

CHAPTER 4

LITERATURE REVIEW OF THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY

4.1 INTRODUCTION

This chapter presents the results of the literature review of the domestic pharmaceutical manufacturing industry. The same approach and methodology for gathering data and writing reports was used as for the global literature review, and is fully explained at the beginning of Chapter 3.

4.2 RESULTS

4.2.1 SIZE AND STRUCTURE

The current size of the South African pharmaceutical industry is estimated by IMS at R7 billion in 1998, growing to R7.6 billion in 1999. This exclude OTC sales in non-pharmacy outlets such as supermarkets. However, another study from First National Bank (Ref 19) estimates the total market at R10 billion, with the following structure:

ESTIMATED PHARMACEUTICAL TURNOVER 1997

Pharmaceutical Drug	Rm	% Share
Prescription	4 712	62% (of private sector market)
- Ethical	3 958	84% (of prescription market)
- Generic	754	16% (of prescription market)
Self-medication-OTC's	2 888	38% (of private sector market)
Total - Private Sector	7 600	76% (of total pharmaceutical market)
Public Medication		
- Ethical	1 200	50% (of public sector market)
- Generic	1 200	50% (of public sector market)
Total - Public Sector	2 400	24% (of total pharmaceutical market)
GRAND TOTAL	10 000	100%

Generics in total account for an estimated 20% of the market by value, which is around half the level of the US market. Relative to major global markets such as the US, the public sector accounts for a much larger portion of the market. Import penetration of the market was 34% in 1996 (Ref 16), and is increasing due to the closure of domestic plants by major international companies. The major segments of the market are:

Institutional Market: A central Co-ordinating Committee for Medical Provisioning (COMED) operates in South Africa to facilitate public sector pharmaceutical purchases. COMED purchased a total of R850 million in 95 pharmaceutical and medical related categories for the year up to September 1998, as well as R82 million in fluids (Ref 16). However, these account only for a portion of purchases, and excludes direct purchases by state hospitals.

The annualised total of public sector (provinces) purchases is estimated by IMS at R2 billion (Ref 16), consisting of **10 Pharmaceutical and 7 medical related tenders**. This is currently around 10% of the total healthcare budget.

Private Sector - Scheduled Drugs: According to IMS data, the private sector market for scheduled drugs (schedule 1 and higher) was R5 billion in 1998. Sales to private pharmacies account for 76,2% of total sales in the private sector for these scheduled drugs (Ref 16).

Private Sector – OTC: Over-the-Counter drugs account for a total of 30% of retail pharmacy sales. This is an important segment due to the Department of Health's focus on self-medication. On an annual basis this equates to sales of around R1,7 billion at retail pharmacy level. This excludes unscheduled products. Excluded from these OTC figures are sales (of unscheduled medicines) to non-retail pharmacies such as grocery stores and the like. The total sales of all OTC products (scheduled and unscheduled) is estimated at around R2,9 to R3,3 billion (Ref 17, 18).

Sales and Employment: The official CSS statistics for the sales and employment levels of the local pharmaceutical manufacturing industry are as follows:

SALES AND EMPLOYMENT 1987-1998

Year	Industry Sales		Employment (‘000)
	Actual Rand Million	Constant 1998 Rand Million	
1987	1 508	4 119	-
1988	1 876	4 500	n/a
1989	2 236	4 675	n/a
1990	2 786	5 193	n/a
1991	3 286	4 593	n/a
1992	3 719	5 771	n/a
1993	3 948	5 755	18 231
1994	4 148	5 556	16 944
1995	5 154	6 245	18 338
1996	5 183	5 799	18 377
1997	5 545	5 736	16 885
1998 (estimate)	5 892	5 755	17 772

Employment has been stable in the industry over the past 5 years. It is alleged that the industry employed greater numbers of people in the 1980's but no figures are available for this period and any guesstimates must be weighed against other factors such as method of reporting data, increasing capital intensity etc. (check and refine). As can be seen from the table there is no real growth in the pharmaceutical sector, with zero real growth in the past 5 years.

