
CHAPTER 3

LITERATURE REVIEW OF THE GLOBAL PHARMACEUTICAL INDUSTRY

3.1 INTRODUCTION

This chapter covers the results of the global literature review undertaken as the first phase of the Pharmaceutical Manufacturing Sector Study. The literature review comprised a global review (Chapter 3) and a domestic literature review (Chapter 4). The purpose of the global and domestic literature review was to identify key trends and developments in the sector and use this information to prepare for the subsequent phases of the project. This includes the sample survey of manufacturing companies, acquisition of international data for product benchmarking, and identification of growth and development opportunities for the domestic manufacture of pharmaceuticals.

3.2 METHODOLOGY

Data was gathered for the global literature review in the following fashion:

- The Counterpart Group was invited to submit any documentation of relevance to the consultants
- The consultants used their own sources of information
- A literature review was produced in draft form (Version 1) and circulated among the Counterpart Group for comments.
- All comments were followed up (areas of further research, views on figures etc) and a revised Version 2) and again circulated.
- This exercise was repeated a number of times, each time gaining more information.

3.3 RESULTS

3.3.1 SIZE AND STRUCTURE

The global pharmaceutical industry is colossal in size with annual sales of US\$222 billion in 1996, and estimated at US\$252 billion for 1998. In perspective, the South African GDP is US\$ 159 billion.

The pharmaceutical manufacturing industry globally has distinct characteristics that set it apart from any other chemical sub-sector. These are such as that:

- ♦ The industry stretches from high value, speciality nature of patent medicines right through to commodity, relative low value of off-patent multi-source and generic medicines. The industry also accommodates both high volume, relatively low value and predominantly public sector contract purchases as well as lower volume, high value private sector sales characterised by considerable marketing acumen.
- ♦ Although superficially the industry seems not to be controlled by major companies (the major player claims less than 5% of sales) the industry in fact consists of a multitude of sub-categories or therapeutic classes, within which the major players with so-called “blockbuster” medicines controls the class of medicines and also the major shares of profits to be made
- ♦ Extremely large amounts of up-front research and development capital is required to bring out so-called New Chemical Entities (NCE's) , or new molecules, which could lead to the introduction of improved patented therapy for diseases and conditions currently not well controlled.

From a business development point of view it is clear both that commercial and technical risks are extremely high, and that the public issues related to the application of medicines in the human health arena are one of the key areas of public and political debate. This includes for example the high costs of medicines aimed mainly at low income target patient categories (i.e. AIDS and Malaria drugs). Disregarding these risks, the returns for a successful, high profile new drug could be tremendous. Two major new drugs, Lipitor and Viagra, are both targeted to reach US \$1 000 million in global sales within one year, for an average R&D outlay of \$200 to \$300 million (Ref 3).

Virtually all pharmaceutical products are specialised, low-volume chemicals sold at relatively high prices when compared to non-pharmaceutical commodity chemicals, and they are consequently classified as part of the speciality chemical sector, a high growth sub-sector of the \$1 000 billion total global chemical sector (Ref 6).

3.3.2 GLOBAL MARKET SIZE AND STRUCTURE

The global market for pharmaceuticals in 1996 was \$222 billion, increasing to an estimated \$252 billion in 1998. Consumption of pharmaceuticals varies considerably in different geographic regions, following more or less a similar distribution to wealth distribution (Ref 6).

The per capita consumption of pharmaceuticals in major regions are as follows (1994 figures):

North America	:	\$283
Western Europe	:	\$167
Central/Eastern Europe	:	\$17
Japan	:	\$409
Latin America	:	\$29
Africa	:	\$3,8
Asia	:	\$7,2
China	:	\$5,5
<i>World average</i>	:	<i>\$44</i>

South Africa's per capita consumption is in the order of \$33, which is 75 % of the world average but well above the Africa average, and more in line with the average for Latin America.

The overall split in pharmaceutical consumption globally is:

North America	:	23%
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Western Europe	:	27%
Japan	:	22%
Central/Eastern Europe	:	9%
All Other	:	19%

The top 27 pharmaceutical companies accounted for sales of \$164 billion in 1997. The top 10 companies globally are:

Company	% of Global Sales (1997)
Merck	4,24
Glaxo-Wellcome	4,07
Bristol-Myers Squibb	3,09
Novartis	3,03
Pfizer	2,77
Roche	2,59
Hoechst Marion Roussel	2,53
Eli Lilly	2,46
Johnson & Johnson	2,39
SmithKline Beecham	2,32

The major branded pharmaceutical products globally are:

1998 World-wide Sales in \$ Millions							
1998 Rank	1997 Rank	Company	Brand	Therapeutic Category	% Market Share (E)	1997 \$ M	1998(E) \$M
1	(1)	Merck	Zocor (simvastatin)	Cholesterol Control	31	3,575	3,926
2	(2)	Astra	Losec (omeprazole)	Acid reducers	n/a	2,845	3,083
3	(3)	Lilly	Prozac (fluoxetine)	Anti-depressants	33	2,559	2,651
4	(4)	Merck	Vasotec (enalapril)	Anti-hypertensives	8	2,510	2,499
5	(6)	Astra Merck	Prilosec (omeprazole)	Acid reducers	n/a	2,240	2,480
6	(7)	Pfizer	Norvasc (amlodipine)	Anti-hypertensives	6	2,217	2,408
7	(8)	Schering-Plough	Claritin (loratadine)	-	n/a	1,700	1,926

8	(5)	Glaxo Wellcome	Zantac (ranitidine)	Acid reducers	n/a	2,320	1,850
9	(10)	SmithKline/Novo Nordisk	Paxil (paroxetine)	Anti-depressants	17	1,519	1,667
10	(9)	SmithKline	Augmentin (amoxicillin)	Anti-microbials	6,5	1,563	1,606

It should be appreciated that the same molecules may be used for different therapeutic areas. For example, Epogen and Procrit from Amgen are essentially similar products marketed separately for dialysis and non-dialysis applications. Together they account for sales of \$2,7 billion.

