Pharmaceutical Investment Scoping Analysis and was commissioned by the Accelerated and Shared Growth Initiative for South Africa (AsgiSA). The South African government launched AsgiSA in 2006 to stimulate investment and economic growth in a number of industry sectors with the aim of reducing poverty and unemployment. In order to select an industry for strategic promotion, AsgiSA decided to investigate the strategic significance of the pharmaceutical sector of South Africa and the sector's potential in contributing to the growth targets of AsgiSA (Maloney and Segal, 2007).

Genesis Analytics were appointed as advisors in February 2007 to conduct an economic analysis to determine whether South Africa could develop a competitive advantage in pharmaceuticals manufacturing.

The significance of such an analysis would be in light of the importance of the role that pharmaceuticals play in providing effective healthcare to the population of South Africa and the high incidence of infectious diseases within the poorest sections of the population (Maloney and Segal, 2007).

AsgiSA, firstly, requested Genesis Analytics to determine if the pharmaceutical sector was of strategic significance and whether the sector offered growth potential. Secondly, if it was found that the sector was of strategic significance and did offer growth potential, AsgiSA further requested Genesis Analytics to determine the obstructions that prevented the pharmaceutical sector from realising growth potential (Maloney and Segal, 2007). The resulting report by Genesis Analytics is known as the “Genesis Study”.

The South African pharmaceutical manufacturing industry in the late 1990s had been well developed and, while operating within a relatively protected environment, it had become the most developed and largest pharmaceutical manufacturing industry in Africa (FRIDGE, 1999). Despite this, however, globalisation and the restructuring of the pharmaceutical industry and in particular the increase in production of generic drugs in India had by the late 1990s resulted in a decline in employment within the local pharmaceutical manufacturing industry, which was about half of what it had been in the 1980s (FRIDGE, 1999).

The pharmaceutical industry’s global restructuring process towards “centres of excellence” has, according to Maloney and Segal (2007), not benefited the South African pharmaceutical industry. This has become evident in the steady decline in the number of multinational pharmaceutical manufacturing facilities operating in South Africa (FRIDGE, 1999; Maloney and Segal, 2007).

In the five years prior to the FRIDGE Study (FRIDGE, 1999) conducted in 1999, over 30 companies had closed their manufacturing facilities. The main reasons for these closures had included downsizing of operations, rationalisation, M&A,

the increased tendency to import drugs and reasons relating to cost which had been related to increased registration times (FRIDGE, 1999).

Through figures obtained from the Pharmaceutical Industry Association of South Africa (PIASA) and the DTI, Maloney and Segal (2007) found that of the 16 multinational pharmaceutical companies operating in South Africa only ten have manufacturing facilities while the remaining six have contracted local companies to manufacture and pack their products. The Genesis Study (Maloney and Segal, 2007) further found that 35 pharmaceutical plants have closed down in South Africa since 1994, the majority being multinational R&D companies. This has led to a decrease in the number of people employed in the local pharmaceutical manufacturing industry. In the year 2000, 16,000 people were employed by this industry (this number had been estimated at 18,000 in 1999 (FRIDGE, 1999) and 18,000 in 2001 (Beare, 2001)) Employment in this industry had been reduced to 11,000 employees by 2007 as a direct result of the closure of manufacturing facilities (Maloney and Segal, 2007).

The FRIDGE Study (FRIDGE, 1999) had found that owing to the opening of the South African economy the total market for wholly imported drugs was 30 per cent compared to 15 per cent ten years prior to the study.

Maloney and Segal (2007) also found that in 1998 the ratio of imported medicines ready for sale to locally produced medicines ready for sale was 8:1.

By 2006 this ratio had increased to 17:1. These ratios do not take into account the imported APIs and other inputs required for the local production of medicines. There has therefore been an increased usage of imported medicines relative to locally produced medicines.

2.2.2 *Inputs required in the South African pharmaceutical industry*

Maloney and Segal (2007) have, through interviews conducted within the local pharmaceutical industry, found that one reason for the decline in pharmaceutical manufacturing is that 90 per cent of the inputs required to produce drugs need to be imported and are not available locally. In the case of generic drug manufacturers these inputs are obtained mainly from India and

China while the inputs required for the manufacturing of innovator or branded drugs are imported from other countries, predominantly in the developed world (Maloney and Segal, 2007). These inputs include both APIs and a wide variety of fine chemicals used in the formulation of an API within a specific dosage form (Maloney and Segal, 2007). While most drugs require only a single API some drugs contain a combination of APIs, for example in analgesic drugs, vitamin combinations, antiretroviral drugs (ARVs) and tuberculosis (TB) combination therapies (Maloney and Segal, 2007). The production of these APIs in a chemical plant can be considered to be part of the fine chemicals industry, which also produces chemicals such as pesticides and dyes (Maloney and Segal, 2007).

This production of APIs can be distinguished from the manufacturing of pharmaceutical preparations that concerns the production of medicines for the market (FRIDGE, 1999). This production of medicines, for example solid oral dosage forms such as tablets, involves physical processes such as compounding, dispersion of ingredients (mixing), granulation, drying, compression of tablets and packaging (FRIDGE, 1999). Pharmaceutical manufacturing of medicines (or pharmaceutical preparations) in South Africa typically involves the abovementioned processes, where the APIs and the variety of other fine chemicals are formulated together (FRIDGE, 1999). The end result of this process would be a dosage form that meets the physical, quality and efficacy standards that are registered at the Medicines Control Council (MCC) by the manufacturer or the applicant that holds the licence for that medicine.

In order for a factory to produce one or more APIs, the demand and market for the API need to be large enough for such a factory to be cost effective and therefore a viable investment. South Africa, in an attempt to integrate its pharmaceutical value chain vertically, would need to produce a large variety of APIs in order to provide APIs for the large variety of locally manufactured drugs (Maloney and Segal, 2007). Maloney and Segal (2007) believe that owing to the relatively small existing size of the local pharmaceutical manufacturing industry the demand for APIs is too small to justify the investment in producing

APIs in South Africa. This contributes to the relatively low value in terms of input that the local pharmaceutical industry is able to add to the entire pharmaceutical value chain in South Africa (Maloney and Segal, 2007).

The smaller companies are also able to manufacture speciality medicines under licence after larger manufacturers have developed them, thus reducing development costs (FRIDGE, 1999). Smaller generic medicine companies would therefore be more viable in South Africa because they would have lower overhead costs even though the variable or marginal costs might be the same as those of larger manufacturers (FRIDGE, 1999).

In contrast, when one compares the local pharmaceutical industry to the Indian pharmaceutical industry it becomes evident that the local industry is almost insignificant in global terms. Ramesh (2008) refers to a report by KPMG India (Mumbai) that claims that there is a global pharmaceutical hub in the western Indian state of Gujarat that is experiencing growth. In addition, KPMG India claims that Gujarat is being used as a major sourcing base for multinational pharmaceutical companies (Ramesh, 2008). Numerous large Indian pharmaceutical companies operate within the state of Gujarat amongst a total of 3,500 manufacturing sites. The state of Gujarat contributes 42 per cent of the total pharmaceutical turnover in India. It therefore plays a large role in India's ability to be a major player in the global pharmaceutical market and particularly in the areas of generic drugs, NCEs, R&D and contract research and manufacturing services (CRAMS) (Ramesh, 2008).

2.2.3 *Infrastructure and capital investments in the South African pharmaceutical industry*

The FRIDGE Study highlighted the issues concerning the local pharmaceutical manufacturing industry. Some of the main issues concerning pharmaceutical manufacturing (FRIDGE, 1999) are outlined below.

a. Manufacturing Capacity

The FRIDGE Study (FRIDGE, 1999) found that in the late 1990s there was excess pharmaceutical manufacturing capacity in South Africa. At this stage it

would have been possible for a new manufacturer to become established by merely contracting the production to existing manufacturers with spare capacity. The problem, however, was that the capital equipment and facilities in most cases were old and the technology was in some cases outdated (FRIDGE, 1999). Machinery would have needed replacement to prevent the constant need for maintenance and therefore additional capital expenditure to attain a competitive level of output.

In the case of manufacturing facilities that produced sterile products it was estimated by the FRIDGE Study (FRIDGE, 1999) that in order to remain competitive such plants would have had to upgrade equipment every five years, which would have required extensive re-investment. These factors coupled with a perceived negative investment climate in the industry in the late 1990s and limited market opportunities for medicines had the effect of discouraging the additional capital expenditure in order to improve manufacturing capacity (FRIDGE, 1999).

b. Manufacturing Plants

The FRIDGE Study (FRIDGE, 1999) found that at the time of the study these manufacturing plants were equipped with technology that was outdated and produced volumes that were too low to supply the international market. The running costs of these plants were therefore high relative to the volumes that they were producing at the time. In comparison with Asian manufacturing plants the unit costs of the local factories were five times higher (FRIDGE, 1999).

With a global drive towards competitiveness manufacturing plants worldwide are maximising their outputs to lower production costs and therefore unit costs so as to spread their overheads over a larger number of units (FRIDGE, 1999; Maloney and Segal, 2007). In order to achieve this, increased capital investment would be required for introducing newer technologies that would lower production costs by increasing the output of the manufacturing facility. The South African manufacturing plants would require additional investment in establishing plants that produce higher volumes with newer updated technology. These plants would therefore need to produce higher volumes than

are required by the domestic market to be able to export products that would justify the additional investment in upgrading the facilities (FRIDGE, 1999).

In light of global restructuring among many multinational manufacturers to attain “centres of expertise” the multinational manufacturers can produce high volumes at lower costs that lead to imported medicines that are more competitive in terms of price than those produced locally (FRIDGE, 1999). The lack of sufficient local capacity and economies of scale therefore leads to a loss of competitiveness in terms of prices of locally produced medicines when compared to imports.

c. Downscaling of Operations

All the multinational and local respondents that took part in the FRIDGE Study (FRIDGE, 1999) claimed that they had recently scaled down their operations or were planning to do so in future. The MNCs claimed that the main reasons for this were the incidents of centres of expertise globally (where the parent company would manufacture products for the entire world market in a limited number of sites), the increased costs associated with local legal compliance and the tendency of the multinationals to limit South African operations to the packaging and labelling of medicines only.

The local respondents claimed that downscaling was mostly the result of cheaper outsourcing alternatives and the threat of imports from India (FRIDGE, 1999).

This decrease in actual manufacturing and outsourcing of manufacturing could further lead to a loss of skills, as manufacturers do not remain in touch with the international pharmaceutical technologies, materials and processes. Many of the employees could then leave the sector and perhaps find employment in other sectors, which would represent a loss of skills, which could be difficult to recoup should the pharmaceutical sector undergo a revival.

2.2.4 The South African drug policy

Maloney and Segal (2007) have found that since 1994 the government has introduced significant shifts in government policies in an attempt to address inequalities in the pharmaceutical and healthcare sectors. These shifts, according to Maloney and Segal (2007), have led to possible negative side effects, particularly within the pharmaceutical industry.

From interviews conducted within the pharmaceutical industry, Maloney and Segal (2007) found that 20 per cent of the South African population is served by the private healthcare sector and consumes about R2,000 (US$286 in May 2007) per capita per annum. Conversely 80 per cent of the population is served by the public sector and only consumes R80 (US$11 in May 2007) per capita per annum. By comparison Maloney and Segal (2007) found that the value of medicines consumed by those served by the private sector was less than in North America but more than the value of consumption in Europe. The value of the consumption of those served by the public sector was closer to the value found in South East Asia and India.

In light of South Africa's high incidences of infectious diseases (e.g. HIV/AIDS, TB and malaria) and the inequity in the provision of healthcare between the "first-world" (private) and "third-world" (public) sectors of the South African population, the government's National Drug Policy (NDP) was implemented to help address these issues (Maloney and Segal, 2007). In September 1994 the Minister of Health, Dr N.C. Dlamini Zuma, appointed a Drug Policy Committee to establish the NDP with the aim of developing the following:

- a pricing plan for drugs used in the public and private sectors of South Africa;
- a plan for testing drugs and an evaluation of the effectiveness of drugs, based on epidemiological approaches in the South African context;
- an essential drugs list and treatment guidelines for the health personnel for usage in the public sector;

- strategies for the increased usage of generic drugs;
- a procurement and distribution plan for drugs in South Africa which effectively increases drug access in the rural areas;
- an investigation of traditional medicines;
- and a rationalisation of pharmaceutical services (DOH, 1996).

The main objective of the NDP is to enable and stimulate a self-sufficient local pharmaceutical industry in terms of its ability to manufacture and market drugs on the South African essential drugs list. The NDP also encourages the export of these locally manufactured essential drugs to neighbouring countries (DOH, 1996). This could be viewed as an attempt to develop and grow the local pharmaceutical industry to make South Africa less reliant on imported medicines. In addition, developing an export market could allow the local industry to reinvest locally and enhance its capacity.

According to Maloney and Segal (2007), the government's policies in addressing inequity in the healthcare sector are justifiable but the nature of the policies; their implementation and the government's capacity to implement them could be contested. If the policies are too aggressive they could cause strain within the healthcare sector, which could result in the loss of skills and in healthcare-related capital leaving the country. If on the other hand the policies are too conservative they will not effectively address the disparity between the public and private healthcare sectors (Maloney and Segal, 2007).

Maloney and Segal (2007) further argue that in order for the policies to be satisfactory from a social perspective and an industrial perspective, a balance between these perspectives needs to be attained.

2.2.5 *The regulation of pharmaceuticals in South Africa*

In South Africa the MCC ensures that all pharmaceutical-manufacturing facilities that produce registered drugs in South Africa meet minimum quality control standards. These minimum standards are based on current Good Manufacturing Practice (cGMP) as determined by the WHO and have become

the global norm in pharmaceutical manufacturing standards, especially for companies that produce drugs for export markets (FRIDGE, 1999).

At the time of the Genesis Study the MCC was found to be inefficient owing to internal capacity constraints, thereby resulting in registration and approval times for drugs and clinical trials of four times longer than international best practice (Maloney and Segal, 2007). This inefficiency would have the result of reducing investment in manufacturing, as delays in the registration of drugs could delay the time it takes for the drug to be marketed. Similarly, these delays also affect clinical trials, especially when these trials need to be coordinated across several countries simultaneously (Maloney and Segal, 2007).

The MCC's licensing of manufacturing facilities has recently required additional international quality standards (e.g. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme – jointly referred to as "PIC/S"). These standards are beneficial in terms of meeting global manufacturing quality standards and accessing donor funds, but the implementation of the standards have been inadequate, making it difficult for manufacturers to adopt these standards (Maloney and Segal, 2007). Adopting these standards could also give rise to additional costs in pharmaceutical manufacturing. For example, when these standards require a change in the layout of the facilities or specific air-handling requirements, large capital outlays would be required to upgrade an existing facility, which in many cases could be relatively outdated or just simply old.

To complicate the implementation of these quality standards the MCC has not provided manufacturers with policies, or financial or technical assistance (Maloney and Segal, 2007). Maloney and Segal (2007) to their knowledge could identify at least two companies that had ceased to produce drugs locally as a result of these changes in the MCC policies.

The MCC's policies and inefficiencies have an impact on the investment and employment within the industry, which could negate industrial policies that aim to encourage investment and employment (Maloney and Segal, 2007). Such policies would include the Industrial Policy Action Plan (IPAP) as established by

the government's National Industrial Policy Framework (NIPF). This framework facilitates the government's move towards industrialisation in South Africa in terms of the AsgiSA, which has the aim of halving unemployment and poverty by 2014 while achieving a minimum targeted growth of at least six per cent per annum from 2010 onwards (DTI, 2007).

2.2.6 *The pricing of pharmaceuticals in South Africa*

Since 1997 The Medicines and Related Substances Control Amendment Act 90 of 1997 (RSA, 1997) and the Regulations relating to a transparent pricing system for medicines and scheduled substances have been the government's main legislative drives in making healthcare more affordable in South Africa (Taylor, 2007). This legislation has, however, been challenged legally by stakeholders within the pharmaceutical industry (Taylor, 2007). The government's Medicines Pricing Committee has successfully implemented the Single Exit Price (SEP) and has also been responsible for developing the dispensing fee of medicines in pharmacies, which still fuels ongoing debate in establishing a dispensing fee which is appropriate (Taylor, 2007). One of the main aims of the Pricing Committee within the framework of the NDP is to ensure complete transparency in the prices provided by pharmaceutical manufacturers, wholesalers, retailers (those who dispense drugs) and private hospitals and clinics (Pearmain, 2007).