4.2.2 MAJOR COMPANIES OPERATING IN SOUTH AFRICA

According to information generated by IMS-SANDS during October 1998, the following manufacturers were suppliers into the various broad segments of the private sector (Ref 16).

MAJOR PHARMACEUTICAL SUPPLIERS: PRIVATE SECTOR

Supplier	% Market Share by Value
Adcock Ingram (RSA)	14,18
Pharmacare (RSA)	8,30
Novartis	5,64
Glaxo Wellcome	5,13
Hoechst	4,69
Schering Plough	4,40
Merck	4,18

SmithKline Beecham	3,73
Warner Lambert	3,30

Expressed in Rand terms, multi-national pharmaceutical manufacturers dominate the market, supplying 73,3% in total. The balance is supplied by South African owned manufacturers. Disaggregated market shares are given in the insert. The table is simply given to reflect the differences in market shares between the two largest South African manufacturers and the multi-nationals. Aspen Healthcare is the largest after Adcock and Pharmicare with a market share of only 0,64% (Ref 16). However, Aspen has now acquired Pharmicare. Although the overall market shares of major suppliers are rather low, there is a domination by major suppliers in certain specific therapeutic categories, leading to poor competition and possible high prices.

According to the South African Pharmacy Council the number of registered pharmaceutical manufacturers (excluding re-packing operations) are as follows:

GEOGRAPHIC DISTRIBUTION OF MANUFACTURERS

Province	No. Of Manufacturing Companies
Eastern Cape	5
Mpumalanga	1
Gauteng	68
KwaZulu Natal	9
Free State	1
Western Cape	10
TOTAL	94

Multi-nationals are especially active in the ethical (patented) market. Here their market share totals 91,9% by value compared with 8,1% of the South African suppliers. However, many of these patented products do face competition from generic substitutes. **Twenty-one South African corporations supply generic substitutes, this representing 70,3% of all generics supplied. The balance is supplied by the multi-nationals.** The self medication (OTC) market is divided between multi-nationals and South African suppliers in the ratio of 58:42 (Ref 16). The estimated supply structure to the public sector is currently as follows (Ref 17):

MARKET SHARES IN THE PUBLIC SECTOR (COMED)

Supplier	% Market Share	
	By Value	By Volume
Pharmacare	16	25
Novartis	6	11
Logos	6	4
Adcock Ingram	7	5
Glaxo Wellcome	5	6
Other	60	49

4.2.3 MAJOR PRODUCT CATEGORIES

The major pharmaceutical categories and their relative importance in the market are shown in the following table (Ref 16).

MARKET BREAKDOWN : KEY THERAPEUTIC CLASS AND CATEGORY

Therapeutic category	% share market category	Key therapeutic category	% share market category	Breakdown OTC : Prescriptn	Estimated % generic or multi-source medicine
Alimentary metabolism	15,6	Anti-ulcerants	2,8	3:97	40+
		Laxatives	1,1	27:73	100
		Tonics	1,2	99:1	100
Cardiovascular	12,5	ACE inhibitors	2,3	0:100	60
		Diuretics	1,2	1:99	100
		Beta blockers	1,2	0:100	90+
		CA antagonists	1,9	0:100	65+
		Cholesterol and triglyceride reducers	2,1	2:98	12+
Dermatology	7,0	Topical corticosteroids	2,2	5:95	60+
		Oral anti-acne preparations	1,4	0:100	100
Genito-urinary plus hormones	5,4	Oestrogens	1,3	0:100	75+
Systemic hormones	1,8	Plain cortisteroids	1,1	0:100	100
Systemic anti-infective	13,8	Broad spectrum penicillins	2,5	0:100	100
		Cephalosporins	4,0	0:100	60
		Macrolides	1,7	0:100	35
		Fluoroquinolones	1,4	0:100	0
Musculo-skeletal	5,6	Non-steroidal anti-	3,4	4:96	90+