Over-the-Counter (OTC) medicines accounted for global sales of \$49 billion in 1996, or around 22% of the total market (Ref 5). In 1998 the value of the market increased to \$75 billion. The major categories in the OTC market are:

- Vitamins and dietary supplements (33,5% of total)
- Cold and allergy remedies (18,8%)
- Medicated skin care (15,0%)
- Analgesics (13,7%)
- Digestive remedies (12,9%)

The US prescription medicines market was \$81,2 billion in 1997 of which \$6,5 billion was generics, accounting for nearly 50% by volume. (Ref 3). The market structure in terms of distribution channels in the US is as follows: (Ref 5)

US TOTAL SALES

Distribution Channel	Sales Value (\$ Billion)
Mail order/courier pharmacy	7,7
Chain stores pharmacies	27,7
Independent pharmacies	16,9
Mass merchandisers	11,3
Foodstores with pharmacies	11,8
Hospitals	11,6
Clinics	4,5
Long term care facilities	2,6
HMO	1,5
Home health	0,7

Distribution Channel	Sales Value (\$ Billion)
Total	96,3

Note: the total figure of US\$ 96.3 billion in the above table includes the OTC and prescription medicines market.

3.3.3 DEVELOPMENT ISSUES

3.3.3.1 Research and New Product Development

The pharmaceutical industry has experienced a dramatic increase in risks and costs of R&D since the 1980's. In 1985 out of 10 000 chemical entities tested, 20 entered pharmacological and toxicological studies, 10 entered clinical trials and 1 received final approval. By 1995, one new approval required 50 000 new compounds being screened, at an average cost of \$200 - \$300 million. In the US new drug applications submitted to the Food and Drug Administration (FDA) declined by 10% yearly, whilst R&D expenditure increased by 15% (Ref 6). The top companies on average release 0,45 new chemical entities (NCE's) per annum, of which only 8% reach sales in excess of \$350 million per annum (Ref 3). It should be understood that the high costs above average out the approximately 7 out of 10 products developed by the pharmaceutical manufacturing sector that do not generate sufficient revenue to cover their investment R&D cost. USA CDC data shows that a new drug for malaria or TB can be developed for \$20 to \$50 million

These high risks in developing new pharmaceutical products place high emphasis on patent protection by the companies involved at this level. The purpose of this patent protection is to provide patentholders with a reasonable period to market products in order to recover investment cost in research and development. This protection resulted in pharmaceutical sector profits being higher than other chemical industry sectors (Dr B to substantiate).

Historically various Intellectual Property, or patent, protection systems existed around the world. The TRIPS Agreement (Trade-Related Aspects of Intellectual Property Rights) was concluded in 1994, and all states wishing to become part of the WTO (World Trade

Organization) have to comply to it. TRIPS requires a minimum period of patent protection for drugs of 20 years.

In addition, marketing requirements need at least a 1 000 representatives (in the US) to assist in the launch of a major new drug. These risks and costs issues necessitated a number of mergers in the industry such as:

- American Home Products/American Cyanamide (\$9,7 billion market capitalisation at merger)
- Glaxo Wellcome (\$15,2 billion)
- Novartis (Sandoz/Ciba Geigy) (\$30 billion)
- AstraZeneca
- Glaxo Wellcome/Smithkline Beecham

With no major company commanding in excess of 5% of the market, further consolidation is certain. R&D expenditure in the pharmaceutical industry among major ethical supplier's account for around 10% of company costs, with typical figures between \$1,5 - \$3,0 billion per annum. These figures clearly indicate that the ethical sector of the pharmaceutical industry will be virtually impossible to penetrate in a sustainable manner by smaller, regionally based independent manufacturers. This exacerbates the need for these companies to register generic products as soon as possible after patent expiry. It is also apparent that major companies replace patent expiring medicines with their own replacements. For example, Merck is recommending doctors to change patients over from Movacor (lovastatin), patent expiring 2001, to Zocor (simvastatin – patent expiry date 2025) as cholesterol reduction drugs. This change-over is done to ensure high prices and market share for the newer product compared to expected losses for the off-patent product.

The current focus of many innovator companies is on major needs such as drugs to treat Hepatitis C and B, which affect 650 million people globally (Ref 5). Innovator companies are mainly focusing on identifying new molecules that would be offering advantages such as:

- New mechanisms to treat diseases

- Improvements on existing mechanisms, such as improved efficacy or less side effects
- First time solutions (i.e. Aids vaccine)

Methods used by research based multinational and generic companies to obtain product improvement and differentiation is the development of alternative delivery systems. Alternative delivery systems have a number of objectives, including:

- Improved efficacy of products (i.e. from oral to injectable)
- Ease of application (i.e. stick-on patches)
- Metered dosages
- Slow-release mechanisms (i.e. single daily dosages), etc.

There are a number of companies focusing on the development of delivery systems, rather than new molecules. These new technologies are then licensed or sold to third parties.

3.3.3.2 Establishment and Upgrading of Manufacturing Facilities

It is apparent that there is excess pharmaceutical manufacturing capacity in SA and that a new manufacturer could establish production merely by contracting out to existing operators. However, much of the machinery is old and has been poorly maintained. Whilst there is a clear need to replace old machinery that keeps breaking down limited market opportunities and a perceived adverse investment climate discourage such capital expenditure. The establishment of a state-of-the-art tableting plant is estimated to cost in the order of R30 million. In other areas such as sterile plants it is necessary to update equipment every five years in order to stay competitive.