The pricing policies of the government have had the main purpose of regulating and lowering drug prices in order to make medicines more affordable (Maloney and Segal, 2007; Taylor, 2007). The government's aim in making medicines more affordable in the private sector is to encourage sectors of the population that are currently served by the public sector to be served by the private sector (Maloney and Segal, 2007).

This would provide the government with the opportunity to reduce the number of people that are reliant on the public health sector. Maloney and Segal (2007) comment that most stakeholders believe that the policies lack transparency and economic feasibility, even though they accept the government's goals of improving the access to and affordability of medicines. As a result of possibly

lacking economic feasibility, these proposals could have a negative impact on local drug manufacturing and development. This impact would mainly be seen in the loss of profitability in the manufacturing industry and the resulting loss of continued investment (FRIDGE, 1999; Maloney and Segal, 2007).

Previously in South Africa, the pharmaceutical industry used price discrimination in order to be able to reach both the private sector and public sector markets. Maloney and Segal (2007) include responses from within the pharmaceutical industry that claimed that this form of price discrimination enabled low prices in the public sector that were subsidised by higher prices in the private sector. Any form of price control could therefore have the possible effect of increasing prices in the public sector if prices are standardised and decreased in the private sector (Maloney and Segal, 2007).

In December 2006 draft regulations were set up by the Pricing Committee to propose a pricing structure that would benchmark South African originator or patented medicines against the prices found in four other countries. These countries were Australia, Canada, New Zealand and Spain, and the lowest price of medicines found between these countries and South Africa would then become the price of a particular medicine in South Africa. Generic medicines' prices according to this proposal would then be set at 40 per cent of the originator drug price (Maloney and Segal, 2007; Taylor, 2007).

If a company finds that the benchmarked price makes the provision of a particular drug unviable, the proposal also has a clause whereby that company could request that the price be reviewed. According to Maloney and Segal (2007), this clause would require that the company would have to disclose sensitive information and data on the variable costs of drugs, which makes the technicalities of such a request to review the price problematic. In addition to this the industry appears to be unclear on how exactly such a request would work. With the emergence of global centres of excellence many multinationals appear to have opted for producing drugs at a lower cost where economies of scale can be realised and then importing the drug into South Africa and still making a profit despite the lower fixed prices at which they are sold (Maloney and Segal, 2007).

Furthermore, the prices provided by some importing firms are allegedly subsidised by the governments of the countries from which these products originate as part of those governments' national programmes to provide incentives for manufacturing pharmaceuticals (Maloney and Segal, 2007).

2.2.7 *The public sector procurement of medicines*

The tender price preference system is a useful way for local manufacturers to secure demand for certain products that they supply to the public sector. This demand helps to utilise spare capacity and spread the overheads of a manufacturing facility over a greater number of units for the duration of the tender. Without a secure demand, the manufacturer would more than likely have to base its forecast of demand on more fickle market trends and other expenses, for example marketing costs, would also increase as a demand would have to be created in the market.

The government's procurement system of medicines for the public sector also raises concerns with regard to the effect that it has on the local pharmaceutical manufacturing industry. Maloney and Segal (2007) found that the government's drug procurement programme in the public sector takes into consideration a ten-point system. Of these ten points four points are awarded for local content, four points for Black Economic Empowerment (BEE) compliance and the remaining two points for purchasing from small and medium enterprises (SMEs). Companies can then tender for providing high volumes of drugs to the public sector for three years in the case of ARVs and two years for any other drugs. A company's relative success in winning the tender to supply a particular drug or drugs to the public sector would then depend on its score in terms of the ten-point system (Maloney and Segal, 2007).Maloney and Segal (2007) claim that importers of drugs can manipulate the government's ten-point system for preferential procurement. These importers simply have to open up a small office with a small BEE compliant staff to attain a higher score.

In contrast local manufacturing companies with a large staff complement would find it harder to be BEE compliant. Government tenders therefore almost favour importers, thereby reducing the potential market a local manufacturer would

have for its locally produced drugs (Maloney and Segal, 2007). This diminished market share would further impact negatively on the viability of producing locally.

2.2.8 *Skills shortages and pharmaceuticals as a knowledge sector*

The pharmaceutical manufacturing industry requires a unique and specific set of skills, especially when one considers the range of skills required in the production, registration and marketing of medicines. Legal compliance to cGMP or other newer requirements such as the newly adopted PIC/S standards require a thorough understanding and continuous management of the pharmaceutical processes in order to meet quality standards while still maintaining production efficiency.

Maloney and Segal (2007) assert that the government's focus on primary healthcare has resulted in a diminished focus on tertiary healthcare as is evident in the decreased government funding of tertiary education in universities.

The resultant effect is that the once world-class medical faculties (and the research units that are associated with these faculties) have recently, together with teaching hospitals, experienced difficulties (Maloney and Segal, 2007).

Pharmacists play an important role in the pharmaceutical manufacturing industry and particularly in the process of manufacturing and packaging, registration, and quality control. Maloney and Segal (2007) have through interviews been able to ascertain that the number of pharmacy graduates a few years ago had been 450 per year, but that this number had decreased to 320 in the year 2007.

Maloney and Segal (2007) have also found that within the higher value components of the pharmaceutical value chain, e.g. the clinical development phase of pharmaceuticals (as exercised through clinical trials), South Africa does indeed have a competitive advantage. There is a large availability of patients who present a vast variety of diseases without any access to medicines. The inefficiencies of the MCC, however, have meant that the

competitive advantage South Africa has in this area is rapidly diminishing. A result of this could also be the loss of skills in this high value area (Maloney and Segal, 2007).

2.2.9 *Intellectual Property Rights (IPRs)*

The area of Intellectual Property Rights (IPRs) is fairly controversial in terms of the relationship between patented and generic medicines. Patented medicine producers seek to protect their intellectual property in order to set higher prices which enable the manufacturer to recover R&D costs (Maloney and Segal, 2007; Reinhardt, 2007). Generic producers on the other hand would prefer weaker patent protection in order to enable them to enter the market sooner should the patent no longer be valid (Maloney and Segal, 2007).

Maloney and Segal (2007) further argue that the presence of R&D or innovator firms within a market benefits a generic market in several ways. The R&D firms provide a source of drugs to the generic market once the patent expires.

The patented drug prior to the patent's expiry is usually extensively marketed and the doctors (as those prescribing the medicines), pharmacists (dispensing the medicines) and patients are relatively well informed of the medicine's usage and benefits (Maloney and Segal, 2007). In essence, when the patent expires the generic medicine manufacturers benefit, as they only need to produce the medicine at a lower cost in order to be competitive. This is achievable as there are fewer R&D expenses and fewer marketing costs in establishing the medicine, which has already had previous market presence in the form of the originator's patented medicine.

In an attempt to lower the costs of medicines in South Africa so as to improve the public's access to medicines, the Medicines and Related Substances Control and Amendment Act of 1997(RSA, 1997) has made provision for compulsory licensing, parallel importing and mandatory generic substitution. In mandatory generic substitution, South African pharmacists are required to dispense cheaper generic substitutes unless the doctor or patient insists on using the patented version of the same drug (Maloney and Segal, 2007).

Although compulsory licensing and parallel importing have not been exercised in South Africa, they serve as a source of threat and uncertainty for R&D companies operating in South Africa (Maloney and Segal, 2007). Compulsory licensing provisions are currently regulated through the Patents Act but have yet to be exercised, and parallel importing is currently allowed in South Africa (Maloney and Segal, 2007).

2.2.10 *Issues relating to the overall pharmaceutical manufacturing environment in South Africa*

Maloney and Segal (2007) have concluded from the overall current state of the local pharmaceutical industry that the industry is uncertain of the government's intentions, especially with respect to the procurement, pricing and dispensing fees of medicines.

This has resulted in the relationship between the industry and the government to lack trust, which further exacerbates the viability of the industry that finds itself within a global climate of M&A, cost cutting and consolidation (Maloney and Segal, 2007). This, according to Maloney and Segal (2007), has led to a general loss in the competitiveness of the local pharmaceutical industry in global terms. This loss of competitiveness has become evident on two macro-economic levels.

Firstly, and as mentioned previously, in section 2.2.1, the ratio of imported medicines ready for sale to locally produced medicines ready for sale in South Africa had increased from the 1998 level of 8:1 to 17:1 by 2006 (Maloney and Segal, 2007). From industry interviews Maloney and Segal (2007) found that pharmaceuticals and their inputs constitute the fifth-largest contributor to South Africa's current account deficit in terms of value. The production of medicines can therefore be seen as being more efficient in countries from which South Africa imports.

The end result is, then, that South Africa is heavily reliant on other nations to supply medicines and is not self-reliant (Maloney and Segal, 2007). With the high prevalence of diseases such as HIV/AIDS, TB and malaria, the local

demand is relatively high and security of supply is therefore important (Maloney and Segal, 2007).

Secondly, the pharmaceutical industry does not compare well with the other sectors that have been prioritised by AsgiSA, according to Maloney and Segal (2007); for example, the biofuels/agricultural, tourism, and business outsourcing sectors. Maloney and Segal (2007) have (by using calculations made by Genesis Analytics from data supplied by James Thurlow and Stats SA) estimated that the trade imbalance in the pharmaceutical sector is high (US$830 million). The low export growth (which is nine per cent in Rand terms and only two per cent in U.S. Dollar terms) in the pharmaceutical sector, coupled with a high demand for scarce skills, places the sector in a disadvantaged position when compared to the other sectors (Maloney and Segal, 2007). Within these other sectors Maloney and Segal (2007) found a positive trade balance and a comparatively high export growth (which was greater than 10 per cent).

In achieving the AsgiSA objectives of reducing unemployment and poverty, the pharmaceutical industry's ability to increase employment is relatively low, as every one million Rand increase in production only leads to the additional employment of two to five people. The other abovementioned priority sectors can, in comparison, provide 12 to 17 jobs for every one million Rand increase in production (Maloney and Segal, 2007). Lastly, Maloney and Segal (2007) state that in light of these macro-economic indications of the industry's loss of competitiveness, the downward trends have been evident for more than ten years and will continue to worsen if public policy changes are not introduced.

From this section it has become clear that the local pharmaceutical industry has lost its competitiveness within the global context. The main reasons for this appear to be the aging infrastructure that was developed in South Africa's years in isolation from the global market and current government policies that are attempting to redress the inequalities in healthcare created in this period.

These policies coupled with a perceived negative investment climate have discouraged multinational pharmaceutical companies in particular from

continued investment in South Africa. This has resulted in a reduction of R&D conducted locally. This absence of R&D within the local pharmaceutical value chain, and the consequent reduction in the supply of patented drugs, has perhaps led to a greater demand for cheaper local and imported generic drugs. With the reduction of medicine prices, this may have the effect of strengthening governmental policies, which appear to favour cheaper imports in an attempt to improve the access to and affordability of medicines locally.

The second sub-problem poses:

Research question 2: How do local factors contribute to the changing structure of pharmaceutical production in South Africa

2.3 Implications of the Changing Structure of Pharmaceutical Production in South Africa and the Local Pharmaceutical Industry's Response

2.3.1 *The pharmaceutical industry's response to the changing structure in pharmaceutical manufacturing in South Africa*

The FRIDGE Study (FRIDGE, 1999) provided useful feedback from companies operating within the South African pharmaceutical industry that helps to understand their concerns regarding the problems they experienced in the industry at the time.

Some of the general comments made by local manufacturers were:

- many imported generic drugs are cheaper than they can be produced locally;
- South African manufacturing facilities are perceived to have high unit costs;
- the labour force does not take ownership of its role in the local industry and also feels that it is not part of restructuring programmes; and

- the regulatory process in registering new products is inefficient (FRIDGE, 1999).

General comments made by multinational manufacturers were:

- South Africa, at a political level, is not perceived to be open to investment;
- South Africa's medicines' regulatory process is perceived to be amongst the slowest in the world;
- Section 15C of the Medicines and Related Substances Control Amendment Act (1997) threatens continued intellectual property right protection;
- high crime levels raise safety concerns regarding property and employees;
- the government's focus on providing low cost medicine threatens profitability;
- only the price of medicines and not their cost effectiveness is being pursued by the government; and
- legal issues pertaining to labour law make it difficult to dismiss employees involved in illegal activities such as theft (FRIDGE 1999).

By recognising the effect that the changing structure of local pharmaceutical manufacturing has on South Africa's industrial capability, the DTI has recognised that South Africa's key challenge in terms of industrialisation is to diversify and grow the tradable services and export manufacturing sectors (DTI, 2007). Within the context of the implementation of the government's NIPF and the resulting IPAP, the pharmaceutical sector has been identified as a target sector through which the government can improve industrialisation in South Africa. This would also assist the achievement of the previously mentioned AsgiSA targets (DTI, 2007).

Within the IPAP, the pharmaceutical sector has been prioritised owing to the threats posed by imports into this sector (DTI, 2007). It has also been recognised by the IPAP that regulatory challenges exist within the sector with respect to the administration of prices, government medicine procurement demands and the licensing procedures of medicines (DTI, 2007). The key project to be led by the DTI is to establish the production of ARV medicines as a strategic industry. A task team has already been designated to look at how to increase locally produced ARVs for the government ARV tender. The stakeholders of this project have been identified as the DOH, the Presidency and the Department of Science and Technology (DST) (DTI, 2007).

2.3.2 *A new regulatory authority for health products*

Owing to the capacity-related inefficiencies within the MCC, the Minister of Health has established a ministerial task team to address the issues and concerns raised by the industry.

This task team has been instrumental in producing a report that provides the DOH recommendations for establishing a new South African Regulatory Authority for Health Products (DOH, 2007).

2.3.3 *Implications of and responses to the pricing policies of pharmaceuticals in South Africa*

When viewing the increase in medical expenditures in terms of the total benefits paid by medical aids in the year 2006 (compared to the benefits paid in 2005) it is interesting to note the relatively small increase in medicine expenditure when compared to other expenditures:

- medicine expenditure increased by four per cent;
- private hospital expenditure increased by 8.6 per cent;
- medical specialist expenditure increased by 11.9 per cent; and
- benefits paid to general practitioners increased by 12.1 per cent (CMS, 2007).

The only expenditure to decrease was benefits paid to dentists, which decreased by 3.6 per cent (CMS, 2007). The relatively low percentage increase in medicines expenditure by medical aids highlights the effect that price controls and generic substitution have had on medicine expenditure.

When looking at the trends in total medical scheme expenditure it is also useful to note the total decrease in expenditure on medicines per beneficiary. Prior to 1994 medical aid expenditure on medicines represented the single largest contributor to medical aid expenditures (almost 32 per cent of total expenditures) (McIntyre and Thiede, 2007).

McIntyre and Thiede (2007) found that there was a six per cent decrease in expenditure on medicines per beneficiary, in real terms, between 1997 and 2005, which appeared to level off in 2006. Historically, in the 1980s and early 1990s this figure had increased more rapidly than any other medical scheme expenditure. By the mid-1990s medicine expenditure had continued to increase but the rate of increase in expenditure on private hospitals had become higher. It was only in the early 2000s that the rate of increase in medicine expenditure levelled off to the level of inflation and it then started to decrease in 2003 and most notably in 2004 and 2005 (McIntyre and Thiede, 2007).

The decreased expenditure in 2004, according to McIntyre and Thiede (2007), was mostly due to the implementation of government's legislation on generic substitution, which resulted in a 14 per cent increase in the usage of generic medicines between 2003 and 2004. Similarly in 2004, the implementation of the government's pricing regulations resulting in the SEP policy resulted in a 22 per cent average decrease in the price of medicines (McIntyre and Thiede, 2007).

The pharmaceutical companies claim that an inadequate allowable increase in the SEP makes it even more difficult for pharmaceutical companies to recover their costs and it impacts negatively on their profit margins (Mzolo, 2008). An analyst from Frost & Sullivan commented that a low increase in the SEP further discourages prospects of foreign investment in the industry and expressed his

fear that more companies will leave South Africa to operate in markets that are more competitive (Mzolo, 2008).

Government interventions have undoubtedly been successful in decreasing medicine prices in the short term, but the implications that these policies will have in the long term, particularly in the way that they impact on the pharmaceutical industry, are unclear. Although newer innovative medicines might represent a higher percentage of healthcare expenditure on medicines, their ability to reduce total healthcare costs (e.g. in terms of reducing hospital and medical specialist costs) deserves further investigation.

The Free Market Foundation (FMF) of Southern Africa in response to the SEP of medicines in November 2005 commented that the establishment of the SEP has had the effect of reducing access to medicines and many other unintended consequences (Davie and Urbach, 2006).