Therapeutic category	% share market category	Key therapeutic category	% share market category	Breakdown OTC : Prescriptn	Estimated % generic or multi-source medicine
		rheumatics			
Central nervous system	18,3	Non-narcotic analgesics	7,6	60:40	97
		Antidepressants	3,2	0:100	65
		Hypnotics and sedatives	1,7	13:87	90+
		Tranquillisers	1,5	0:100	100
Respiratory	12,9	Cold preparations	2,3	98:2	100
		Topical nasal preparations	1,8	26:74	90+
		Antihistamines	1,4	99:1	25
		Expectorants	1,8	93:7	100
Total	92,9		54,1		

4.2.4 IMPORTATION OF PHARMACEUTICAL PRODUCTS

Local production of pharmaceutical products is under serious threat from both international ethical companies downsizing/closing local licensed operations, as well as imported generic products. Some recent closures of operations are shown in the next table:

RECENT CLOSURES OF DOMESTIC PHARMACEUTICAL PLANTS

Company	Location	Jobs Lost	Reason
Searle	Johannesburg	77	Restructuring post Monsanto merger
Pharmacia/Upjohn	Isando	75	Merger between the companies
Bristol Myers Squibb	Wadeville	50	Merger between the companies
Wellcome	Spartan	150	Restructuring-merger with Glaxo
Adcock Ingram	Various	1 000	Merger with Prempharm
Boots	Isando	Unknown	Company bought out by Knoll
Noristan	Pretoria	Unknown	Company bought out by Hoechst
Wyeth	Isando	Unknown	Internal restructuring

Source : Financial Mail, 31 July 1998

The value of imports according to Customs and Excise on a f.o.b. value basis for 1997 of major pharmaceuticals are shown below:

MAJOR PHARMACEUTICAL IMPORT CATEGORIES, 1997

Product	Tariff	1997 f.o.b. value : Rand Million
Extracts of Glands or Other Organs	30.01.20	3.7
Other Extracts of Glands or Other Organs or of their Secretions	30.01.90	5.4
Antisera and other Blood Fractions and Modified Immunological Products, whether or not obtained by means of Biotechnological Processes	30.02.10	71.2
Vaccines for Human Medicines	30.02.20	63.6
Vaccines for Veterinary Medicines	30.02.30	41.3
Other Vaccines	30.02.90	61.4
Containing Penicillins or Derivatives thereof, with a Penicillanic Acid Structure, or Streptomycins or their Derivatives	30.03.10	2.3
Containing Other Antibiotics	30.03.20	4.4
Other Containing Insulin	30.03.39	6.7
Other Containing Alkaloids or Derivatives thereof	30.03.90	89.5
Containing Penicillins or Derivatives thereof	30.04.10	76.2
Containing Other Antibiotics	30.04.20	285.6
Containing Insulin	30.04.31	28.9
Containing Adrenal Cortical Hormones	30.04.32	62.3
Other Pills, Tablets & Capsules	30.04.39	143.5
Containing Alkaloids or Derivatives thereof	30.04.40	23.0
Other Medicaments Containing Vitamins or Other Products of Heading 29.36	30.04.50	16.8
Other Medicaments Containing Vitamins or Other Products of Heading 29.36	30.04.90	1 260.2
Total		2 246.0

The total value of pharmaceutical imports under tariff code 30 was R2,426 billion on a free on board (f.o.b.) basis for 1997. The f.o.b. import value represents a value ex-supplier in South Africa of around R3.2 - R3,8 billion, depending upon local margins added. This is close to half of the estimated total value of the industry at manufacturer/supplier level. An analysis of import statistics for tariff 30 between 1997 and 1998 showed an increase from R2,426 billion to R2,953 billion, or 21,7%. This is more or less in line with the devaluation of the Rand to the US\$ of around 20% over the same period.