There is no clear link between the physical location of R&D facilities, regions for clinical trials and actual manufacturing sites. Multinational companies often operate R&D facilities at separate facilities to their manufacturing operations. Clinical trials are also conducted in required geographic areas that suit trial requirements. South Africa, for example, is estimated by various sources to attract nearly 10% of clinical trial work done by major multinational

companies, whilst practically no original research into new molecules is being conducted here.

Note: a Pharmaceutical Zone in Singapore (initially focused on API production rather than formulation but now moving downstream) has been established and provides major manufacturers with strategic advantages in terms of logistics, trade concessions, communications and ease of access to major markets, together with a politically and economically stable environment. In this context Merck has made a \$300 million investment to manufacture ethical actives Singulair (montelukast sodium) and Vioxx (rofecoxib). The plant will produce around 10% of Merck's global requirement for these actives (Ref 7). A question that should be asked is under which conditions major companies could be encouraged to make similar investments in South Africa. These conditions must have Government support and backing.

3.3.4 PRICING ISSUES

Pricing issues are very contentious in the pharmaceutical industry. These mainly originate from major differences between pricing of ethical (patented) versus off-patent products, as well as privately purchased products versus public sector purchased products. The dramatic rise in sales of off-patent "copies" has saved the US purchasers \$8 to \$10 billion by 1994, and this figure is rising (Ref 8). **Changing legislation to speed up approval and registration of generic substitutes has lowered the average life-cycle returns for new drugs by around 12%.**

The following descriptions build on definitions provided earlier and are useful in understanding pricing issues.

Innovator Drug	A drug that receives a patent on its chemical formulation or manufacturing process, obtains approval from the FDA or any regulatory authority after extensive testing, and is sold under a brand name.
Brand-Name Drug (patented)	As used in this study, an innovator drug.
Generic Drug	A copy of an innovator drug, containing the same active

	ingredients, that the FDA or any regulatory authority judges to be comparable in terms of such factors as strength, quality and therapeutic effectiveness. Generic copies may be sold after the patent on a brand-name drug has expired. Generic drugs are generally sold under their official name rather than under a brand name.
Breakthrough Drug	The first brand name drug to use a particular therapeutic mechanism - that is, to use a particular method of treating a given disease.
Me-Too Drug	A brand-name drug that uses the same therapeutic mechanism as a breakthrough drug and therefore competes with it directly.
Single-Source Drug	A brand-name drug that is still under patent and thus is usually available from only one manufacturer.
Multiple-Source Drug	A drug available in both brand name and generic versions from a variety of manufacturers.

Although no single manufacturer controls the overall industry, competition is less in specific therapeutic classes. In the US around 58% of all therapeutic classes are dominated by a maximum of three innovator drugs (Ref 8). This concentration opens up the possibility of high prices, but this is limited by so-called “me-too” patented drugs, which are using similar mechanisms but different chemicals to breakthrough drugs (this could be the same firm or another firm). Usually patented “me-too’s” appear within six years of the registration of a breakthrough drug, which is well within patent protection periods

Branded patented medicines lose an average of 44% market share within one year of patent expiring, but (generally) in the US the prices of recently off-patented branded drugs do not fall (Ref 8). Initial generics sell at a discount of around 10 to 25%. When more generic producers enter the market (i.e. up to 10) prices are around 40% lower, and when there are in excess of 10 generics, prices are below 50%. Other reports indicate a 75% discount for further entrants. **It is estimated that 80% of profits in generic manufacturing are obtained within 18 months of the first appearance of a generic alternative (Ref 9).**

In order to sustain price levels for branded products (on- and off patent) major companies are increasing expenditure on direct-to-consumer advertising. In the US this spending reached \$1,4 billion in 1997, with major spenders Glaxo Wellcome (\$200 million), Bristol-Myers Squibb (\$120 million), Pfizer (\$103 million) and Merck (\$95 million). Doctors reported a

53% increase in-patients requesting brand name prescriptions (Ref 3). A price evaluation of generic versus innovator drugs in the US is shown in the following table (Ref 8).

**PRICE COMPARISON OF GENERIC AND INNOVATOR DRUGS,
BY NUMBER OF MANUFACTURERS, 1994 (US)**

*Number of Manufacturers Selling Generic Copies of a Given Innovator Drug^{@@@}	Number of Innovator Drugs in Category	Average Prescription Price of All Generic Drugs in Category (Dollars)	Average Prescription Price of All Innovator Drugs in Category (Dollars)	Average Ratio of the Generic Price to the Innovator Price for the Same Drug^{%%%}
1 to 5	34	23.40	37.20	0.61
6 to 10	26	26.40	42.60	0.61
11 to 15	29	20.90	50.20	0.42
16 to 20	19	19.90	45.00	0.46
21 to 24	4	11.50	33.90	0.39
Average	n/a	22.40	43.00	0.53

Source: Congressional Budget Office based on tabulations of retail pharmacy sales data from Scott-Levin.

^{@@@} Includes manufacturers and distributors of dosage forms with annual sales above \$100 000.

^{%%%} An unweighted average of the ratios of generic to brand name retail pharmacy prices for the drugs in each category. The ratio for a multiple-source drug is equal to: (total generic sales/number of generic prescriptions) (total brand-name sales/number of brand-name prescriptions).

Note: The retail pharmacy data covered 177 multiple-source drugs, but only 112 had both brand name and generic versions and came in tablet or capsule form. Only tablet and capsule formulations were used for calculating average prescription prices. The average number of generic manufacturers and distributors for a given drug was 10. Only manufacturers with sales above \$100 000 for at least one dosage form were counted in the groupings, although all generic sales were used to calculate the average generic price.