The FMF further argues that price controls do not allow for a dynamic action to take place between supply and demand. In the case where governments set prices at below the equilibrium price level (i.e. to a level where the supply falls short of the demand) the profit incentives that manufacturers would normally have in increasing the supply are then diminished. This has the result of shortages in supply and welfare losses. In developed countries such as Japan and Canada medicines' price regulations have the effect of delaying the registration of new drugs as the incentives of marketing the medicines are reduced (Davie and Urbach, 2006). In South Africa, Davie and Urbach (2006) argue that, with a registration process that is already slow, price regulation will further delay registration and in some cases might prevent manufacturers from registering any medicines.

The FMF (Davie and Urbach, 2006) further states that the SEP will have the following negative consequences:

- a reduced access to drugs;
- drug shortages, resulting in an increase in parallel importing and theft;

- reduced profits, leading to a decrease in R&D;
- a decline in local drug manufacturing;
- complex and burdensome regulations;
- reduced economies of scale for drug manufacturers; and
- reduced price competition between producers (Davie and Urbach, 2006).

In conclusion Davie and Urbach (2006) argue that the former price discrimination between the public sector and private sector enabled the poorest sectors to have access to innovative drugs, as the manufacturers were able to cross-subsidise their losses in the public sector through profits attained in the private sector.

Taylor (2007) has found, through communications with G. Goolab of the executive council of the PIASA, that multinational manufacturers have supported the principle of government's proposal of internationally benchmarking medicine prices. Despite this, these manufacturers have raised concerns regarding the selection of the countries included in the proposal.

In their opinion New Zealand and Spain should not be included in the selection owing to the harsh price regulations imposed on medicines in these countries. In addition, the multinational manufacturers suggest that the average price, rather than the lowest price within these countries, should be benchmarked (Taylor, 2007).

Concerns have also been raised with regard to the proposal that generic medicines should be set to be 40 per cent lower than the current price of the originator medicine. A Medscheme analysis found that the SEP of a first-to-market, non-parenteral generic product was on average 36 per cent cheaper than the originator drug at the time of introducing the generic medicine into the market (Taylor, 2007). It was also found that the average price of the generic medicine became 52 per cent cheaper than the originator drug when competing generics of the same medicine entered the market (Taylor, 2007). The argument therefore is that competition within the generic medicine market is

more effective than the regulations in reducing the prices of generic medicines. Reekie (1998) supports this argument for free market competition and its ability to reduce medicine prices, as mentioned earlier in this research report under section 2.1.6.

Taylor (2007) has indicated that the industry argues that by introducing tighter price controls over the first generic medicines to enter the market the incentive to be the first generic entrant would be lost. This is because the manufacturer would not benefit from the transitory higher price that the first generic entrant into the market could attain. By reducing this incentive the more expensive originator drug would effectively remain longer in the market without competition, thereby still contributing to high medicine prices (Taylor, 2007). Maloney and Segal (2007) state that although many manufacturers can understand the government's rationale behind reducing prices in the private sector they feel that the economic rationale behind the price controls fails to take the economics and the dynamics of the local industry into account.

This, according to Maloney and Segal (2007), increases the uncertainty within the industry and has a negative effect on the attractiveness of investing in the local industry. Uncertain impacts of various pricing policies could therefore create a general uncertainty within the industry, which makes forecasting and future investment more risky. This would probably be of greater concern for multinational manufacturers, who would view profitability as being important in achieving sustainable competitive advantages and innovation through R&D, as mentioned by previous authors (Angell, 2000; Henderson, 2002; Henry and Lexchin, 2002; Scherer, 2004).

Biermann (2003) suggests that the South African government could reduce the prices of drugs by declaring South Africa a "Pharmaceutical Manufacturing Free Zone". This could be achieved if the government were to exempt medicines from value added tax (VAT) and exempt pharmaceutical manufacturers from income tax and import duties normally imposed on equipment used in the manufacturing process. In addition, the reduction of unnecessary government regulations and even exempting the entire healthcare industry from tax would, according to Biermann (2003), lead to an increased provision of affordable

healthcare. These incentives would have the net result of attracting and retaining investors within the local pharmaceutical industry, which would lead to lower costs owing to the resulting, increased competition (Biermann, 2003).

2.3.4 *The public sector procurement of medicines*

Local manufacturers, in the old tender price preference system (awarded to manufacturers that supplied medicines to the public sector), were given price preferences above competing imported products. The aim of the previous system was to provide the local manufacturers with an advantage over competing imported medicines and thereby increase the usage of locally manufactured medicines and the creation of jobs within the local pharmaceutical industry (FRIDGE, 1999).

Maloney and Segal (2007) state that the procurement of medicines in the public sector requires a full review so as not to be manipulated by importers.

This review, according to Maloney and Segal (2007), would need to consider the value that the companies within the pharmaceutical industry add to the economy in terms GDP and employment. Lastly, if the procurement system were not changed, local pharmaceutical production would not be sustainable if the government did not promote it effectively (Maloney and Segal, 2007).

In July 2007 at the Board of Healthcare Funders Annual Conference the NAPM declared that as a result of the SEP policy the cross-subsidisation of prices between the private and public healthcare sectors would be negatively affected. As a result the generic medicines producers' tender prices to the state could increase (Taylor, 2007). The possible implication of this is that the government would continue to seek cheaper medicine prices from imported medicines, thus reducing the market for local manufacturers.

2.3.5 *Implications of and responses to skills shortages*

Professor P.F.K. Eagles, president of the South African Pharmacy Council (SAPC), has acknowledged the shortage of pharmacists in South Africa, a situation that according to him was never foreseen a decade ago (Eagles,

2008). The increased number of pharmacist's assistants has, however, contributed to offset the shortage of pharmacists, according to Eagles (2008). This shortage will be further compensated with the forthcoming prospect of programmes between the South African government and other governments that will allow foreign pharmacists to work in the overburdened public sector and perhaps the private sector (Eagles, 2008).

Within the pharmaceutical industry, Eagles (2008) claims that there are many changes that are due to occur in the near future. These changes will include the MCC Bill, the National Health Act Bill, and the new Pharmacy Council in addition to the challenges that are presented by the pricing and dispensing policies. These changes will have an impact on the enthusiasm and professionalism of pharmacists in South Africa and present a considerable challenge.

Eagles (2008) also emphasises the importance of pharmacists as seen by the financial loss experienced by countries when pharmacists are absent from the medicines' value chain. This shortage of pharmacists overall could have an impact on pharmaceutical manufacturing, as the transfer of skills between pharmacists and other employees in this sector would be diminished. With the reduction of actual manufacturing and especially higher value R&D activities in the sector the shortage of skills would not just be evident in the reduced number of pharmacists but also in the experience and skills of the pharmacists that are currently practising in this environment.

To highlight the lack of skills further in terms of tertiary education in the local pharmaceutical industry, it is interesting to compare the level of education, for example, in India. Stephen Saad, CEO of Aspen Pharmacare, has commented that, although South Africa has advantages in terms of its infrastructure and ports, he has, in his experience, observed that there are more employees with PhDs within one generic company in India than there are within the whole local pharmaceutical industry (Pile, 2005).

2.3.6 *Legal dispute*

Between 1998 and 1999, a legal dispute arose between the U.S. pharmaceutical industry and the South African government. In 1997 the South African Parliament passed the Medicines and Related Substances Control and Amendment Act (RSA, 1997), which contained a very controversial clause (section 15 C) which became the centre of the dispute between the South African government and the U.S. pharmaceutical manufacturers (Bond, 1999).

According to Bond (1999), the most controversial parts of clause 15C was that it provided the government with the means to import the cheapest drugs globally through parallel importing. In addition this clause meant that the government could grant compulsory drug licensing while it followed safeguards and paid a royalty to the patent owner (Bond, 1999). This dispute was taken to the South African courts and was eventually settled by the pharmaceutical industry in April 2001 (Barton, 2004).

Maloney and Segal (2007) argue that compulsory licensing will cause innovator companies to lose value in the local market and encourage them to disinvest, which would further increase the conditions under which compulsory licences are usually granted.

In terms of parallel imports Maloney and Segal (2007) also argue that the reputation of a drug can be damaged if the drug lacks quality and if it is not truly equivalent to existing drugs (which increases the onus on the MCC to exercise quality controls). Although the practice of parallel imports has not been used, the threat posed by such a practice would nonetheless damage local production of drugs.

2.3.7 *Conclusion*

Maloney and Segal (2007), through investigating the local pharmaceutical sector, conclude that:

- the sector is essential in terms of providing healthcare and is therefore of strategic significance in order to secure the supply of medicines in South Africa, which has a rising incidence of infectious diseases; and

- the sector does show growth potential to supply drugs for infectious diseases found in sub-Saharan Africa in partnership with other countries (Maloney and Segal, 2007).

South Africa needs to decide whether its drug market should be restricted to a local market or broadened out to an export market. The focus of the market then has to be decided and this could either be a focus on developing the entire pharmaceutical value chain or creating a competitive niche in strategic products and activities (Maloney and Segal, 2007).

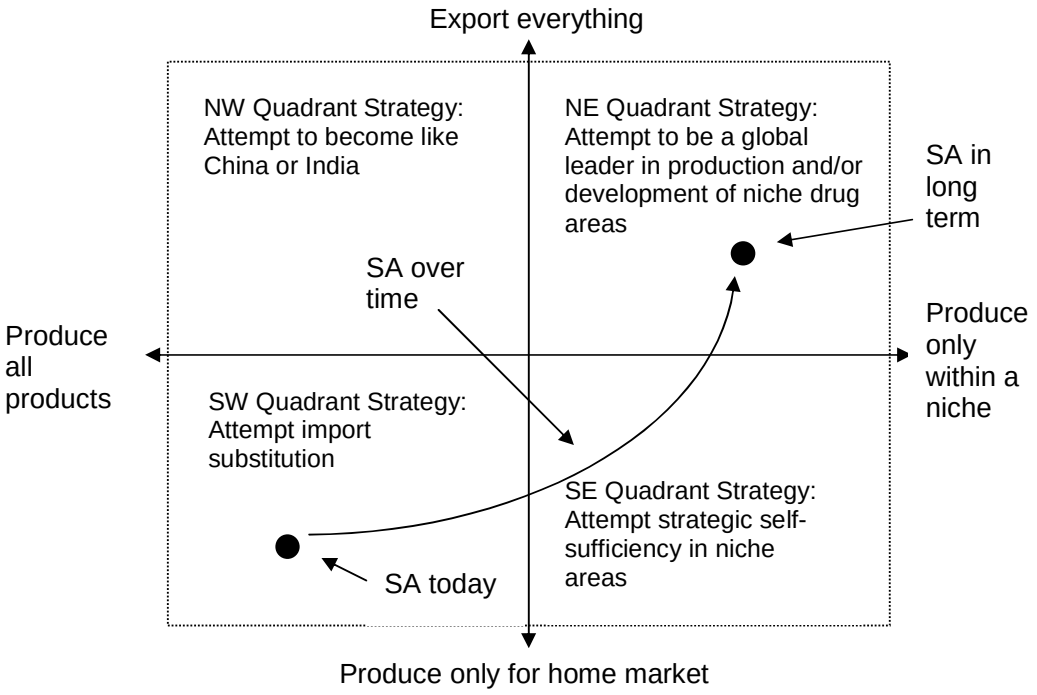


Figure 4: Proposed way forward for pharmaceuticals in South Africa

Source: (Maloney and Segal, 2007)

These two dimensions are illustrated in Figure 4. The dimensions provide four main strategic areas that become possible when the two dimensions are combined.

These main strategic areas are the North West (NW), the North East (NE), the South West (SW) and South East (SE) quadrant strategies. Currently, according to Maloney and Segal (2007), South Africa is following the SW quadrant strategy, where it attempts to substitute local production and activities across the value chain with imports. This strategy is uncompetitive and inefficient when confronted with global competition and produces very little for an export market.

Maloney and Segal (2007) suggest that South Africa has the ability to develop sustainable competitive advantages in areas where it has demonstrated potential. In doing so, it can first meet the demand of the local and regional markets before expanding to export markets as its competitiveness increases in global terms. The ability to achieve this, however, will be restricted if the six main determinants of growth are not addressed.

These determinants all require a balance between the interests of the industry and those of the government. The implications of not addressing these are that the local pharmaceutical industry will remain in its current uncompetitive position. The main determinants are summarised by Maloney and Segal (2007) as follows:

- *Quality of regulatory body*. It is essential to have a quality regulatory body to achieve the balance between low prices for medicines in the private sector and still maintaining economically viable pharmaceutical production;

- *Intellectual Property Rights (IPRs).* Regulations should recognise the balance between IPRs that benefits the generic drug market by providing more affordable drugs and protecting the interest and viability of manufacturing drugs produced under patent protection;

- *Innovative capacity.* The government should provide a balance between providing fiscal support for producing innovative pharmaceuticals and providing fiscal support in other incentive programmes;

- *Skills and healthcare provision.* There should be a balance between developing skills for the pharmaceutical sector and other sectors of healthcare;

- *Market scale.* The government should recognise a balance between the private sector's role in lessening the burden of the public sector and improving the public sector itself;

- *Cost competitiveness*. The cost drivers within the pharmaceutical value chain must be assessed and must be addressed in terms of their potential to avoid competition and maintain protection.

The third sub-problem poses:

Research question 3: What are the implications of the changing structure of pharmaceutical production for the South African industry and how have companies within the industry responded?

2.4 Literature Review Summary

Establishing the global factors within the pharmaceutical industry aids in identifying the trends within the industry and in particular in developing countries. Understanding these factors would help to place the South African pharmaceutical industry in a global context. On a macro level these factors combined with the economic, social and political factors within the South African context will aid in providing insight into the changing structure of pharmaceutical production in South Africa.

In summary, the global pharmaceutical industry is in a continuing state of flux as issues internal to the industry such as diminishing drug pipelines force the industry to consolidate and seek new areas of profitable innovation in order to sustain growth through R&D and the sourcing of technology from the

biotechnology sector. External issues such as drug regulation, pricing policies and intellectual property further complicate the issues internal to the industry.

In addition to this, the industry continues to strive towards creating new demand through innovative products.

At the same time, however, the industry's social responsibility is questioned when it appears to supply drugs reluctantly to less profitable markets in developing countries where the demand is very high. The industry in developed countries is fiercely attempting to demand intellectual property protection in order to remain profitable and sustain innovation through R&D made possible through high profits. Conversely, governments (especially in developing countries) are attempting to limit this protection and force the industry to lower prices in order to make drugs more accessible and affordable.

In addition, parallel importation and compulsory licensing while benefiting developing countries serve as a threat to companies in developed countries. This, however, also reduces the industry's incentives for remaining innovative, which is becoming seemingly more difficult to sustain.

The influence of generic drugs, however, opens up a new interesting competitive environment within the industry and in many cases seems to fulfil governments' needs to reduce the cost of medicines. However, when one views drug therapy in terms of its ability to be therapeutically beneficial to the end-user, one should perhaps consider the advantages of allowing a free market for medicines. In the short term this could imply higher medicine prices. In the long term these prices could translate into increased innovation and increased competition that would lead to a decrease in total healthcare costs. If innovation is enhanced it would also mean that future generic drugs would be of a greater therapeutic value at a lower cost.

From investigating the local contributing factors to the changing structure of pharmaceutical manufacturing in South Africa it has become evident that the local industry has become less competitive. This is especially evident when the efficiency of local pharmaceutical manufacturing is compared to "centres of excellence" and the scale of manufacturing conducted in Asia. This has

resulted in an increased number of cheaper imported drugs in South Africa, which further reduces the viability of local manufacturing which in itself requires a large proportion of imported inputs.

With the rising demand for medicines (due to the high incidence of infectious diseases) and the historical inequalities in the affordability and accessibility of medicines amongst the population of South Africa, the South African government has further emphasised the importance of reducing the overall cost of medicines. This has become evident in the government regulations and policies for reducing the overall cost of medicines. The overall demand for less expensive medicines, coupled with problems such as regulatory inefficiencies, unclear policies, skills shortages and aging infrastructures, places further pressure on the local pharmaceutical manufacturing companies.

The changing structure of pharmaceutical manufacturing appears to be at a stage where drastic measures and policy changes need to be implemented to make the industry viable once again.

Despite this there appears to be growth within the generic medicine manufacturing that could perhaps serve as an innovative example of how the industry can remain viable.