The major countries from which imported pharmaceuticals are sourced are : (% of total f.o.b. value in brackets)

- Australia	(2,2%)	- Belgium	(6,0%)
- Denmark	(2,3%)	- France	(10,9%)
- Germany	(16,2%)	- India	(1,4%)
- Ireland	(3,7%)	- Italy	(4,6%)
- Japan	(1,2%)	- Netherlands	(3,5%)
- Sweden	(2,3%)	- Switzerland	(13,2%)
- United Kingdom	(16,2%)	- USA	(10,9%)
- All other	(5,4%)		

Source: Customs and Excise

The major European countries account for nearly 80% of imports, and together with the USA their share approaches 90% of the total. Total exports of pharmaceutical products under tariff 30 during 1997 was R284,8 million (f.o.b.) increasing to R385,3 million for 1998, an increase of 35,3%. Not all exports are accounted for by domestic manufacturing. A significant portion of exports is based on re-exportation of previously imported products.

The major countries to which South Africa are exporting pharmaceuticals to are:

- Algeria (R 53.6 mil; 13,9%)	- Angola (R 20.4 mil; 5,3%)
- Australia (R 15.8 mil; 4,1%)	- Cameroon (R 5 mil; 1,3%)
- Canada (R 5 mil; 1,3%)	- Italy (R 4.6 mil; 1,2%)
- Kenya (R 23.1 mil; 6,0%)	- Malawi (R 8.5 mil; 2,2%)
- Mauritius (R 14.3 mil; 3,7%)	- Mozambique (R 14.3 mil; 3,7%)
- Uganda (R 8.9 mil; 2,3%)	- United Kingdom (R 9.6 mil; 2,5%)
- USA (R 30.8 mil; 8%)	- Zaire (R 18.5 mil; 4,8%)
- Zambia (R 10.4 mil; 2,7%)	- Zimbabwe (R 80.1 mil; 20,8%)
- All other (R 62.4 mil; 16,2%)	

Source: Customs and Excise

Southern African countries account for more than 40% of total exports.

4.2.5 PRICING ISSUES IN THE SOUTH AFRICAN MARKET CONTEXT

Pricing issues in the South African market context are as contentious as in any other global market. This is mainly caused by the substantial level of public (COMED) purchasing which accounts for 80% of the volume market but only 20% by value for prescription medicines. This creates the impression that private sector prices are unduly high. Furthermore, the Government is focusing on providing affordable healthcare at all levels, and is looking at a number of drastic issues to reduce price levels at the private and public levels. From a domestic production point of view a concerted effort to reduce domestic price levels will have a negative impact on the potential commercial viability of manufacturing operations. There appears to be a considerable amount of cross-subsidisation of the public sector by the private sector, but this has not been objectively quantified.

Price patterns are similar in South Africa as far as patented versus off-patented products are concerned, compared to major market such as the USA. According to Medikredit, the MMAP reference price system for medical schemes shows an average price drop of 20 to 30% for the first generic substitute available, while subsequent listings are at 50 to 80% below original branded products (Ref 16). The average saving for medical funds sourcing generic substitutes is 40 to 60%. As in the global context, South African pricing levels are influenced by competition and the number of suppliers in a particular therapeutic category (as far as off-patent multi-source or generics are concerned).

An analysis was conducted in 1997 (Ref 19) to evaluate private sector pricing in South Africa compared to other countries. The evaluation followed strict criteria to ensure direct comparison, including:

- 80 out of the 100 therapeutic sub-market identified by the Anatomic Therapeutic Classification (ATC) system devised by the WHO, which categorises direct substitutes in the same category.
- the five best selling products (brands) in each country were evaluated.
- products in the process of losing market share were excluded.
- prices were taken at manufacturers level (i.e. ex-factory).

- similar pack sizes and forms were used.
- all prices were converted to Rands based on exchange rates.