In bulk generics the over capacity caused by new plants in mainly India and China has also negatively affected prices. Bulk penicillins, for example, are selling at less than \$10 per billion units, down from \$40 to \$80 (Ref 10). Due to over capacity in China and India the market is not expected to recover above \$15 per billion units again. This applies only to products where technology barriers are low (e.g. Penicillin) but not cephalosporings.

3.3.5 REGULATIONS AND REGISTRATIONS

The drug industry is one of the most highly regulated businesses in the world. Companies developing new drugs are subject to very strict control related to quality and safety, pricing and protection of intellectual property (patents). These regulations are set by government health departments and drug regulatory divisions, for example, the United States Food and Drug Administration (FDA) and the Medicines Control Agency of the United Kingdom (MCA). Officials of the European Union (EU) believe that harmonisation of drug regulations will boost possibilities for eliminating trade barriers throughout the Union. The European Medicines Evaluation Agency (EMEA), an agency based in London which has recently been set up for the centralised licensing of certain high technology and innovative medicinal products, administers applications for mutual recognition of medicinal products that have been licensed and in a manner to facilitate marketing of pharmaceuticals in EU member states. Companies are expected to manage their R&D programmes in such a way that the pharmaceuticals pass through the process relatively efficiently. Nonetheless, it often takes over 10 years and up to \$300 million in R&D to take a new drug from the laboratory bench stage to marketing. The rules devised by these drug regulatory departments mainly involve hundreds, if not thousands, of tests that the chemicals in new drugs have to satisfy before they can be passed as safe and efficacious.

The tests can involve the following different procedures:

- ♦ chemical, pharmaceutical and biological testing
- ♦ toxicological and pharmacological testing
- ♦ pharmaceutical dosage formulation and stability testing
- ♦ clinical trials up to phase III

- ♦ process development for manufacturing and quality control
- ♦ bio-availability and bio-equivalence testing.

Only after the drug in question has passed all these regulatory stages will it receive a product licence enabling doctors to prescribe it to patients and pharmacies to stock it for OTC purchases by the public (Ref 6). Further tests may be required including clinical trials and market surveillance

Manufacturing sites in the pharmaceutical industry are generally adhering to minimum standards of manufacturing laid down by various regulatory authorities such as the mentioned FDA and MCA. This is similar to South Africa, where the Medicine Control Council (MCC) ensures minimum quality control standards at all sites manufacturing products registered in South Africa. Globally the minimum standards for current Good Manufacturing Practice (cGMP) as prescribed by the World Health Organisation (WHO) are becoming the norm, especially for operations involved in exports. In countries such as India there are government incentives in place to promote cGMP compliance by manufacturers.

Generally the **minimum requirements** of the various regulatory authorities are fairly similar. However, the actual inspection procedures allow for subjective interpretations by inspectors. For example South African companies wishing to export to the USA found FDA inspections particularly difficult and costly to comply with and that the cost of upgrading facilities to FDA approval could be as high as twice the requirement for registration with the MCC.

The International Conference on Harmonisation (ICH) is determining the harmonised standards for the evaluation and registration of medicines (new and generics) in the most efficient and cost effective way world-wide (Ref 3). By mid-1997 agreement was reached on 36 guidelines to reduce duplication of time consuming and expensive testing for registration of new drugs. The current program involves a single International dossier for new drugs and cGMP. The general trend is towards shorter and easier registration requirements, without compromising patent protection issues.

The Uruguay round of the General Agreement on Tariffs and Trade (GATT) includes in important topic, namely the Trade-Related Aspects of Intellectual Property Rights (TRIP's) Agreement.

Of all the Uruguay texts, the TRIP's Agreement (Intellectual Property Rights (IPR's)) is of most relevance to the pharmaceutical sector. The seven IPR's which the Agreement deals with are copyright and related rights, trademarks, geographical indications, industrial designs, patents, layout-designs of integrated circuits and undisclosed information (trade secrets). TRIP's requires that term of patents shall be at least 20 years from the filing date. Transitional arrangements permit some delay in implementing the Agreement. Developing countries and countries in transition have five years to bring their legislation in compliance with the Agreement (i.e. by 1 January 2000). However, if a country does not introduce pharmaceutical product patent protection by the end of this initial five-year period, its implementation of the Agreement may be postponed for a further five years.

The Agreement applies only to inventions where a patent application has been filed after 1 January 1995, excluding products in the pipeline (i.e. products in clinical trials). For the research-based pharmaceutical industry, pipeline protection is a vital component of a new patent law because of the interval between patenting of a NCE by the inventor and his receiving the licence from the national regulatory control authorities for its marketing.

Mailbox protection under the Agreement implies that a country that chooses to delay the introduction of a patent law consistent with the Agreement and does not currently offer product patent protection has to provide a mechanism to accept patent applications for products invented after the Agreement enters into force, i.e. 1st January 1995. These applications will sit unprocessed in a mailbox until the day the country introduces its new patent law with product patent protection.

The Agreement may have a severe disadvantage for some developing countries, especially in the high-technology sectors such as pharmaceuticals, in two main respects:

- Domestic manufacturers wishing to produce and commercialise products covered by patents will be forced into licensing agreements involving royalty payments to patent holders;
- R&D activities may be hindered since the Agreement is likely to inhibit “reverse engineering” - the process by which research-based industry products are copied, and adapted for developing-country usage. Copies are sometimes produced by different processes, which might even be protected under process patents.