2.5 Research Questions to be Explored

The literature review provided a background against which the research questions were formulated. These questions focused the research problem and responses to these questions were investigated in an attempt to answer the research problem and sub-problems.

The three research questions are listed below:

Research question 1: How do global factors contribute to the changing structure of pharmaceutical production in South Africa?

Research question 2: How do local factors contribute to the changing structure of pharmaceutical production in South Africa?

Research question 3: What are the implications of the changing structure of pharmaceutical production for the South African pharmaceutical industry and how have companies within the industry responded?

CHAPTER 3: RESEARCH METHODOLOGY

This research was exploratory in nature and a qualitative approach was used to investigate the responses to the research questions, which were asked in interviews with stakeholders within the pharmaceutical industry.

3.1 The Qualitative Research Approach

The qualitative research approach can be used to describe and study concepts and cases to which particular theories do not apply (Welman, Kruger and Mitchell, 2008). Qualitative research is therefore also, according to Welman et al. (2008), a descriptive form of research that can be applied to groups or organisations. Unstructured in-depth interviews are used as a form of qualitative research in order to identify important issues in the particular areas of research and to develop further questions to be investigated and explored (Welman et al., 2008).

Unstructured in depth interviews, according to Welman et al. (2008), are used in explorative research in order to identify important variables in a particular area, formulate pertaining questions on these variables and to generate a hypotheses for further research. Welman et al. (2008) describe qualitative research as being used for its ability to investigate and explore the participant's first-hand experience rather than their speculative explanations of the research topic. Welman et al. (2008) further suggest that in conducting an unstructured interview the interviewer should suggest general themes of discussion and ask further questions as the interaction between the interviewer and respondent develops spontaneously.

Welman et al (2008) suggest that the interviewer remains in control of the interview situation by encouraging the respondent to remain on the theme that is under discussion if the discussion happens to stray from the topic. This was achieved by having questions in the form of an actual research instrument (please see Appendix A) that guided the general theme of the interview.

3.2 Population Studied

The targeted population includes all the stakeholders within the South African pharmaceutical industry that have a direct connection with pharmaceutical production or have the ability to influence the nature or structure of pharmaceutical production in South Africa. The population therefore includes all organisations or companies that have direct involvement in pharmaceutical production at present, including those that have had direct involvement in pharmaceutical production in the past.

Industry organisations and government departments that have influential power to make decisions that can impact local pharmaceutical production are also included in the population.

3.3 Sampling Methodology

Welman et al (2008) describe a convenience sample as a sample that is taken due to the ease of obtaining the sample. The disadvantage of such a sample is that the choice of the sample is likely to be biased (Welman et al., 2008). A convenience sample of 13 individuals was selected to take part in the interviews. To reduce the biased nature of the sample individuals from different areas of the industry were selected. Three individuals from MNCs involved in local manufacturing were interviewed; one of these individuals represented a large MNC specialising in generic medicines. Three individuals from each of the three largest local manufacturers were interviewed as well as two individuals from smaller local manufacturers, one of which is involved exclusively in contract manufacturing. One respondent was selected from the DOH and more specifically from the MCC, and another from the DTI in order to gain the government's perspective on the research topic. Two individuals were selected from industry organisations and, lastly, one individual was selected from a professional organisation that represents pharmacists in the pharmaceutical industry.

All the respondents were geographically situated in Gauteng. The selected individuals all had either direct involvement or intimate knowledge of the local

pharmaceutical production industry. In addition to this, all the individuals had senior positions within the organisations.

Please refer to Appendix B for the list of interviewees.

3.4 Data Collection

In-depth interviews were conducted using the pre-determined questions that served as a guideline for a detailed discussion. The interviews were all conducted in person, with the exception of one telephonic interview. A portable electronic recording device was used to record all the interviews, including the telephonic interview. Prior to the interview all the respondents had provided permission for the interviews to be recorded.

The recorded data was then analysed and categorised in terms of the way in which the data pertained to the main research questions generated by the literature review.

In some cases information was voluntarily offered by the respondent and not directly prompted by the interview questions but rather by the unstructured in-depth interview. Where this additional information proved to be relevant in the context of the research questions it was also collected and collated in order to aid the understanding of the individual respondent's perspective, experience and perception of the issues covered by the research questions.

3.5 Data Analysis

Welman et al (2008) suggest that "raw field notes" need to be processed and converted into write-ups or text in order that they can be read, edited and commented on. The recorded data collected from the interviews was therefore transcribed, analysed and sorted in terms of the broader contexts or factors under which they fell. Interesting phenomena that arose in the course of the interview were also analysed and placed into the broader contexts of the research questions. Although the questions in the actual research instrument were based on the three research questions, the respondents' answers did not always fall into the correct contexts in which the questions were asked.

Discretion was therefore used in the presentation and interpretation of the results to place respondents' answers into the context of the broader research questions to which they had the greatest relevance.

3.6 Validity and Reliability

3.6.1 *Internal validity*

Welman et al. (2008) describe internal validity in terms of the extent to which changes in the dependent variable can be attributed to the independent variable and not to other factors that have not previously been considered. In terms of this research, independent variables have been identified in the literature review as factors that could influence the changing structure of pharmaceutical manufacturing in South Africa.

The dependent variable can be viewed in terms of the actual reasons for the changing structure. If the research questions are too specific the chances exist that the internal validity might be compromised in that the responses to these questions may not elucidate the actual reasons for the changing structure in manufacturing that were not previously identified.

The open-ended interview questions served as a way of reducing the risk of compromising internal validity. The interview questions served to elucidate and uncover any additional factors that pertain to the actual changing structure of pharmaceutical manufacturing in South Africa in each respondent's opinion.

"Construct validity", according to Welman et al. (2008), refers to the process by which the independent variables are used to elucidate the actual independent variables of interest rather than other variables. In terms of this research the construct validity would be determined by the manner in which the literature review has informed the nature of the questions to be asked. The open-ended, unstructured nature of the interview questions was such that they allowed for further construct validity in their ability to evoke responses that had possibly not been revealed through the literature review but were pertinent to the research questions.

3.6.2 *External validity*

Welman et al. (2008) define external validity and in particular population validity as the extent to which the findings from the sample considered in the research can be extrapolated to the entire population from which the sample was taken. The findings from the interviewed sample were considered from the unique perspective of the individual respondents that made up the sample. It was assumed that the individuals' perspectives were informed their experience and by the manner in which they participate in the industry. These findings may not all be influenced by the same factors that occur in a broader context but rather by the distinctive combination of these factors and the manner in which they (and possibly additional factors) contribute to the individual respondent's perception regarding pharmaceutical manufacturing in South Africa.

The external validity of this research is therefore limited, as the results do not provide sufficient information on which to base, for example, investment decisions. The exploratory nature of the open-ended questions, however, was used to highlight additional factors that may or may not be relevant to the entire local pharmaceutical manufacturing industry as a whole.

3.6.3 *Reliability*

Welman et al. (2008) claim that the reliability of research involves the findings of the research and the extent to which the findings are credible. The reliability also pertains to the manner in which the findings could be comparable if the research were to be replicated (Welman et al., 2008). The reliability of this research is reduced by the nature of the open-ended questions and the particular circumstances that prevailed at the time of the interviews. The nature of the factors that influence pharmaceutical manufacturing and the manner in which they influence diverse organisations under varying conditions (for example, macro-economic and regulatory conditions) further reduce the reliability. The reliability of the research is, however, not of utmost importance as the research also has the aim of creating a general qualitative understanding of the industry rather than creating an accurate factual record.

CHAPTER 4: PRESENTATION AND DISCUSSION OF RESULTS

4.1 Introduction

The literature review explored the global and local factors influencing the South African pharmaceutical manufacturing industry as well as their possible implications and the local industry's response to the factors. These factors were reviewed in the literature in terms of the three problem statements.

Three research questions emerged from the literature review and further provided a basis for establishing questions that served as a guide when conducting the in-depth interviews with stakeholders within the South African pharmaceutical industry and government departments. Data was collected from the interviews, collated and analysed in order to investigate the changing structure of pharmaceutical manufacturing.

The analysis of the responses of the interviewees serves to provide an understanding of the global and local factors that impact on the local pharmaceutical manufacturing industry as well as their implications and the local industry's response. This serves the purpose of clarifying the issues currently facing this industry and aids in achieving a possible analysis of how this changing structure could be addressed to ensure that the industry remains viable and sustainable.

4.2 The Global Pharmaceutical Industry's Impact on the Changing Structure of South African Pharmaceutical Production

All of the respondents indicated that the two largest global factors that have impacted on local pharmaceutical production have been the consolidation of global manufacturing activities of MNCs and the increased global usage of generic medicines.

4.2.1 *Consolidation of global pharmaceutical production*

All the respondents agreed that the single biggest global factor that has influenced pharmaceutical production by both South African companies and MNCs in South Africa has been the events that have taken place within global pharmaceutical manufacturing in recent decades. In the last 15 to 20 years global pharmaceutical manufacturing by MNCs has undergone a transition, whereby MNCs have consolidated their manufacturing facilities globally to create centres of excellence. These centres are typically large consolidated manufacturing facilities that often produce specific drugs or drug categories for geographic regions, particular markets and in some cases for the entire global market of an MNC. Previous to this period in the late 1980s and early 1990s MNCs often had many manufacturing facilities globally in countries where they had marketing, sales and distribution activities.

One respondent from an MNC commented that the MNC often only had manufacturing presence in a country if the government of that country required it through legislation. The manufacturing facilities often also included a production facility for APIs that were incorporated into the medicines that were formulated in each country. South Africa was no exception to this phenomenon, particularly as the country was in relative isolation with respect to the global pharmaceutical market.

4.2.2 *Efficiencies and quality in consolidated manufacturing facilities*

The main drive towards establishing these centres of excellence has been to achieve two objectives simultaneously. Firstly, economies of scale can be achieved when large volumes of a limited variety of drugs are produced in one facility. This would result in a lower cost per unit of a particular drug when compared to the average cost of that drug if it were produced in each country, region or market in which the drug is sold. All companies and industry organisations interviewed were in agreement that this drive to lower costs and improve production efficiencies has also been motivated by the MNCs' need to remain viable and sustainable in markets. These markets have experienced an

increase in competition based mostly on price owing to the increasing demand and supply of generic drugs globally in combination with a diminishing “drug pipeline”. Drug patents are essential in providing protection against competition from generic drugs. Lowering the production costs of these patented drugs while maintaining a relatively high price leads to greater profit margins. Improving the cost efficiency of production therefore plays an important role in providing funds for R&D investments (potentially leading to the discovery and introduction of new innovative drugs) and investments in the continuing marketing of existing drugs. Both these continued investments are important in light of diminishing drug pipelines and increased competition from generic drugs.

Secondly, by producing the total supply of a drug for the global market in one facility a manufacturer would also be able to maintain and assure uniform high quality standards of produced drugs. A respondent from a large multinational generic company commented that the emphasis on high drug quality standards has become both a requirement and an expectation globally, regardless of whether the drug is a new innovative drug or a generic drug.

Three respondents from MNCs and industry organisations of MNCs all emphasised that the drive towards centres of excellence also coincided with a rise in costs associated with improving the quality of products.

Owing to the increasing competition from cheaper generic drugs globally, the industry had to find ways of improving the efficiency of drug production, while maintaining and improving quality without increasing costs. The improvement in pharmaceutical production technology worldwide also played a role in making production processes more efficient and proficient at consistently delivering high quality products. These new technologies would represent high capital expenditures that could only be justified with the production of larger volumes.

A respondent from a professional organisation also commented that global quality standards and quality expectations for medicines have increased and that by maintaining high levels of quality assurance the risk of litigation against low or inconsistent quality can be reduced. In addition to this, a respondent

from a large global generics company noted that the FDA's willingness to accept risk has also declined in recent years, which has resulted in the approval of fewer new drugs than before.

Five of the respondents agreed that merger and acquisition (M&A) activity amongst MNCs further resulted in the establishment of centres of excellence. The main reason for the M&A activity in this industry has been to gain synergies in R&D capabilities that result in the delivery of new innovative drugs that can be protected by a patent. Typically with this trend the manufacturing functions of the merged companies would also be consolidated and merged in order to achieve manufacturing synergies and uniform quality controls over the production of a larger variety of drugs. One respondent from a large multinational generic company noted that the M&A activity within the industry has also recently become a trend amongst companies producing generic drugs. Most companies would thereby seek to increase their product portfolios, market shares and cost efficiencies brought about through economies of scale and manufacturing synergies.

Almost half of the respondents believed that R&D activity within MNCs has recently been focused on producing newer drugs from the biotechnology sector. This has also further resulted in M&A activity with biotechnology companies or focusing R&D activities in producing innovative and marketable NCEs by applying biotechnology principles.

A CEO of an MNC that has recently merged with a biotechnology company commented that there is a drive within the global R&D-based pharmaceutical industry to meet unmet drug needs and to replenish drug pipelines. In doing so R&D activity is now focused on creating a demand for drugs used in the treatment of diseases like cancer and multiple sclerosis that have a lower incidence in the general population and for which there are no cures at this stage. These drugs are for the most part sold in niche markets in predominantly developed countries at relatively high prices and with significant profit margins.

Currently, the drugs emerging from the biotechnology sector still predominantly originate mostly from developed countries, where the skills, technology and

R&D capabilities in the biotechnology sector are still primarily concentrated. Companies that are starting to focus on the markets for biotechnology products are seeking to scale down their existing global manufacturing presence and are reinvesting in R&D and newer production facilities. These new production facilities are specifically designed to suit the high-technology production requirements of biotechnology drugs that are generally produced in lower volumes than conventional medicines. The respondents from the MNC that had merged with a biotechnology company mentioned that the company is currently divesting in its manufacturing sites in three South American countries, two Asian countries, one European country and in South Africa in order to focus on the R&D and the production of newer innovative biotechnology drugs. The facilities involved within each of the countries are generally being sold to independent companies with contracts to continue the production and supply of the conventional medicines that the MNC currently requires in those markets.

Half of the people interviewed and in particular those affiliated to large MNCs all agreed that the centres of excellence are mostly established in countries or regions that fulfil certain criteria. These criteria most often include cost advantages such as tax incentives and other incentives provided by the governments of these countries in order to attract foreign direct investment (FDI).

In addition to this, these countries often have a large skills base as a result of high education standards coupled with a relatively low cost of skilled and semi-skilled labour. Countries like Puerto Rico, Brazil, Singapore, China and most notably India were given as examples of nations that provided the MNCs with attractive incentives for the establishment of these centres of excellence. A respondent from a large local generic company commented that the MNCs assess the political climate, infrastructure and economic stability of these countries prior to investing in regional manufacturing facilities in order to minimise the risks of such large investments.

Individuals from both industry organisations and a government department that were interviewed emphasised that at the time of these developments the South African government had perhaps not provided global MNCs with sufficient

incentives to invest in the expansion of their existing operations or in the establishment of new large manufacturing facilities in South Africa.

4.2.3 *Global generic medicine demand*

Simultaneous to the developments that have occurred within the environment in which global MNCs, traditionally situated in western developed nations, operate another change has occurred in the global pharmaceutical manufacturing industry. The majority of the people interviewed from industry organisations, MNCs and a company with direct ties to a large Indian pharmaceutical company stated that in the last 20 years there has been an increase in the production of generic drugs predominantly in developing countries in Asia and most notably in India and China. This general shift of total global drug production volumes from the west to the east of the globe has been driven by the rising demand for generic medicines in developing countries. These developing countries previously had poor access to affordable medicines. Often the governments of developing countries have provided their local pharmaceutical industry with protection from competing with imported drugs by establishing high import tariffs for imported medicines. These governments also often provide incentives, e.g. tax incentives when the manufacturers are able to export medicines.

A respondent from an industry organisation remarked that the WHO has also emphasised the important role that generic drugs play in increasing the access to medicines and essential drugs in particular. The increase in the demand for generic drugs in developing Asian countries has also generated large growing markets for generic drug companies within these regions.

Owing to the affordability and quality of generic medicines, their usage in developed countries has also increased dramatically. A respondent from a multinational generic medicine producer estimated that the percentage of generic medicine usage relative to the total medicine usage in the U.S. and Germany is at 70 per cent and at 65 per cent in the U.K.

This large generic drug market has also led to the establishment and growth of companies that specialise in producing APIs and other raw materials used in

the formulation of medicines. These industries have grown to such an extent that they have, with time, also been able to exploit export markets that have large demands for cheaper generic APIs and raw materials. A respondent from an industry organisation commented that the generic drug industry has low barriers of entry as relatively low levels of R&D expenditure are involved in formulating a generic equivalent of a drug. In addition to this, there is no need for large capital investments to discover, develop, and conduct clinical trials on an NCE.