At the beginning of the Uruguay Round almost 50 countries did not have product patent provisions governing pharmaceuticals. The lack of such provisions probably had more to do with a lack of need than intent to allow domestic firms to produce pharmaceutical products in violation of a foreign patent. Most developing countries satisfied domestic consumption by importing, primarily from developed countries. More than 80% of world production of pharmaceutical products occurs in developed countries; and almost 75% of the production-taking place in developing countries are conducted by only six countries. There are therefore a relative small number of developing countries for which the implementation of TRIPS would have major implications as far as pharmaceuticals are concerned. However, TRIPS will generally result in medicines becoming more expensive in all developing countries.

3.3.6 GROWTH IN THE GLOBAL PHARMACEUTICAL INDUSTRY

In value terms, the growth of the global pharmaceutical industry was around 10% per annum in the 1980's, decreasing to 5% in the 1990's. The decrease in value growth is not withstanding a volume growth increase of around 7,5% per annum over the same period. Decreasing value growth is mainly caused by generic substitution and improved purchasing by government and private health agencies (Ref 6). Regionally, South East Asia and Central America are the fastest growing markets recording sales growth at double the global average. The Chinese market is set to become the world's largest by 2020 (Ref 11). Growth patterns will also vary considerably within therapeutic categories. For example, bulk penicillins are expected to grow overall at around 5% per annum, but newer amoxicillin is forecast to grow at 8% per annum, while older ampicillin will grow at less than 4% per annum.

3.3.7 MARKETING ASPECTS

Marketing strategies followed by global pharmaceutical producers have a two-fold goal in mind, namely maximising market share within a therapeutic category, but also the maintenance of the highest possible prices. Whilst on patent, market share and prices are determined by the relative performance of the drug compared to other chemical entities. Once off-patent competition factors decrease prices and market shares and different marketing approaches are being followed. These include:

- Focus on branding, where brand awareness and preference stabilise price (but not so much market shares).
- Focus on differentiation, i.e. reformulation or improved delivery systems.
- The least preferred marketing strategy is a pure commodity focus on lowest-cost as a non-branded generic.

An example of marketing strategies is the introduction of Monsanto's Celebrex (celecoxib) and Merck's Vioxx (rofecoxib). These were competing to be first in the market as an arthritis (non-steroidal anti-inflammatory) drug. These two products are no more efficacious than existing drugs, but they do have fewer side effects (i.e. ulcers). Both will take market share away from existing patented and generic products (Ref 12). The marketing advantage is related to cost-effectiveness, as no protective drugs to prevent ulcers will be required.

The major international manufacturers typically have in excess of 100 products in their portfolio, but focus on relatively few (from a marketing perspective). For example, Pfizer, with 4 500 sales representatives in the US, actively promotes only 12 products, while Merck only promotes 9.

3.3.8 GENERICS

3.3.8.1 Background On The Global Generics Pharmaceutical Sector

The focus of the study is mostly in the generic sector of the pharmaceutical industry. As indicated in the preceding sections generics have to be evaluated in the context of product marketing. A public sector tender calling for a formulation-based product would result in bids from multi-source branded products, as well as true generics. However, multi-source branded products in the private sector demand higher prices and brand preferences. In the South African context all generics have to be registered under a brand name, which implies that they could be regarded as multi-source branded products. The COMED (Co-ordinating Committee for Medical Provisioning) purchasing system for public purchases, however, specifies medicines on a generic basis.

Entry of a company into the manufacturing of generic products is not a simple decision. US-based research indicates that the technical and market characteristics of a generic firm's portfolio determine which markets it is most likely to enter. The more experience a firm has with the form, therapy or ingredient, the more likely it is to enter that market. This is based on low cost of entry, where lower costs that come from experience could be interpreted as "capabilities" or "resources" (Ref 13). **In other words, the future portfolio of a generics producer is largely determined by its current portfolio.**

The generic drug market is not particularly concentrated at aggregate level. In the US, Mylan and Geneva, the largest generic firms in 1994, accounted for 16% and 12% respectively of all generic sales in the retail pharmacy data set. Most generic firms had just 1% to 5% of total generic sales. The markets for individual multiple-source drugs, by contrast, are much more concentrated. For 94 of 110 multiple-source drugs in the retail pharmacy data set, the top two generic firms were responsible for more than half of generic sales. And for 57 of those drugs, the single top generic firm accounted for more than half of generic sales.

Leading generic firms may lower their price when new competitors enter the market so as to maintain their dominant position. That would explain how the average generic price falls as the number of manufacturers rises, but sales of many generic drugs remain dominated by one or two companies. However, Grabowski and Vernon found that in only half of the 18 markets they examined did the lowest-priced generic manufacturer have the largest market share. **Factors other than price, such as being the first to enter a market, as well as quality and**

reliability, probably also play a role in determining a generic manufacturer's market share.

3.3.8.2 Generic Manufacturing by Brand Name Firms

Although the same company rarely produces both a brand-name drug and its generic copy, some generic manufacturers are subsidiaries of brand-name firms. In 1994, eight of the 15 largest generic companies in the retail pharmacy data set in the US were owned by innovator firms. Today, the proportion of generic drugs produced by subsidiaries of innovator firms is probably somewhat smaller than in 1994 because several brand-name manufacturers have left the generic drug business. For example, three of the eight larger generic firms owned by a brand-name company (Rugby, Hamilton, and Warner-Chilcott) have been sold or disbanded in recent years. Some of those brand-name companies experimented with producing generic copies of their own drugs in the early 1990's and found that it was not very profitable. For example, generic manufacturer Hamilton offered copies of the brand-name drugs Anaprox and Naprosyn produced by its parent company Syntex. During the first calendar year after patent expiration, the average generic price quickly dropped, and Syntex lost 70% of its market for those two drugs to generic competition. A few of the brand-name companies that tried to get further into the generic business in the early 1990's, including Hoechst Marion Roussel and Merck, have recently sold generic subsidiaries. Nevertheless, There are brand-name companies that have long held generic subsidiaries and remain committed to their generic business. Today, at least 13 manufacturers of innovator drugs have a generic subsidiary or division.