The increasing demand for generic medicines globally in both developed and developing countries, has represented market opportunities for many MNCs. A respondent that was interviewed from a large MNC noted how this MNC had acquired a large global generic medicine business in the mid-1990s that it was able to grow significantly. This generic medicine business was then sold to another global generics business in 2008 when the MNC merged with a biotechnology company in order to focus on R&D so that it could fill new product pipelines with more profitable and biotechnology drugs that would be protected by patents.

A respondent from a large multinational generic business noted that the increased demand for generic medicines had also resulted in the establishment of large global generic medicine companies in the U.S. and Europe that had originally started off as small local generic businesses.

Most respondents noted that with the expiration of the patents of former “blockbuster” drugs the supply and usage of cheaper generic equivalents of these drugs have increased globally.

A large share of the total global drug market previously dominated by patented drugs originating from large global R&D-based MNCs has now been lost to a large number of generic drug producers situated mostly in developing countries. This trend has enabled the pharmaceutical manufacturing capability and capacity in a country like India to advance and grow. A representative from the DTI mentioned that up until fairly recently India used to be the seventh-largest producer of medicines globally. With the tremendous growth experienced in the

Indian pharmaceutical industry, India has, in the last four years, become the world's second-largest producer of medicines and has a pharmaceutical production volume output equivalent to Germany's.

The capability of the Indian pharmaceutical industry has resulted in its ability to attract contract-manufacturing opportunities from large MNCs that have outsourced their production activities in order to focus on R&D. An interviewee from a large local generic medicine manufacturer claimed that India has the largest number of FDA-approved production facilities outside of the U.S. and has, according to another local manufacturer and importer, become the "pharmacy to the world". The respondents from the three largest generic medicine producers locally also highlighted that a new trend has developed, in which large MNCs also partner with large generic medicine producers in order to manufacture drugs that have come off patent or are close to the end of their patent protection period. This enables the MNCs to outsource the production and sometimes marketing and sales of large volumes of these drugs prior to the expiration of the patent so that they can be the first to market a generic version of a patented medicine in various markets. This enables the former patent holder to maintain market share and pre-empt the competition posed by generic medicine producers.

A respondent from a large local generic medicine producer noted that many Indian companies also develop cost-effective formulas of generic medicines that they then licence to other small producers of generic medicines.

These arrangements are then also often coupled with supply agreements, in which the smaller generic medicine producers source the APIs and other raw materials used in the formulation of these generic medicines from the licensee, which is often a large generic medicine producer.

A respondent from the world's third-largest generic medicine producer also indicated that large generic medicine producers, including themselves, often integrate their business backward by purchasing a producer of APIs in order to secure a constant and growing supply of APIs and other raw materials used in

their medicines. These API producers typically do not supply APIs exclusively to the holding companies but also exploit export markets for APIs globally.

A respondent from an industry organisation noted that there is often a collaborative approach to the production of APIs amongst companies in India, in which numerous companies are involved in the different stages of the chemical synthesis of APIs. Another respondent from a large generic medicine producer suggested that many of the chemical precursors used in the manufacturing of APIs in India are sourced from China.

4.2.4 *The global impact on local pharmaceutical production*

The global trends towards the establishment of centres of excellence and the growth in the demand for generic drugs globally have affected the local pharmaceutical manufacturing industry in many different and sometimes indirect ways. The majority of the people interviewed were aware of the Genesis Study's (Maloney and Segal, 2007) account of the 35 local pharmaceutical manufacturing sites that had closed since 1994.

These closures have undoubtedly had an effect on the local pharmaceutical manufacturing industry and the general perception appears to be that this withdrawal of predominantly MNC manufacturing presence had left a temporary void in the local manufacturing industry. A respondent from an industry organisation mentioned that the withdrawal had, however, been fairly gradual since 1994.

The facilities operated by MNCs that eventually would close, would typically cease to formulate certain product lines locally as they would be procured from other global manufacturing sites at a lower cost than they could be produced locally. At this stage the imported bulk products would still be packaged locally while the formulation and packaging of a limited number of product lines would be continued. In some cases the products would eventually even be imported pre-packed from facilities outside of South Africa. Ultimately, however, the volumes of both formulated and packaged products decreased to a level far below the designed production capacity of the facility.

A respondent from a government department indicated that a local MNC facility that was recently sold was running at 30 per cent of its designed production capacity immediately prior to the sale. With high manufacturing overheads and costs, maintaining a manufacturing facility with relatively low volumes no longer remains economically viable.

Respondents from an MNC and from industry organisations commented that in many cases the manufacturing facilities of MNCs withdrawing from South Africa would then be sold to local pharmaceutical companies that then re-invested in the facilities to upgrade them to produce their own products. In some cases these companies would also conduct contract-manufacturing activities for MNCs that no longer desired to have a production facility locally.

Another trend as highlighted by a quarter of the companies and industry organisations that were interviewed is that the facilities previously owned by MNCs are being sold to BEE companies coupled with extended supply agreements with the original owner of the facility. This enables the MNC to obtain local BEE accreditation by sourcing from a local BEE supplier. One of the six manufacturers that were interviewed is a black empowered company that operates a manufacturing facility that was previously owned by an MNC. The new business entity has an agreement with its previous owner to continue the supply of medicines required by the MNC in the local market while producing its own branded generic products. Another MNC that was interviewed is currently undergoing an identical process.

With an increase in the usage of generic medicines globally the demand for generic medicines has also increased in South Africa. Post-1994 and especially after the establishment of the South African government's NDP in 1996 an emphasis has been placed on increasing the general population's access to medicines. A respondent from an industry organisation noted that the government wants South Africa to be seen as a developing country when addressing the country's need to increase access to affordable medicines. This has led to a general emphasis in the DOH to increase the usage of cheaper generic medicines in order to reduce the total expenditure in both the public and private healthcare sectors. The SEP system, applied to both generic and

patented medicines, has also been implemented to ensure lower medicine prices in both the private and public sectors.

An opportunity has therefore been created for both large and small local manufacturers of generic medicines and in particular those that have already been manufacturing generic medicines. Importers of finished generic products, APIs and raw materials into South Africa have also benefited from this increase in demand. A respondent from an MNC based locally stated that this has created an opportunity for local importers to import finished generic products, APIs and raw materials predominantly from India, as local pharmaceutical manufacturers do not possess the economies of scale to meet the total demand for generic medicines locally. The importation of cheaper generic medicines has increased the competition within the local industry, which has placed a greater emphasis on low cost and high volume production locally.

4.2.5 *Price controls and TRIPS*

It is evident from the literature review that price controls on medicines have had an impact on the production of medicines globally. The effect of these price controls, however, is unique to the government in each country that establishes a system of price controls. Most price controls implemented globally have been to reduce medicine prices and this has also resulted in the increased demand and usage of generic medicines in both developed and developing countries.

All of the respondents noted that price controls established globally do not have an effect on medicines produced locally. A respondent from the largest generic producer locally added that not enough locally manufactured medicines have been exported to countries where price controls exist in order for international price controls to have a large effect on local pharmaceutical manufacturing.

IPR issues have had an effect on both global and local pharmaceutical manufacturing. The Medicines and Related Substances Act 90 of 1997 (RSA, 1997) has made provision for both parallel importation and compulsory licensing. All the respondents noted that the South African government respects IPRs, as South Africa is a signatory to the TRIPS agreement and a member of the WTO. The fact that the government has made provision for parallel

importation and compulsory licensing has had an important effect on local production and this can be seen as a local factor that impacts on the local production of medicines (see Section 4.3 below). Respondents from a large local generic medicine producer, a multinational generic medicine producer and an industry organisation all noted that the legal provision for parallel importation and compulsory licensing poses a minor risk for MNCs wishing to invest in South Africa. The risk exists that the IPRs of MNCs on a patented medicine could be threatened in the event of a national health crisis like HIV/AIDS that requires large-scale treatment with that medicine.

Despite the perceived risks, all the respondents agreed that intellectual property issues had little effect on the decisions made by MNCs to withdraw their manufacturing presence from South Africa. In general, these decisions had been driven by economic considerations and global strategies made at corporate head offices.

In summary, the global consolidation of MNC manufacturing facilities and new developments in biotechnology drug production could be seen as large influences that have resulted in the closure of manufacturing facilities in South Africa. The closures of local manufacturing facilities owned by MNCs still continually represent a gradual decrease in the number of pharmaceutical producers locally.

This void in the local production of medicines has been partially filled by an increase in volumes produced by existing larger local generic companies and companies that have entered the industry and succeeded. The increased global and local demand for generic medicines has provided further opportunities for local generic manufacturers but also for importers of cheaper generic medicines. This has led to an increase in competition based on price, which places the remaining local producers under greater pressure to become more cost effective and gain economies of scale. In addition to this, new business models are being derived locally in order to supply MNCs with products that they require in the local market without being obliged to have a physical manufacturing presence.

This represents a simplified representation of the global impacts on the local pharmaceutical industry when in reality these global impacts are extremely intricate and are further complicated by the local factors influencing local pharmaceutical production.

4.3 Local Factors Impacting on the Changing Structure of South African Pharmaceutical Production

For the most part, the environment of the local pharmaceutical production industry appears to be influenced by two apposing objectives. The first objective is the South African government's objective of ensuring a continuous and sustainable supply of affordable quality medicines to meet the healthcare needs of the entire population. The government achieves this objective by creating legislative frameworks, such as the NDP, and policies within the industry while maintaining a responsibility in keeping the industry competitive and viable.

The industry's objective, on the other hand, is to remain sustainable and profitable in order to reward its shareholders. In doing so, the industry has to find ways to operate successfully within the confines of the government's legislation and policies by responding collectively in order to influence new legislation and policies. Both the government and the industry therefore need to be able to work together harmoniously in order to achieve these interdependent objectives.

The factors influencing the local pharmaceutical manufacturing industry therefore mostly stem from the desire of both the industry and the government to achieve their independent objectives. Despite this, the government has a greater influence over the local factors that influence pharmaceutical production within South Africa.

All the respondents stated both directly and indirectly that the largest factor to influence the local manufacturing industry was the government's responsibility in increasing the entire South African population's access to affordable quality medicines. This responsibility has further been given a higher priority with the

growing prevalence of diseases such as HIV/AIDS and TB. The DOH has increased access to affordable medicines by introducing price controls in the form of the SEP and by providing for parallel importation and compulsory licensing. At the same time the quality of medicines, manufactured locally and those that are imported, has been controlled by the MCC, which forms part of the DOH. The Treasury has the objective of improving the nation's balance of payments and of reducing the total expenditure on medicines locally. The DTI, and to a lesser extent the DST, assists the Treasury to reduce the negative trade balance by ensuring that the industry remains economically viable and sustainable. The industry should also be able to reduce South Africa's dependence on imported medicines without reducing the access to medicines or threatening the security of medicine supply. These economically active companies operating within the industry also contribute to taxes, employment and export activities, which contribution enables the government to achieve other broader objectives.

4.3.1 *Strategic vision of large local manufacturers*

From the pharmaceutical manufacturers' point of view the greatest change that has occurred is the response of the largest local generic medicine producers to the decline in manufacturing presence locally. With a growing market for affordable medicines globally and, the South African government's increased drive to improve access to medicines, opportunities still exist for local pharmaceutical manufacturers, particularly for the three or four largest companies manufacturing generic medicines. One respondent from an MNC with a local manufacturing presence emphatically stated that the market for generic medicines in South Africa would: "grow and grow and grow and grow and grow". All of the manufacturers that were interviewed agreed that this response to external global factors and internal legislative parameters and objectives has resulted in the largest change in recent pharmaceutical production. South Africa's largest generic drug producer appears to have been the most innovative in capturing local opportunities, firstly, and then international opportunities, thereby taking the lead within the local pharmaceutical manufacturing industry.

With the government's legal provision for compulsory licensing, the largest generic producer was the first to negotiate an alternative solution to overcome the government's intention to issue compulsory licences to provide ARVs in the treatment of HIV/AIDS. A senior executive from this company that was interviewed commented that in the late 1990s the company realised that it needed to achieve economies of scale in order to fund the investments required in its production facilities to upgrade them from local MCC standards to gain international accreditation from organisations such as the WHO and the FDA. This was undertaken in order to exploit future export markets as part of an expansion strategy. At the same time there was an increase in global funding available for the manufacturing of ARVs and this included funding from the Clinton Foundation and PEPFAR shortly thereafter. Together with the available funding there was a large market with a large demand for ARVs but no local manufacturer with the capacity to meet this demand.

This company had also approached large global MNCs like GlaxoSmithKline (GSK), Bristol-Myers Squibb (BMS), Eli Lilly and Gilead Sciences to gain voluntary licences to manufacture ARVs. These voluntary licences included technology transfers from the MNCs and enabled the large local manufacturer to increase its economies of scale. The manufacturer also became the first manufacturer globally to gain FDA approval to manufacture generic ARVs. These successes have enabled the company to reinvest in its manufacturing capabilities, which has resulted in gaining FDA approval for a sterile manufacturing plant, which has enabled the company to export large volumes of eye drops to the U.S. The respondent commented that the company's success had been achieved through vision and fortitude.

This vision has led to this company to attain 11 manufacturing plants locally, export products to 100 markets globally and attain a physical presence in the U.K., U.S., Latin America, East and West Africa, Australia, the Middle East, Asia, and shortly in South East Asia (at the time of the interview in 2009). The second-biggest global MNC, GSK, now has a 19% stake in the business and the company is licensing products to GSK and manufacturing branded products for Eli Lilly and Gilead Sciences. At the time of the interview the company was

between the twelfth- and fourteenth-largest generic medicines manufacturer globally.

The two largest local generic medicine manufacturers have been the first to produce ARVs under voluntary licensing agreements. Individuals from the largest local company and another MNC commented that the voluntary licensing agreements granted for the manufacturing of ARVs have not been statutory solutions. Instead, these agreements have been business, political and philanthropic solutions between the companies involved and not the result of normal economic developments. Nonetheless, these agreements have enabled local manufacturers to gain economies of scale, international accreditation and the ability to exploit export markets.

A respondent from a smaller local manufacturing company commented that the MNCs had not been able to achieve the same success with ARVs as they had with “blockbuster” drugs owing to the pressures imposed by governments to decrease the price of ARVs in the interest of addressing a public health crisis.

A respondent from the second-largest local manufacturer also indicated that this manufacturer is in the process of gaining FDA approval for two of its local manufacturing facilities in South Africa. A respondent from the third-largest supplier of medicines locally mentioned that this supplier is considering whether to upgrade a local manufacturing facility to gain FDA approval but it is uncertain at this stage whether the supplier will do this.

The largest local manufacturer has therefore provided examples to other local manufacturers of how to remain viable and grow within the possible confinement of government policies and legislation.

4.3.2 *Capacity constraints of the MCC*

Five of the respondents indicated that the inefficiency of the MCC has resulted in delays in the registration process of new patented and generic medicines and delays in other administrative functions performed by the MCC. With such delays companies could potentially lose market share to other suppliers of therapeutically similar medicines in the market.

The respondent from the MCC explained that the MCC has experienced capacity constraints because it is understaffed. In 1998 it employed 100 staff members and received about 300 applications for the registration of new medicines. Currently it employs 107 staff members and receives about 1,700 applications per annum. This, according to the respondent, is the main reason for the administrative backlog of the MCC and for the local registration of medicines being four times longer than the global average. The MCC, according the respondent, is moving towards becoming a statutory body as an independent organisation, which would enable it to negotiate its own salary levels and staff requirements.

Previously the MCC was forced to work within the boundaries of the DOH, where posts for specific technical requirements were restricted to a limited number of people. The new entity that will replace the MCC and that will be called the "South African Health Products Regulatory Authority" is scheduled to be up and running in 2012.

A respondent from a local manufacturer and importer of generic medicines commented that the inefficiency of the MCC has inadvertently protected the local industry. Had the MCC had been more efficient, in this respondent's opinion, a greater number of competing Indian importers would have registered many more products locally, resulting in greater competition on the basis of price. If the MCC's efficiency were therefore to be improved, the government would have to find other means to protect local players from competing with cheaper imported products.

The greatest impact on local production from the point of view of the MCC came about with the amendment to the Medicines and Related Substances Control Amendment Act 90 of 1997 (RSA, 1997), which was promulgated in 2003. In particular section 22C of the Act, which has granted the MCC the authorisation to issue manufacturing licences to local manufacturing companies that comply with the PIC/S and the 2009 GMP standards, has had a big impact on the MCC. These current standards, according to the respondent, are ironically more lenient than the GMP standards enforced by the MCC in 1998.