Most generic subsidiaries do not produce copies of their parent company's drugs. In general, the incentives to lower price in order to gain market share are the same for all generic manufacturers, whether or not they are the subsidiary of an innovator firm. But an important exception occurs when the generic subsidiary produces a copy of the parent company's innovator drug. Though infrequent, in such cases the subsidiary may have less incentive to lower price than other generic producers may because it does not want to take more sales away from the parent company's drug. And when the generic subsidiary does lower price dramatically, the innovator firm suffers (Ref 8). In the South African context a

number of generic subsidiary operations do manufacturer generic copies (for example Rolab-Novartis,). Most generic subsidiaries lower prices in order to compete with local companies, as well as to meet prices on medical aid lists.

3.3.8.3 Patent Protection

The profitability situation in the generic sector dictates that a firm has to strive to become one of the first off-patent producers of a drug, focusing on a multi-source branded approach rather than commodity generic. This chase to become a first off-patent producer is causing major problems for the generics sector. Firstly, in the US the Abbreviated New Drug Application (ANDA) has a 180 days exclusivity period for a first applicant, which prevents other applicants to enter the market within the short period of high profitability. Ethical producers are also requesting patent extensions, which negatively influences generic producers.

Another tactic followed by ethical producers is to replace the original drug entity with an improved entity shortly before the patent expires. The old entity is withdrawn from the market, which makes it difficult for generic suppliers to enter (Ref 14). The current patent dispensation in the US allows generic producers to start development of drugs prior to expiry of patents on the condition they not released before the patent expires. This is not the case in the EC (or in South Africa). There is a risk in transgressing patent restrictions - the Japanese company, Fijimoto, was fined \$25,7 million in Japan, payable to SmithKline for manufacturing Cylock (cimetidine), a generic form of Tagamet, before Tagamet's patent expiry date (Ref 7). It is important for generic producers to keep track of patent expiry dates for major drugs, in order to be able to become one of the first off-patent suppliers. Some of the major recent and near-future patent-expiring products in the USA are listed in the table below (Ref 5).

**SOME OF THE MAJOR BRANDED DRUGS COMING
OFF PATENT 1997 - 2007**

Drug	Chemical Name	Company	Coming off Patent	Global \$ Value 1996
Zantac	Ranitidine HCL	Glaxo Wellcome	1997	\$3 billion
Zovirax	Acyclovir	Glaxo Wellcome	1997	\$1,3 billion
Taxol	Paclitaxel	Bristol-Myers Squibb	1997	\$813 million
Diprivan	Propofol	Stuart	1997	\$590 million
Hytrin	terazosin HCL	Abbott	1998	\$540 million
Atroven	ipratropium bromide	Boehringer Ingelheim	1998	\$747 million
Beclovent	beclomethasone dipropionate	Glaxo Wellcome	1999	\$600 million
Prilosec	omeprazole	Astra Merck	2000	\$3,7 billion
Vasotec	enalapril maleate	Merck	2000	\$2,5 billion
Pepcid	famotadine	Merck	2000	\$1 billion
Ceftin	cefuroxime axetil	Glaxo Wellcome	2000	\$650 million
Cardura	doxazosin mesylate	Pfizer	2000	\$500 million
Sporanox	itraconazole	Janssen	2000	\$500 million
Prozac	fluoxetine HCL	Eli Lilly	1999	\$2,4 billion
Mevaco	lovastatin	Merck	2001	\$1,3 billion
Zestril/Prinivil	lisinopril	Merck	2001	\$700 million
Augmentin	amoxicillin/clavulanate potassium	SmithKline Beecham	1999	\$1,4 billion
Novladex	Tamoxifen	Novartis	2002	\$560 million
Primaxin	imipenem-cilastatin sodium	Merck	2002	\$550 million
Axid	Nizatidine	Eli Lilly	2002	\$550 million
Intron A	interferon alfa-2b recombinant	Schering	2002	\$500 million
Cipro	Ciprofloxacin	Bayer	2003	\$1,3 billion
Ortho-Novum	Norethindrone/ethinyl estradiol	Ortho Pharmaceutical	2003	\$600 million
Claritin	loratadine	Schering	2004	\$1 billion
Diflucan	fluconazole	Pfizer	2004	\$900 million
Engerix-B	hepatitis B vaccine recombinant	SmithKline Beecham	2004	\$570 million
Zocor	simvastatin	Merck	2005	\$2,8 billion
Zoloft	sertraline HCL	Pfizer	2005	\$1,4 billion
Biaxin	clarithromycin	Abbott	2005	\$1,2 billion
Pravachol	pravastatin sodium	Bristol-Myers Squibb	2005	\$1 billion
Rocefin	ceftriaxone	Roche	2005	\$900 million
Zithromax	azithromycin	Pfizer	2005	\$625 million
Zofran	goserelin acetate	Zeneca	2005	\$570 million
Zoladex	goserelin acetate	Zeneca	2005	\$570 million
Imitrex	sumatriptan succinate	Cerenex	2006	\$850 million

Drug	Chemical Name	Company	Coming off Patent	Global \$ Value 1996
Norvasc	amlodipine besylate	Pfizer	2007	\$1,8 billion
Propulsid	cisapride	Janssen	2007	\$920 million
Risperdal	isperidone	Janssen	2007	\$650 million

These 38 drugs account for nearly 20% of the global pharmaceutical market.

3.3.8.4 Access to Active Pharmaceutical Ingredients

A critical issue in generic manufacturing is access to active pharmaceutical ingredients (APIs). Without access to competitively priced APIs it is very difficult for a producer to be commercially viable. The global market for generic APIs is estimated at \$6 billion, growing at 8 to 10% annually (Ref 5). One problem is that the relative quantities of APIs required for specific products are rather small. Products such as Prozac (fluoxetine), Pepcid (famotidine), Prilosec (omeprazole), Vasotec (enalapril) and Prinivil (lisinopril) represents global consumption volumes of only 20 to 40 tons per annum.

A viable API industry seems to be a major asset for a country to become a successful generics producer. It is suggested that an API producer only reaches critical mass at a sales level of \$50 million (Ref 5). The cost of establishing API manufacturing facilities is relatively high. In the South African context based on recent work done by CMCS on the establishment of Chem City it is estimated that on average around R 50 million is required to establish a single API production facility. This amount, coupled with the relatively small local market size, clearly indicates that the focus must be upon globally competitive facilities capable of exporting the bulk of production. Another critical aspect is to look at clustering of manufacturing technologies as well as out-sourcing opportunities and multi-purpose facilities.

An interesting observation is that a focus on cost optimisation of existing processes by API producers could lead to improved new processes for actives used in generics. The Indian producer, Ranbaxy, was successful in improving Eli Lilly's cefachlor process, leading Eli Lilly to enter into a 50/50 joint venture with them (Ref 9).

A further observation is the trend for pharmaceutical producers to outsource API manufacturing to dedicated fine chemical producers, which are able to produce at lower cost. Factors that determine the optimum size for API production include the diversity of output, asset base, customer service requirements and process economics (Ref 15). Patented and generic pharmaceutical manufacturers are more and more reliant on the outsourcing of API production. This is driven by their need to focusing on core business activities (Ref 21). This trend should be explored within the South African context to stimulate further API manufacturing.

Whilst the volumes (of APIs) used are relatively small, APIs are very high value products. Growth is also very high. An example of consumption and growth of some relatively new, patented APIs are (Ref 21):

LAUNCHED API's WITH HIGH GROWTH

Molecule	1998 Kg Sales	US\$ (+ / - %) from 1997
Loratadine	19,100	+26
Atorvastatin	19,100	+209
Lansoprazole	26,300	+66
Paroxetine	29,000	+23
Olanzapine	2,000	+94
Fluticasone	534	+52
Azithromycin	75,700	+27
Risperidone	1,100	+24
Losartan	53,400	+55
Salmeterol	226	+26
Cetirizine	18,600	+31
Lamivudine	25,000	+47
Levofloxacin	46,000	+33

3.3.8.5 Delivery Systems

A major issue in generics is differentiation of products in terms of delivery systems. For example, converting from injectable to oral, or oral to transdermal, as well as timed-release applications (i.e. single-daily dosages). Another new technology involves the improved delivery of water-insoluble drugs. Such drugs account for 40% of the total market (Ref 3).

3.3.8.6 Case Studies Of Generic Sectors In Developing Countries

The development of the South African generics sector is expected to follow the pattern created by other developing countries. An overview of the generic sector in two regions, Eastern Europe and India is provided from a conference held in London during 1998, called Generics; and Effectively Sourcing Active Pharmaceutical Ingredients.

Central Eastern Europe (CEE)

The CEE includes Poland, Czech Republic, Hungary, Romania, Russia and Ukraine. In the CEE the breakdown of the pharmaceutical sector in 1996 was as follows (Ref 22):

Patented drugs	:	27 %
Generics	:	51 %
OTC	:	22 %

The characteristics of individual pharmaceutical markets in the CEE are as follows:

CEE PHARMACEUTICAL MARKETS: 1996 - 2000						
Country	Pop'n in millions	1996 Market \$ M	Drug Spend Per Capita \$	2000 Market \$ M	Drug Spend Per Capita \$	p.a. growth 1996 - 2000
Poland	38.3	1,600	42	3,000	78	17 %
Hungary	10.4	700	67	835	80	4.5 %
Czech Rep.	10.4	1,050	101	1,300	125	5.5 %
Slovakia	5.5	200	36	300	55	10.7 %
Slovenia	1.9	230	121	270	142	4 %
Romania	23.2	300	13	440	19	10 %
Bulgaria	8.5	220	26	300	35	8 %
Russia	148.8	2,940	20	4,630	31	12 %
Belarus.	10.3	100	10	150	15	10 %

CEE PHARMACEUTICAL MARKETS: 1996 - 2000						
Country	Pop'n in millions	1996 Market \$ M	Drug Spend Per Capita \$	2000 Market \$ M	Drug Spend Per Capita \$	p.a. growth 1996 - 2000
Ukraine	52.1	390	7	610	12	12 %
Macedonia	2.2	60	27	90	41	10 %
Bosnia & Herzogovina	3.5	30	9	62	18	20 %
Croatia	4.8	320	67	405	84	6 %
Total		8,140		12,392		10.3 %
Source: Pliva's estimates			*Excluding Humanitarian Aid			

Characteristics of the CEE situation:

- CEE markets generally have price structures which favour generics and there is also a tradition of prescribing generics in these countries
- The generics sector is dominated by old and sometimes obsolete products, especially in Russia and old Soviet countries
- Prices are low and little capabilities exist to conduct research and product development
- Companies generally offer baskets of products rather than single lines.
- Isolated cases exist of Western and Indian companies which have established themselves in the CEE. However, relatively few major local generic companies exist in the CEE;
- In Russia and Ukraine (who have the largest populations in the CEE) generics account for 60% of the 30 most often prescribed products. The equivalent figures for Czech Republic is 40%, Croatia and Slovakia 35% each, Slovak Republic 18%, and only 11% in Poland.