In the respondent's opinion this is in contrast to what many local manufacturers believe. The regulatory authority also now has the authority to withdraw a licence should a local manufacturing company not comply with these current standards. Prior to this the MCC had no real authority to close down non-compliant facilities.

Two of the respondents indicated that the manner in which the MCC has enforced compliance with the PIC/S and the 2009 GMP standards has been problematic. A respondent from a global generics producer that relies on the production capacity of smaller local contract manufacturers said that the requirements to attain a manufacturing licence are often below the requirements of the company's global production standards. This makes sourcing local companies to conduct contract manufacturing problematic, as their standards are often too low. This respondent suggested that a greater collaborative approach between manufacturers and the MCC must be adopted in order to ensure that manufacturers become compliant with current local manufacturing standards. In doing so, this respondent felt that manufacturers that comply with standards must be provided with incentives or stand a greater chance to provide medicines for government tenders.

Another respondent from a smaller local manufacturing concern emphasised the importance of quality and achieving manufacturing quality standards and competencies that match the standards in the U.S. and Europe. In doing so, local companies can remain competitive within the local industry and gain contract-manufacturing agreements with MNCs. In this respondent's opinion the MCC is often seen to be too slow in responding to invitations to inspect facilities and conduct follow-up inspections in order to grant manufacturing licences that are required by law.

4.3.3 *Single Exit Pricing (SEP)*

The government introduced the SEP system in 2004 in order to increase the access to affordable medicines and reduce healthcare costs in general.

The respondent from the DTI made the observation that South Africa used to be the only country outside the U.S. that did not have some form of price

control over medicines. Another respondent from an industry organisation commented that because of this South Africa used to be an attractive market for MNCs.

All the respondents commented that price controls have had the effect of reducing the profit margins on medicines that are sold locally.

This has resulted in increased pressure on suppliers to increase their economies of scale in order to reduce the cost per unit produced. One small local manufacturer commented that the reduction in prices could also result in local supply issues, where some companies stop the production of certain products, as it no longer remains economically viable to produce them locally. An extreme example of this is where a company had to close down a production facility dedicated to one product that could not compete against the lower price of an imported product.

Two respondents from local manufacturers of generic medicines mentioned that the price controls also force local companies to source certain finished products from other markets like India. In some cases one of these local companies has also moved some of its manufacturing facilities to India in order to reduce costs to compete locally on price. This practice may lead to a greater trend towards importing products into the local market in order to compete on price. An individual from an industry organisation also commented that MNCs often source products produced in their global facilities in order to remain profitable locally, which further reduces the viability of maintaining a production facility locally.

The irony regarding price controls appears to be that if the products produced locally cannot be priced competitively a greater emphasis will be placed on importing cheaper generic medicines. A government department has estimated that imported generics already represent 70 per cent of the generic medicines used in South Africa. Medicines, APIs and raw materials are currently a high contributor to the trade deficit and importing more would increase this deficit further.

Two executives from local generic medicine suppliers noted that the importation of medicines is inevitable in order to increase access to medicines. In addition to this, the cost of APIs contributes an estimated 70 to 80 per cent of the cost of the product and almost all of these APIs and raw materials are imported. Local manufacturers therefore only have control over 20-30 per cent of the cost of medicines produced locally.

Low production volumes, production inefficiencies and the inability to achieve economies of scale further inhibit local manufacturers from selling locally manufactured medicines at competitive prices. A local manufacturer remarked that the SEP's effect on the decision to import products has up until this stage been greater on solid oral dosage forms than it has on other dosage forms like liquids, creams and ointments. The main reason for this is that tablets and capsules are easier to transport and represent a higher value to weight ratio. Liquid, creams and ointments are more bulky and have a lower value to weight ratio, making them more expensive to transport and import.

From a regulatory point of view, a respondent from the regulatory authority had noticed that local producers often send in applications to amend their product registrations to change the source of their APIs and raw materials to cheaper suppliers in order to reduce costs and prices. However, after experiencing quality problems with the cheaper ingredients, they eventually apply to re-register the original material. This causes an additional administrative backlog to the regulatory authority, which already experiences capacity constraints.

Two of the smaller suppliers of medicines who rely on contract manufacturing claimed that the SEP determined for the year is not predictable and this 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.

Respondents from the largest local producer and a government department commented that although the price controls have an effect on the margins of a product they do not affect the volumes of the products that are produced. Larger manufacturers with greater abilities to realise economies of scale could

therefore reduce unit costs by increasing output volumes. These increased volumes then reduce the unit cost without having too great an impact on the profit margins. In many cases the products produced by the larger producers are often priced outside the SEP in order to remain competitive.

Respondents from two MNCs and an industry organisation expressed the fear that the benchmark pricing regulations that are currently being considered by the government could further reduce the viability of producing medicines locally. Benchmark pricing could mean that the local price of medicines would be determined by lowest price at which these products are sold in a grouping of four other countries. The outcome and implementation of this proposal is, however, not certain at this stage and pricing is currently only determined by the SEP system. A respondent from an industry organisation commented that this uncertainty over the implementation of benchmark pricing further contributes to a general uncertain investment environment.

The government's intention of establishing a unified, equitable and integrated national health insurance system in the form of the proposed National Health Insurance (NHI) would in theory create a very large market for medicines in South Africa. Five of the respondents raised concerns about the NHI and what implications it might have, but as the implementation of such a system is not clear at this stage they could only speculate.

One respondent from a large generic producer chose not to comment other than to point out that there would have to be collaboration between the government and the industry in addressing the role that the local pharmaceutical industry would play within the confines of an NHI system. Two respondents from MNCs and two from industry organisations predicted that under such a system the demand for generic medicines within South Africa could increase drastically. Concerns were raised about the influence and downward pressures this would have on medicine prices. The respondents speculated that under these conditions the market would initially be very competitive until the prices dropped to such an extent that the local manufacturers would withdraw their products from the market. The government

would then have to import cheaper medicines to meet the local demand and this might impact on security of supply and quality issues.

One respondent from an industry organisation stated that in order to prevent further divestments, the MNCs would have to look at ways of placing an emphasis on creating access to innovative medicines. By applying differential pricing within the framework of the NHI, the MNCs could benefit by supplying larger volumes of newer therapeutically superior medicines at a price that is still affordable and cost effective to the state.

One small local contract manufacturer and respondents from an industry organisation and from a professional organisation also noted that another major influence on manufacturing costs of manufacturers is labour inefficiencies. Loss in productivity due to industrial actions has also placed an increased pressure on costs as the relatively high overheads of the manufacturing facility still need to be covered during industrial action.

4.3.4 *Industrial policies*

A respondent from one of the largest local manufacturers commented: “The intense regulatory period that the industry has faced in the last ten to 15 years has been unabated and every time you think you pass a regulatory hurdle for example benchmark pricing or NHI, another arises. The industry has been characterised by regulatory uncertainty and unpredictability.”

The respondents’ reactions to the government’s policies were for the most part not particularly favourable. A respondent from a government department claimed that the NDP is becoming outdated and that a new policy is required to provide the industry with an industrial strategy. The recent IPAP was mostly driven to reduce a trade deficit that had resulted from the closure of many pharmaceutical factories. The IPAP involved two main objectives: the ARV plan and the establishment of investment incentives for the manufacturing of pharmaceuticals by local pharmaceutical manufacturers, which are subject to certain criteria.

The respondent added that since 1999 the DTI has attempted to aid the government in the establishment of a coherent industrial policy for the pharmaceutical industry. The most recent attempt had been Minister Barbara Hogan's Medical Products Task Team, which was also responsible for the Genesis Study (Maloney and Segal, 2007), but nothing concrete had resulted from this. The DTI has tried to balance the points of view of the DOH, the Treasury and the pharmaceutical industry, but as all these stakeholders have different interests it is essential that they agree on the same strategy that is able to accommodate and provide benefit to all the parties involved.

Half of the respondents believed that the government's IPAP for the industry is incoherent, lacking in focus, not predictably applied and not clearly implemented. One respondent also claimed that the IPAP could be seen as being indifferent or even hostile to the industry's needs. Despite this, a large generic medicine producer commented that the DTI had fortunately been proactive in recognising the pharmaceutical industry as one of the four priority sectors of the IPAP. One other respondent commented that the IPAP should have been implemented five to ten years previously when facilities had started to close down, as this could have possibly prevented the closure of many additional sites.

Some local manufacturers have benefited from the incentives that have been provided to local manufacturers, but as one respondent from an industry organisation commented the provision of these incentives mostly favours large generic medicine producers with a manufacturing presence. This could result in a declining demand for innovative-patented medicines provided by MNCs. MNCs could then potentially decide to withdraw from the market, which could result in the decline of future newer generic medicines entering the market.

A respondent from a large generic medicine producer also commented that the Indian pharmaceutical industry enjoys many more incentives, such as tax breaks and defensive import tariffs against importing medicines into India. This generally puts local manufacturers at a disadvantage against importers, who are often able to compete for the public procurement programmes based on the fact that their medicines are set at a lower price

A respondent from a large generic medicine producer and importer commented that despite the tax incentives provided locally on capital expenditures the manufacturing capacity locally will decline as the demand for cheaper imported generic medicines increases. A smaller local contract manufacturer commented that applying for tax incentives on capital expenditures had been so complicated that the company gradually abandoned the attempt to qualify for these incentives. One respondent from a large MNC commented that, in general, the individual policies in isolation are sound but that the sum of all the policies is not conducive to ensuring a viable and sustainable opportunity for local manufacturers.

A respondent from a small manufacturing concern had mentioned how he had applied for a grant from the DTI as part of their incentive scheme for local manufacturers. The rules of the grant were that the DTI would pay pack 30 per cent of capital investments within the pharmaceutical production plant over a three-year period. In order to receive the grant the manufacturer must comply with certain conditions. For example, one of these conditions is that the employed workforce had to grow over the period of receiving the grant. The manufacturer was entitled to receive three million Rand back from the DTI after investing nine million Rand in processing equipment. After filling in numerous documents and application forms the grant did not materialise. This manufacturer had added that: “I had resubmitted the documents and still got nothing. Who benefits from these grants?” The respondent then added that in most cases only the largest manufacturers benefit from these incentives and that they amount to: “hundreds of millions of Rands for setting up ARV plants.”

From this it can be seen that the incentives provided to the industry are perhaps limited to the largest companies where smaller players feel that the entire industry should benefit in order for the industry to grow.

4.3.5 *Imported inputs*

All of the respondents were in agreement that importing APIs, raw materials and in some cases processing equipment has had a negative impact on the cost of producing medicines locally. Risks are also evident when APIs are in

short supply, causing a shortage of a locally produced medicine. One respondent also noted that large suppliers often focus on supplying larger markets like the U.S. and Europe first, which could further lead to a local shortage. A respondent from a government department claimed that 99 per cent of the APIs and raw materials used in locally produced formulations are imported. This has an additional negative impact on the local trade balance, especially when one views the high costs of the APIs used for ARVs.

Three respondents estimated that APIs in general contribute about 60 to 80 per cent of the cost of medicines and that, therefore, if these APIs were produced locally this would improve the trade deficit. The DTI is meeting regularly with the top producers of ARV APIs to encourage them to produce these APIs in South Africa. The willingness of these producers to invest in an API production facility locally appears to depend on the type of incentives that the government is willing to provide them with for establishing an API plant in South Africa.

Respondents from an MNC and two industry organisations doubted the viability of such a venture because to justify the expense of establishing an API plant the volumes produced would have to be larger than the local demand in order to make such a facility economically viable. It therefore seems doubtful that any manufacturers would be willing to invest in such an endeavour. One industry organisation after analysing this proposition found that sourcing from a local API producer would not be viable if the price of that API on the global market was less than the local suppliers' price.

Similarly, a respondent noted that one of the APIs produced locally in large volumes by Fine Chemicals Corporation is paracetamol. Local manufacturers have to source their paracetamol from the local producer in order to keep this local API production viable. Ironically, nothing prevents importers from importing low-priced finished products containing paracetamol and supplying them to the government tender. This defeats the purpose of manufacturing the API locally, especially if protective strategies are not employed to prevent the importation of products containing the API. In light of producing an ARV API locally, the prohibition of importing finished products containing the API may mean that the local price would have to be protected and might possibly be

higher than in many other countries. This could have a further negative impact on access to medicines.

Two respondents noted that it would be strategically important for South Africa to produce a limited range of APIs required for diseases that are prevalent regionally and in the rest of Africa. South Africa could then exploit the markets within Africa with locally produced APIs and medicines and even become a centre of excellence for products demanded in Africa. Starting such an industry could also lead to other opportunities in the chemical industry that would supply intermediate chemicals used in the production of APIs. These industries could further provide opportunities to build skills locally and provide opportunities for innovation within the local pharmaceutical sector.

The largest local generic medicine producer owns Fine Chemicals Corporation, which primarily exports niche APIs to export markets outside of South Africa. A respondent from this generic medicine producer commented that importing APIs impacts on the costs of locally produced medicines but that these costs can be reduced by establishing significant supply agreements with large API producers. This respondent commented that: “you don’t need to own the cow to get the milk” and added that by investing in the production of APIs the company would struggle to justify the investment even if it was able to export the API. According to this respondent, becoming vertically integrated could potentially save costs on APIs. The capital expenditure costs, opportunity costs and the distraction from their core business would, however, be the main negative aspects of such an investment.

Two respondents noted that large Indian companies that are integrated backwards are in direct control of their source of APIs. They do, however, have a large local market and a growing export market for both APIs and the products containing them. With these economies of scale, industrial capabilities and a growing global market, India can afford to invest in developing such an infrastructure. A respondent from a large global generic medicine supplier commented that the company had purchased a large Indian API producer in order to exploit the advantages of being vertically integrated and having greater control over the source of APIs and raw materials used in global operations.

This Indian API producer, for example, supplies 80 per cent of the ARV APIs used globally.

Only one respondent specifically commented on the unavailability of pharmaceutical processing equipment and the advantages that Indian manufacturers have in sourcing such equipment in India at relatively low prices.

Generally speaking, the unavailability of processing equipment locally seems to be a less important factor or rather not more of a factor than it is for many other specialised industries in South Africa that have to rely on the importation of specialised equipment. A small local contract manufacturer had noted that some smaller South African suppliers of processing equipment like high-speed mixers and coating pans are able to supply the local market with quality processing equipment. The locally manufactured equipment, according to this manufacturer, is very reasonably priced and cheaper than similar imported equipment.

4.3.6 *Local skills shortage*

All the respondents saw the local skills shortage within the pharmaceutical manufacturing industry as being problematic. The skills that appear to be in the shortest supply are the skills of pharmacists within the manufacturing industry. A third of the respondents emphasised that South African pharmacists at university level are primarily trained to become community pharmacists and as a result of this are fairly ill equipped to operate affectively in a pharmaceutical production environment.

A respondent from a professional organisation was well aware of the shortage of skills that industrial pharmacists have in ensuring production efficiencies and quality. This person believed that a greater emphasis should be placed on the training of pharmacists at university level that would enable them to work effectively in both community pharmacies and the manufacturing industry. In addition to this there appear to be very few training providers outside of universities that are able to give pharmacists training that is relevant to the industry once they are in the industry. Even with the introduction of the Continued Professional Development (CPD) programme initiated by the

Pharmacy Council, the emphasis is still on community pharmacy rather than industrial pharmacy. This has, however, been noted and is in the process of being addressed by the professional organisation.

In addition to this, employers often see pharmacists as being purely technicians and not professionals with influence in the manufacturing environment. Pharmacists within the industry should also be given the opportunity to attend conferences or visit parent companies in order to broaden their understanding of pharmaceutical production technologies and engineering functions that improve production efficiencies and quality.

A respondent from an industry association and the largest local manufacturer noted in particular that there is a shortage of pharmacists who are skilled at formulating medicines. This is ironic as the local industry relies heavily on formulation and the ability to formulate cost-effective quality medicines.

A respondent from a government department noted that it might be necessary to send pharmacists and technicians overseas to receive training. These local skills shortages of pharmacists also affect registration pharmacists, who are also unable to get adequate training at university level and have to rely on experience, which in many cases also results in a lack of shared knowledge amongst registration pharmacists in the industry and at the MCC.

The largest local manufacturer noted that its in-house skills had lagged behind its manufacturing ability and that this had been corrected by bringing in skilled people from Europe and India to act as trainers within local facilities to facilitate in addressing this lag. The second-largest local manufacturer commented that it had been necessary to import skills to facilitate local in-house skills transfer. Another respondent noted that the industry should find ways of providing pharmacist interns with opportunities to gain industrial experience and also find ways of increasing the skills of other technical people within the facilities to reduce the dependence of pharmacists at all the levels of pharmaceutical production.

Numerous other issues were raised by respondents, such as:

- impacts that BEE has on the employment of persons who lack sufficient skills and require an opportunity to gain skills, which impacts on costs;
- high costs of employing professional skills compared to India;
- the demise of the Pharmaceutical Production Technology course that offered pharmaceutical technicians training within a production environment (this course was previously administered by the Pharmaceutical Manufacturers Association (PMA));
- the reduced number of people entering the pharmacy profession;
- the important contribution that the pharmaceutical industry makes to skills within South Africa; and
- the generally high cost of skilled and semi-skilled labour within the industry.

A respondent from an industry organisation explained the complexities of employing "black" skills within the local pharmaceutical manufacturing industry in the following manner: "BEE has had an influence in the availability of technical skills locally. South Africa is in a unique position compared to the rest of the world in that an emphasis is placed locally on providing opportunities to skilled black people. At this stage it is difficult in finding black people with the right set of technical skills within this environment. Many members of... [the industry organisation] experience difficulties in explaining the impact that the BEE imperative has on local businesses when reporting to their corporate head offices outside of South Africa. These corporate head offices often find this impact difficult to grasp and embrace. From a practical and a cost point of view BEE has an impact as it may imply extra costs in training people. In the global manufacturing environment there is an increased trend towards reducing staff in order to increase efficiencies. Locally it is unlikely that manufacturers would employ extra pharmacists in order to provide extra training to black people within this environment."

A respondent from a large manufacturer emphasised that in light of the IPAP these skills issues should be addressed as they impact on the Treasury, DTI, Department of Labour and employment equity. In general it has been noted that to improve this, the industry should work together with the government and professional bodies to address the shortage of skills within this industry.

In summary the local factors impacting on local production are numerous and, for the most part, are caused by well-intended but often misguided attempts by the government to provide an environment that is conducive to local manufacturing. Despite this the largest manufacturers appear to be more innovative in finding ways to remain viable and influence government policies. Within the collective whole of manufacturers the smaller manufacturers appear to have less influence and have to find operational advantages and contract-manufacturing opportunities in order to remain viable.

4.4 Implications of the Changing Structure of the Local Pharmaceutical Industry and how the Local Industry has Responded

On a broad level the local pharmaceutical production industry's structure has changed from being dominated mostly by MNCs and a few local players to becoming an industry with a few large local generic medicine companies. With the gradual closure of manufacturing facilities by large MNCs and the government's emphasis on increasing access to cheaper generic medicines, the biggest change has come about by the largest generic medicine producers attempting to find value within the local market. The constraints of government legislations and policies and the general regulation environment have provided the largest local manufacturers with hurdles that have been overcome through innovation and a determination to remain viable. The potentials of a large local market and the prospects of unexploited export markets have created further opportunities for growth and sustainability for local manufacturers and local contract manufacturing.

The growth of the local industry has become of strategic importance to the government, as seen by the IPAP, with its emphasis on ensuring the security of

the supply of medicines locally and on stimulating the economy in order to reduce the trade imbalance. It has become clear that an improvement in the cooperation and communication between the government and the industry is of strategic importance to both parties in achieving their objectives.

Two respondents, one from an industry organisation and another from a local manufacturer, coincidentally both used the expression: “you need to fatten the goose that lays the golden eggs”, implying that the government needs to look after the industry that could possibly help the government to achieve its responsibility in providing affordable healthcare.

4.4.1 *Opportunities within the transformed industry*

As mentioned previously, with the closure of the MNCs’ production facilities, the largest local companies experienced growth. This growth was facilitated by the manufacturing of ARVs through voluntary licensing agreements which enabled technology transfers, the achieving of economies of scale and the gaining of international accreditation, in particular FDA approval of the two largest manufacturers’ facilities.

This situation has also resulted in local manufacturers with the potential to exploit export markets in developed countries. One respondent noted that despite the higher cost of local production it is in some cases still lower than the cost in developed countries like the U.S. and countries in Europe. In addition to this, South Africa has good infrastructure and a sound regulatory environment, with an emphasis on quality compared to other countries where low-cost medicines are produced.

The increased competition in the local market, especially amongst the three largest players, has also resulted in different strategies for gaining opportunities, which include pursuing global expansions and acquisitions, establishing manufacturing sites in India, or focusing on the importation of medicines.

Part of the intention of the IPAP was to place an emphasis on preferential procurement from local manufacturers, especially with the provision of ARVs to the public sector.

A respondent from the largest local manufacturer commented at the time of the interview that the ten-point system on which the government bases preferential procurement normally allocates four out of ten points for local content; however, for the local ARV tender this had been shifted to nine out of ten points. This has been undertaken in order to ensure the security of the local supply of ARVs.

Another respondent from a local generic medicine producer and importer commented that the price of one particular ARV supplied to the state tender is still nine times more expensive than the price at which Indian companies sell the drug to other African countries. In this respondent's opinion sourcing medicines locally is not necessarily going to increase the access to medicines in the long term. Furthermore it will not be viable to protect local pharmaceutical manufacturing and the employment within this industry at the cost of denying about 50 million people access to affordable medicines.

The respondent from the largest local manufacturer stated that sourcing from importers may be cheaper but by denying the economic viability of local producers the government, in addition to negatively affecting the balance of payments through increased importation, could lose in terms of tax collection and the local producers' ability to improve employment and skills locally. The purpose of the IPAP in this respondent's opinion is to allow South African companies to compete on equal terms with other countries like India, which are primarily able to be low-cost suppliers owing to the protection they enjoy from their government. Three respondents noted that the government's implementation of industrial policy and intervention in the pharmaceutical industry have mostly impacted on local manufacturers and that these interventions may provide little protection or benefit to companies selling imported and patented medicines. On the other hand, these responses, according to one respondent, are primarily driven by the companies' own interests and not by what is in the national interest.

A local manufacturer, however, noted that providing incentives for local manufacturers might present opportunities that are attractive for Indian or Chinese companies to manufacture in South Africa. If the government made it a prerequisite for interested foreign manufacturers to manufacture in South Africa and to have an empowered company when supplying drugs to the public sector, this would provide fair competition to other players within the local industry.

Almost all the respondents mentioned that the local industry had not yet been able to exploit the growing market for medicines in Africa, and that South Africa has the infrastructure and a good regulatory environment for supplying quality medicines to Africa. Two respondents commented that South Africa should become a regional hub for pharmaceuticals where medicines required in Africa should be produced in Africa.

Two respondents from the second- and third-largest local companies indicated that the greatest future demand for medicines produced in South Africa would be from Africa. The second-largest producer said that this potential demand is already being addressed, and the company now owns a manufacturing site in one country and has established marketing presence in another.

One respondent noted that Indian companies are currently supplying the basic essential drugs demanded in Africa, but with an increase in the tendency towards self-medicating the South African companies could, with their marketing capacity, enter these African markets and the self-medication market in particular. An additional benefit would be that within these markets the South African medicines could be seen as being superior in terms of quality when compared to the basic Indian drugs currently available.

In support of this, another local manufacturer suggested that, in order to assist the introduction of products into the rest of Africa there should be an attempt at establishing a regional regulatory authority. This would in theory minimise the occurrence of counterfeit medicines and increase the quality of regionally produced medicines. The respondent from the MCC commented that this would not be feasible as local standards are far more advanced than they are

regionally. The respondent added that other African countries might not be able to comply with South African standards and would prefer to regulate the medicines sold in their countries themselves.

In the future, within the Southern African Development Community (SADC) region it may, however, be possible to have a system similar to that, which exists in Europe, where there is a regional regulatory authority in addition to regulatory authorities in each country. Registration dossiers for medicines could be submitted to the regional authority for a basic approval prior to being submitted to local regulatory authorities in order to ensure that medicines have a basic compliance to quality standards.

A respondent from the third-largest local pharmaceutical company predicted that OTC, consumer healthcare (CHC) and complementary medicine markets in South Africa and Africa represent the largest potential demand for locally produced medicines. These markets in many African countries are growing as these products often save consumers costs by reducing the need to visit a doctor in order to gain a prescription. The Indian companies that predominantly supply low-cost essential drugs do not normally capture these markets and this could further enable local companies to create a niche market for high quality OTCs and complementary medicines.

A small local contract manufacturer also observed that the current market for complementary medicines in South Africa is not adequately regulated at this stage. If the MCC were to address the registration, quality and manufacturing requirements of complementary medicines, with the prerequisite that they need to be produced in facilities with valid pharmaceutical manufacturing licences, this could provide smaller local players with greater opportunities. As the prices of these products do not fall under the SEP, the set prices could be determined through competitive market forces, which might enable them to be profitable to produce. This could enable smaller manufacturers to lower manufacturing costs in general, which could attract further opportunities to provide quality contract-manufacturing services to larger local companies and MNCs.

In order to exploit further opportunities in the local industry there has been an attempt at consolidation in order to diversify and expand product lines and possibly exploit product pipelines from India.

A respondent from South Africa's third-largest pharmaceutical company referred to the unsuccessful attempt at consolidation within the local industry when the second-largest local player had attempted to take over this company. In this respondent's opinion this attempt was misguided. It appears that the ties that the company has with its partner in India were underestimated as they are founded on trusting personal relationships between senior individuals and not just mutually inclusive business objectives. The respondent commented that: "The Indian business model is very different and is based more on trust, emotional intelligence and relationship." According to this respondent, this made the local company more resilient against competition and able to realise more value in being a key stakeholder within the market. This company also sees itself as being capable of being the second-largest local supplier of medicines locally within the next three years.

4.4.2 *Co-operation within the industry and with government departments*

All the respondents that were interviewed commented on the increasing trend in which local companies enter into marketing, licensing or manufacturing agreements with larger MNCs. The motivation behind this trend appears to be supported by a new confidence that the large global pharmaceutical corporations have in local manufacturing capabilities. For the largest local manufacturer, this has resulted in being 19 per cent owned by GSK, which appears to be a mutually beneficial arrangement for both parties to extend product lines and exploit global markets. The second-largest manufacturer, according to a respondent, is now also entering into marketing agreements with another large MNC, which apart from recognising the manufacturer's production capabilities also realises the value of this manufacturer's exclusive distribution network within South Africa and regionally. All the other companies that were interviewed are either MNCs that have contracted work out to local companies or are local manufacturers that conduct contract manufacturing for MNCs. In

addition to this, there are also MNCs that still have manufacturing presence and have spare capacity to manufacture products for other MNCs that no longer have facilities to manufacture locally marketed products.

This represents another important change within the local pharmaceutical industry, as very few companies now operate in complete isolation from other companies. This trend could result in greater co-operation within the manufacturing industry and the creation of new smaller manufacturing companies and perhaps a regional manufacturing hub. Respondents from industry organisations also highlighted possible further trends that may occur within the manufacturing industry. One of these trends is the possible backward integration of large medicine retailers into pharmaceutical production in order to manufacture their own brands and to save on the costs of sourcing from contract manufacturers. Another possibility is that the government may itself establish state-owned pharmaceutical manufacturing facilities in order to achieve economies of scale with a large market. The establishment of Public Private Partnerships (PPPs) between local companies and the government has also been mentioned as a possible solution for reducing prices and increasing access to medicines predominantly in the public sector.

Almost all the respondents agreed that the industry through its various industry organisations is able to respond to and communicate collectively with government departments. In many cases the nature of the interactions between the industry and government seems to be influenced by distrust from both parties, which fail to create a constructive forum to address important issues and to understand the other party's concerns, objectives and points of view.

Two respondents, however, noted that the nature of the interactions between the government and the industry is becoming more co-operative. The ability of the industry to respond collectively through industry organisations, according to one respondent from the regulatory authority, has been evident through the industry's recent collective preparation of the Marketing Code on Advertising of Medicines. In this instance, the industry had collectively drawn up a marketing code and had as a group agreed to adhere to this code prior to submitting it to the government.

A respondent from a large generic company commented that the industry's adherence to the SEP could also be seen as evidence of a growing partnership between the government and the industry. From the largest local manufacturer's point of view, it is important to establish co-operation and mutually beneficial objectives with the government in order to do what is in the interest of the nation as a whole.

A respondent from a professional organisation suggested that it might be more effective for the industry to respond collectively as one industry organisation rather than through various fragmented organisations. This would enable the industry as a whole to communicate with government collectively in order to establish co-operation between the whole industry and the government.

The majority of the respondents also commented on the lack of cohesion between the various government departments. A respondent from a government department specifically mentioned that there is as yet no clear industrial policy for the pharmaceutical industry and that when the DTI had started to establish a policy in 1999 the DOH and the Treasury were not forthcoming or willing to adopt a strategy as these stakeholders had their own interests. This respondent claimed that: "The DTI tries to balance the points of view of the DOH, Treasury and the pharmaceutical industry. All these stakeholders have different interests and it is essential that they agree on the same strategy."

4.4.3 *Volumes of locally produced medicines*

Ten of the companies and organisations interviewed indicated that there has been an increase in the volumes produced locally, especially the volumes of ARVs, generic medicines and medicines for the export market produced by the largest manufacturer. In particular, the locally produced volumes of the largest two local producers have increased dramatically in the last four years. The respondent from the largest producer commented that in four years' time South Africa would be able to produce the same volumes as were produced 20 years ago when the industry consisted largely of multinational manufacturers.

In terms of the total physical investment in local manufacturing, this respondent commented, at the time of the interview, that South Africa is in a neutral position relative to 20 years ago.

One smaller local manufacturer indicated that volumes had stagnated in the last two years but that no negative growth had been evident. Another respondent from a large generic medicine producer and importer commented that the company's locally produced volumes are dependent on the demand from the public sector. This organisation had, however, experienced growth in sales primarily through medicines imported from India.

According to a respondent from a government department, the DTI has estimated that the volumes of locally produced medicines peaked in 1995 and have declined since then. By comparison, in 1980 the value of the total locally produced volumes was similar to the value of the volumes produced in India at the time. In contrast to this, the value of volumes produced in India currently is estimated to be about 80 times greater than the value of volumes produced locally.

Despite the increasing volumes by the estimated 15 remaining local manufacturers, the employment within the industry decreased by roughly 50 per cent between 1999 and 2009. Relating the change in employment to volumes does not take into consideration the improved efficiency in pharmaceutical production brought about by newer technology. The newer technology enables the volume output per person to be increased drastically. The relative volumes of locally produced medicines that are exported did not emerge in the interviews.

According to the MCC, the number of applications to register new medicines has increased dramatically, of which 92 per cent are for generic medicines and the remaining eight per cent are for NCEs.

4.4.4 *The future of pharmaceutical production in South Africa*

Of the 12 respondents, all apart from two believed that the future holds many opportunities for local pharmaceutical production and in particular the

production of generic medicines. In contrast, one respondent from a government department indicated that if there is no intervention from government in the form of a strategic plan or comprehensive industrial policy there will be a complete decline in local pharmaceutical production by the year 2020.

Another respondent from a large local producer and importer of generic medicines commented that increasing access to medicines by importing less expensive generic medicines is of greater importance than creating capacity in local manufacturing facilities.

The remaining ten respondents raised several issues that could determine the future success of local pharmaceutical manufacturing. In general, the quality of produced medicines appears to be recognised as one of the main characteristics that will determine the acceptance of locally produced medicines in the local market and in export markets. A high quality can only be achieved by re-capitalising existing facilities in order to meet the local and where applicable international regulatory requirements. The MCC in particular has noted that the upgrade in local facilities is indicative of growth and expansion.

These investments have been made possible by companies with vision and confidence in their ability to grow the local manufacturing capacity. The government's industrial policies that provide a certain level of protection and incentives could further aid the industry to succeed. If enough incentives are provided other manufacturers based outside of the country may decide to invest or re-invest locally but this seems to depend on the nature and the extent of the incentives provided. The respondents affiliated to MNCs were, however, less optimistic about the feasibility of manufacturing conducted by MNCs locally.