- Before 1990 CEE countries did not recognise international patent laws and the copying and production of patent producers was common. Although most countries now respect patent laws, some major patented products are still being copied.
- The distribution of generics is a critical issue as market shares of the three major distributors per country vary from 85% in Slovenia to as low as 11% in Russia. In Russia it is a bigger problem to distribute generics than the selling thereof.
- In terms of the regulatory environment, all CEE countries accepted European Union legislation. Registration criteria are the same in terms of quality, safety and efficacy. However, a “need” clause requires a price to be stated when files are submitted for registration.
- Before 1990, almost all healthcare systems were state monopolies and publicly funded. However, many private services have since started up, with a focus on insurance systems. Increasingly the patient pays for the service.
- The OTC sector is growing significantly in the CEE. Russia is particularly large, and patients have to pay in cash. Some reimbursements are done to these with illnesses such as diabetes.
- Growth in the generics sector up to 2005 is estimated at 12% real per annum, and the development is following Western trends. Branding of generics is becoming important, and quick development/registration is becoming imperative.
- Acquisition of domestic players is rampant, and particularly all Hungarian companies have been acquired. In Poland the four major generic companies have been acquired, and the other eight will be privatised. Privatisation is also common in Russia, the Czech Republic, and Slovakia.

Although the region has very different circumstances to the West, the generics sector is showing similar characteristics to the Western countries, with a focus on branding and value for money.

India

India has a federal constitution, and health policies are regulated concurrently by the Delhi Government as well as 26 state governments. For the last few years India has re-oriented its

health strategy towards the under privileged. Increased funding for healthcare is aimed towards the 35% of the population which is living below the poverty line (mostly in rural areas). Concentrated attention is given to diseases of importance, such as tuberculosis, leprosy, malaria, filaria trachoma/blindness and dehydration (Ref. 23).

Healthcare is provided through both the public and private sector. Health insurance is limited to around 3% of the population (mainly government and industrial workers). Eighty percent of health care is provided by the private sector through hospitals, nursing homes and practitioners. Western or modern medicines reaches only 30% of the population - mostly in urban areas.

The Drug Controller General of India (DCGI) grants approval for marketing, new drugs, indication of dosage and different combinations. The individual states have control authorities, which issue manufacturing permissions, supervise CGMP and GLP and scrutinise OTC advertisements. New product approval requires a certificate of sale in the country of origin, marketing permission in North America or Europe, and phase III clinical trials in India. Actives for import are tested by an official laboratory in Calcutta, and bio-equivalence has to be demonstrated. The process requires around two years. CGMP's laid down in statute are the minimum requirements. The industry is talking to the Government to provide incentives for superior quality, but none is forthcoming. Indian consumers expect rigorous quality standards from drugs whether they are branded or generics. Single ingredient generics are free from price control. Branded drugs also carry a 15% excise duty, compared to 8% for generic drugs.

India historically did not have strong product patent legislation. The focus was on process patents, which lasted for seven years. Having joined the WTO, India is now harmonising legislation with international requirements. India started to liberalise its economy in 1991, which resulted in a trend towards deregulation. Foreign investment is encouraged, and import duties have been slashed from 200% to around 40%. In the pharmaceutical industry, deregulation only started in 1994. The prices of bulk drugs and formulations are controlled and there is also a regulation on profits. In 1994 licensing was practically abolished for bulk drugs, formulations and intermediates. Foreign ownership of companies has been increased

to 51%, and for high technology 70% is allowed. A higher rate of return has also been allowed.

Pricing rules and criteria are based on turnover and competition. With sufficient competition there is no need for price control. Single ingredient formulations based on controlled bulk drugs and sold under generic names are exempt from price controls. Every new price and revision has to be approved by the National Pharmaceutical Pricing Authority (NPPA). This is a government agency, but is deemed to be independent and technical. Price approvals require 6-8 weeks. The Indian pharmaceutical industry is a net foreign exchange earner, which is an exception for an Indian industry.

There are over 20 000 manufacturers in India. These include all major multinationals. Glaxo Wellcome is the largest with 7,2% market share, while the other nine companies in the top ten have between 4 and 2% of the market. The total Indian market is valued at US \$3 billion, and growing at 13-14% annually, which is slightly lower than before. India accounts for 8% of the global market in volume, but only 1,2% in value. In volume terms it is the sixth largest in the world, but only the fourteenth in terms of value. The market is mainly driven by a growing middle class of business executives and professionals with high disposable incomes and a high health consciousness. The OTC sector is weak, and sales by pharmacies account for 70% and institutions 30%. The public sector agencies buy mainly generics in large quantities at discounted or contract rates. There is a large network of distributors, which has to service 500 000 pharmacists.

In terms of the Indian generics market, the market is dominated by branded generics. The generics sector is worth around US \$270 million, or 9% of the total, and growing at 20% annually. Excluding institutional sales, the market share is only 6%. With an increased political pressure to develop national health insurance, as well as health access to the rural population, the generic sector has tremendous development scope. The generic sector is dominated by IV fluids, systemic corticosteroids, vaccines and systemic antibiotics. The generic sector includes both multinationals such as Abbott and Wyeth, as well as numerous locals, of which the majors are Wockhardt, Ranbaxy, Rallis, Dabur, Cadilla, Natco and Cipla.

The major competitive strengths of the Indian generic-manufacturing sector are:

- Relatively large number of quality producers, including some with FDA and MCA approval (however, this only represents a small % of the total 20 000 plants). There is a large fiercely competitive local market;
- Good pool of scientific talent and an educated workforce, with managerial and technical competence;
- An excellent record in development of improved cost-beneficial chemical synthesis for API's, and a well-developed API manufacturing sector, and
- Excess production capacity off a low cost base (plant, land, labour)
- The level of competition in the generic sector is extremely high and restructuring of the sector is ongoing. Mergers, joint ventures and acquisitions occur frequently.