The emphasis on the provision of cheaper generic medicines and essential drugs locally appears to be the main threat to the market share of patented innovative medicines. Issues regarding the protection of intellectual property and price controls pose further threats not just to manufacturing presence but to the marketing of patented medicines in general, especially in the environment of the proposed NHI. The MNCs are, however, in consultation with the

government to emphasise the important role that innovative or patented medicines can play locally. These medicines are often therapeutically superior to older generic medicines and have a high benefit to cost ratio which could reduce other healthcare needs such as hospitalisation. Within the context of the NHI there may also be certain medicines that are required for obscure diseases that are only supplied by companies providing innovative-patented medicines. In addition to this, the patented medicines on the local market are able to become the generic medicines of the future once the patent has expired. Despite this, MNCs are beginning to partner with local companies to manufacture products that are unique to the local market and are not produced elsewhere. At another level MNCs are approaching local companies to manufacture for global markets.

In general, the next step in the industry's growth appears to be to capture profitable export markets in Africa and beyond. So far, only South Africa's largest manufacturer has had the vision and the capacity to execute a global expansion strategy successfully. For the remaining manufacturers success will most likely depend on how they embrace market opportunities with their current product portfolios and how they devise strategies to exploit other markets with large growth potentials. A comprehensive industrial strategy will have to be implemented after consultation with the entire local manufacturing industry in order for both industrial and government objectives to be achieved.

4.5 Conclusion of the Presentation and Discussion of Results

From the interviews it is evident that for the most part the respondents were in agreement with the majority of the global and local factors suggested by the literature review as impacting on local pharmaceutical production. The main issues as highlighted by the literature review appear to be a fair reflection of what the respondents perceived to be the main issues. The different respondents did, however, have slightly different perspectives or interpretations of the main factors impacting on local production. These perspectives and interpretations are probably influenced by the respondents' unique involvement or experience within the industry.

So from this chapter it can be seen that the local pharmaceutical industry has indeed been influenced by changes that have occurred in the global pharmaceutical production environment. The largest of these changes to impact on the local industry appear to be the global consolidation of manufacturing sites and the global increase in demand for generic medicines. In the last 15 to 20 years this has resulted in the closure of many manufacturing facilities that were previously operated by MNCs. The closure of these facilities left a temporary void within the local pharmaceutical manufacturing industry's local capacity that was soon filled with increased production capacity and reinvestment by the largest local generic manufacturers. In addition to this, the supply of medicines is increasingly being supplemented by the importation of cheaper generic medicines, predominantly from India.

The simultaneous emphasis of the government's NDP on improving access to affordable medicines provides further opportunity to local generic medicine manufacturers and importers of generic medicines. This has resulted in the fairly rapid growth of the four largest local generic medicine producers, particularly with the governments' emphasis on providing treatment for HIV/AIDS.

The voluntary licensing agreements between MNCs and large local manufacturers have further opened up opportunities for local manufacturers to expand, gain international manufacturing accreditations and exploit export markets. This has led to a new phase where MNCs are now perceived to have become more confident about the local industry's manufacturing and marketing capabilities. This will perhaps lead to a new phase where local companies will partner with MNCs in exploiting newer markets in Africa with greater growth potential than many other markets.

Local issues such as conflicting government policies and conflicting departmental objectives still appear to present the local industry with many hurdles. The innovative companies locally have learnt to overcome these and in some cases have also aided the government in achieving their objectives.

Going forward there does, however, appear to be a desire from some government departments such as the DTI to work together with the industry in developing a pharmaceutical strategy that encompasses the objectives of all the stakeholders in the government and individual manufacturers. In the end the overall objective will probably be to sustain a viable local pharmaceutical manufacturing capacity, which can reduce the government's need to rely on imports that negatively affect the trade balance while enabling the industry to become a viable export business which may have further positive effects on the trade balance.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

In this chapter a conclusion to the research is provided, with recommendations made as to how the local pharmaceutical industry could maintain the momentum that it is currently experiencing. Lastly, suggestions for three areas of future research are given that may further address important issues within the local pharmaceutical industry.

5.2 Conclusion of the Study

The global pharmaceutical industry has undergone changes due to shifting changes in pharmaceutical technology, global drug demand, and intellectual property issues. The expiration of patents of former “blockbuster” drugs has been met with an increasing global demand for lower-priced generic medicines. Generic medicines have their source in the R&D innovation of primarily MNCs based in developing countries. With diminishing drug pipelines the R&D-based companies had to find ways in which to improve efficiencies to reduce costs while maintaining quality. In doing so, global manufacturing sites were consolidated to centres of excellence in countries that provided advantages like investment incentives and skills. The cost savings were primarily focused on expanding marketing activities to promote the continued sale of existing drugs and fund R&D activities in new areas such as biotechnology in order to fill drug pipelines. M&A activities have also become evident to provide MNCs with manufacturing and R&D synergies.

Concurrently the increased global availability and acceptance of cost-effective generic medicines resulted in an increased global market for generic medicines. This demand also encouraged developing countries to develop the capabilities and capacity to formulate the previously patented APIs as generic medicines to supply the increasing needs of governments to provide affordable healthcare. This was often carried out without respecting the patents of the originator companies.

With the increased capability and capacity to produce quality generic medicines and generic APIs in high volumes, generic medicine manufacturers worldwide have also been provided with opportunities to conduct contract-manufacturing activities for large MNCs. More recently these MNCs have also often realised that large markets exist in regions that were previously unexploited. These markets can then be supplied with generic medicines that have recently come off patent or that have patents that have almost expired. With a large manufacturer based in a growing market, the MNCs could potentially be the first to enter these markets with generic versions of their patented medicines. These medicines would either be sold under licensing agreements by the manufacturer or as their own brands. This would be a way in which an MNC could extend the longevity of its medicines and grow its market share without having to invest in a local manufacturing site. This would then allow the innovator MNC to continue investing in R&D to ensure its long-term viability.

This is perhaps a simplified version of very complex events that have occurred in the global manufacturing industry. This summary could, however, be used to explain the changes that have occurred within the local manufacturing industry in the last 15 to 20 years.

A respondent from a large generic medicine producer and importer conveniently described the recent history of pharmaceutical production in South Africa in three distinct phases.

The first phase can be described as the manufacturing growth phase prior to 1994 where local manufacturing capacity existed because of the sanctions against South Africa. The industry at this stage had focused on its ability to produce and supply drugs locally. The second phase started post-1994 when the local industry experienced ruthless competition from imported Indian medicines. This competition was mostly driven by price and caused the local manufacturing capacity to be reduced, which resulted in the largest three or four companies remaining with significant presence. The third and current phase has resulted from the government's emphasis on providing treatment for HIV/AIDS in South Africa. This has provided a new growth phase for the three or four largest South African manufacturers. Some of largest manufacturers

have gained FDA approval for their manufacturing facilities and have begun adhering to global pharmaceutical manufacturing standards. This has enabled them to remain viable through gaining access to export markets and offering contract-manufacturing services to MNCs.

Generally speaking, the changing structure of pharmaceutical manufacturing in South Africa can be characterised as an industry that previously had many manufacturing facilities operated by MNCs and a few local players. The global and local factors impacting on the industry had resulted in the largest local manufacturers playing more dominant roles within the local industry and the MNC manufacturers gradually decreasing their manufacturing presence locally. At the same time a few smaller local manufacturers have been able to remain viable by producing lower volumes of products destined for smaller niche local markets and in some cases export markets.

On a broader policy level the government and in particular the DTI, has realised the need to establish the IPAP in order to ensure that the industry remains viable and sustainable. This has mostly been implemented to reduce the balance of payments and to stimulate industrialisation. Unfortunately, the DTI's attempt at providing a pharmaceutical strategy is not met with tremendous support and strategic cohesion from the other government departments like the DOH and the Treasury. The pharmaceutical industry, in general, also appears reluctant to become involved in aiding the government in establishing a general strategy for the pharmaceutical sector. If a successful strategy is established for the pharmaceutical industry after joint consultation of all the stakeholders, it could mean that some manufacturers would invest locally or possibly re-invest locally provided that such an industrial strategy is able to offer sufficient incentives that make such investments attractive. It does, however, seem unlikely that any particular organisation, at this stage, is willing to invest in establishing an API plant locally and in particular for ARVs despite the government incentives that might be provided. In addition to providing incentives the government should also address the skills shortages and regulatory uncertainties as part of the industrial strategy.

It appears as though many companies are operating in isolation from one another and focus mainly on maintaining and growing their own market shares and using their own initiatives to navigate their way through a fairly complex regulatory and market environment. Although companies participate within industry organisations the perception, is that individual concerns are being addressed rather than collective concerns for the industry as a whole. In light of the proposed NHI, greater cooperation within the industry may be needed in order for the industry as a whole to look after its own interests whilst working within legislative and regulatory frameworks imposed by the government.

A general understanding of the factors that have influenced the changing structure of the pharmaceutical industry in South Africa has been gained throughout the process of the interviews. Because of the qualitative nature of the research no attempt has been made to conduct a quantitative analysis of actual figures, e.g. volumes produced relative to the number of manufacturers or the relative volumes of imported vs. locally manufactured medicines. In addition to this, respondents and particularly those involved with manufacturing were understandably very guarded when providing actual figures, e.g. percentages of locally manufactured products that are imported.

The issues raised in the literature review appear to have been relevant to what the respondents have experienced and served as a good background that provided an understanding of the issues discussed in the interviews. The literature used to uncover possible factors within the local pharmaceutical environment relied rather heavily on two main industry reports: the FRIDGE Study (FRIDGE, 1999) and the Genesis Study (Maloney and Segal, 2007). Very little additional freely available information on the local pharmaceutical industry was uncovered in the literature review. Most of the respondents were aware of the findings of these reports but at the time of the interviews the information appeared to have become slightly dated but still relevant, as no other recent reports have provided a clear overview of this particular sector. These reports also seem to paint a very negative picture of the pharmaceutical industry, whereas the responses of the interviewees and in particular those

directly involved in manufacturing seemed comparatively positive with regard to potential opportunities.

What also became evident was that issues in the literature review were addressed in a very focused academic manner and sometimes in isolation from other issues. In such a literature review topics are often given equal emphasis or treated with too much emphasis owing to the fact that the topic has been extensively researched and relatively large amounts of information is available on the topic. In practice, however, the same topic could possibly have very little relevance, especially in light of other topics or factors that have a greater impact on a particular organisation's manufacturing operations.

A factor such as price controls, for example, can be discussed at length in terms of its implications and the ways of mitigating the possible threats that price controls have on profitability. In the research it became evident that price controls do in fact have a large impact, especially on profitability, but apart from that the manufacturers all seem to have accepted price controls and have mitigated the risks that they have posed.

This is an example of how manufacturers have typically dealt with many of the global and local factors impacting on local manufacturing. In general these factors have been recognised and understood and then possible opportunities or alternative solutions have been sought to mitigate them.

5.3 Recommendations

While striving to maintain and improve the quality of locally produced medicines larger manufacturers can seek to exploit export markets and manufacturing agreements with other large MNCs. Smaller manufacturers that are capable of achieving high quality standards at lower costs will also be able to exploit contract-manufacturing opportunities for other large local manufacturers or limited product ranges for MNCs that seek local manufacturers to produce locally marketed medicines. In addition to this, smaller manufacturers with their own brands can also seek export markets for their brands allowing them to

increase their economies of scale without having to increase their variety of products.

Individual companies and key employees within these companies must strive to remain up to date with regard to changes that affect the local industry. By attending meetings and discussion forums held by professional organisations, industry organisations and government departments, individuals can seek to understand the implications of changes occurring within the industry. With a thorough understanding of a company's strengths, greater opportunities could be exploited with an increased awareness of the changes within the industry. Lastly companies within the industry must continue to co-operate more collectively within their respective industry organisations so that the issues addressed by these organisations can be coherently communicated to government departments.

Going forward, the industry organisations should perhaps become more affiliated and even eventually be represented under one body with different divisions pertaining to the different functional areas within the industry. In doing so, the industry could strive to communicate collectively with the government on important issues like industrial policies or decide collectively on agendas that are of primary concern to the industry as a whole.

Likewise, the government departments in future should also be able to develop policies that affect the local pharmaceutical industry under the guidance of a coherent strategy for the industry. Individual departmental policies could then be non-conflicting and supportive of the broader industrial strategy.

In general employers and employees participating within the industry should be able to look beyond the traditional isolated mindset and enjoy greater involvement within the industry through industry organisations or professional organisations by and interacting with other employees within the industry through industry and professional organisations. Skills shortages should also be addressed collectively within the industry and this can perhaps be driven by the industry organisations, as had been done in the past with production technology courses. The industry should also be in consultation with the Pharmacy Council

and the Pharmaceutical Society of South Africa (PSSA) in addressing the skills shortages of pharmaceutical personnel within the pharmaceutical manufacturing environment.

A possible opportunity exists for small local manufacturers when future legislation may require stricter control over the manufacturing of complimentary medicines. Smaller manufacturers with existing capacity could play a greater role in the manufacturing of complimentary medicines this would enable them to achieve economies of scale which could fund further re-investment in improving the quality of produced products. The improvement of quality standards could furthermore attract future contract manufacturing opportunities for small manufacturers.

5.4 Suggestions for Future Research

Three main suggestions can be made for future research. The first area that deserves future research is identifying the key success factors (KSFs) for small, medium and large local South African pharmaceutical manufacturers. This research could highlight the relevant roles that various manufacturers play within the broader context of the manufacturing industry. The KSFs could identify the abilities or organisational behaviours that local pharmaceutical manufacturing organisations typically possess in order to remain viable and competitive within the constraints of local legislation and market forces. A case study format could be useful in tracking the successes of a small, medium or large pharmaceutical manufacturer. This research could primarily benefit senior executives of manufacturing divisions of pharmaceutical companies by providing examples of how previous successes of other pharmaceutical manufacturers were attained.

Secondly, future research could be conducted on the government's legislation, policies and regulations that affect local pharmaceutical manufacturing. Ideally a person conducting research of this nature should have a legal background in order to understand and evaluate the legal implications of government legislation on the local pharmaceutical industry.

Lastly, research could be conducted on the skills required within the pharmaceutical manufacturing industry. Skills shortages could be identified with possible solutions to address theses shortages at a company level, industry level and at a university level.

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APPENDIX A

Actual Research Instrument

1. What recent trends and changes in the global pharmaceutical industry have had an impact on local pharmaceutical production in general?

2. How have the characteristics or behaviours of global multinational pharmaceutical companies affected the local pharmaceutical industry?

3. How has global drug demand influenced the demand for locally manufactured pharmaceuticals and how has this influenced competition within the industry?

4. How have global price controls affected the pharmaceutical production in South Africa?

5. How have global patent protection and Intellectual Property Rights (IPRs) issues (e.g. parallel importing and compulsory licensing) influenced local pharmaceutical manufacturing?

6. Which factors within South Africa have had the greatest impact on local pharmaceutical production?

7. How have the characteristics or behaviours of local pharmaceutical companies affected the local pharmaceutical industry?

8. How does the unavailability of locally manufactured inputs (e.g. active pharmaceutical ingredients and processing equipment) impact on local manufacturing?

9. What government regulations, legislations or industrial policies have had an impact on manufacturing medicines in South Africa (e.g.DOH's drug policy, MCC manufacturing licensing requirements, medicines registration, pricing policies or Industrial Policy Action Plans)?

10. Is there a skills shortage within the industry and if so how does this affect the local manufacturing industry?

11. What are the main implications of the changing structure in local pharmaceutical manufacturing and how has the local pharmaceutical manufacturing industry responded?

12. What are the implications of the government's regulations, legislations or industrial policies mentioned in section 2 and how has the pharmaceutical industry responded?

13. How are local manufacturers adapting to changes within the local pharmaceutical industry?

14. How have the volumes of locally produced drugs changed for this company or in general and what are the reasons for these changes?

15. What is the future of pharmaceutical production in South Africa?

APPENDIX B

List of Interviewees

Table 5: List of Interviewees

No.	Position	Organisation	Interview Location
1.	CEO	Merck Serono	Longmeadow
2.	Senior Executive	Aspen Pharmacare	Morningside
3.	CEO	IMSA	Glenhove
4.	CEO	SAAPI	Glenhove
5.	Director: Technical Infrastructure Unit	DTI	Pretoria
6.	CEO	Mylan	Modderfontein
7.	Director: Inspectorate and Law Enforcement	MCC	Pretoria
8.	CEO	Specpharm Holdings	Midrand
9.	COO	PIASA	Midrand
10.	Senior Executive	Cipla Medpro	Midrand
11.	Supply Chain Executive	Adcock Ingram	Telephonic Interview
12.	CEO	Columbia Pharmaceuticals	Boksburg
13.	General Manager	Merck Pharmaceutical Manufacturing	Wadeville