For 1995 the evaluation revealed the following results:

RSA/USA	:-	1 : 1,73
RSA/UK	:-	1 : 0,723
RSA/Germany	:-	1 : 1,177
RSA/Denmark	:-	1 : 1,157
RSA/Netherlands	:-	1 : 1,059

This analysis indicated that pricing for major brands (on- and off-patent) in South Africa is more or less competitive compared to open-market, major economies. However, a point to make is that major pharmaceutical companies follow brand/pricing strategies in different markets that accommodate the affordability of the medicine to the country. In that regard, it would have been more useful to compare countries with similar per capita PDE (personal disposable expenditure) levels to South Africa, such as Brazil, Indonesia or Malaysia.

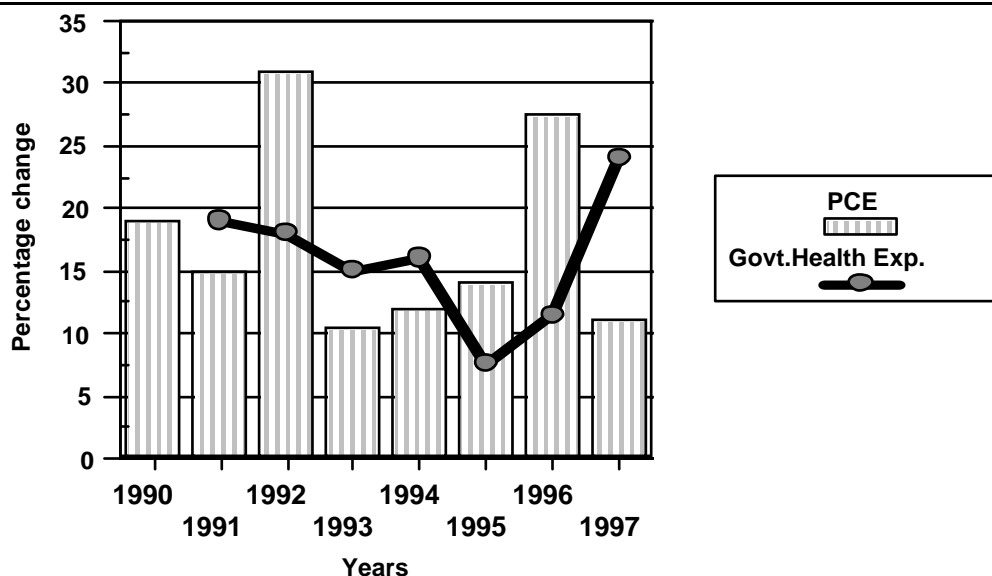
A similar evaluation was also conducted on public sector purchases, where tender prices were compared with prices from:

- a) International Dispensary Association (IDA)
- b) International Drug Pricing Indicator Guide (IDPIG)

By adjusting tender prices from multi-packs to bulk, it was found that tenders are fairly competitive, even against these non-profit driven pricing agencies (Ref 20).

4.2.6 DEMAND DRIVERS AND GROWTH EXPECTATIONS

Private consumption expenditure (PCE) growth is a major driver in the domestic demand for pharmaceutical products, especially for non-medical aid members. This indicates that changes in pharmaceutical demand could be the result of population growth trends, income distribution and access to health facilities. Membership of medical aid schemes are also an



GROWTH IN PCE AND GOVERNMENT HEALTH EXPENDITURE

indication of private sector demand, since medical aid scheme members, who only pay for a portion of their pharmaceutical cost directly, will more easily visit a doctor than someone who is not a member of a medical aid scheme. The public sector demand is determined by the growth in the Government's annual health expenditure. The accompanying graph gives an indication of how **private consumption expenditure** and **government health expenditure**, and thus possibly the demand for pharmaceutical drugs, may have fluctuated during recent years. (Ref 17).

Other lesser factors that could also influence supply are the availability of generic medicines, promotion and advertising and the introduction of managed health care (Ref 17).

Forecasts of future demand growth are based on the following assumptions (Ref 17) :

- ◆ GDP growth is forecast as follows for the 1998 to 2000 period.

FORECAST OF GDP AND PCE

National Account Aggregate Forecasts		
Year	GDP (%)	PCE (%)
1998	1.2	1.6
1999	3.1	2.8
2000	2.4	2.5

- ◆ Whatever the outcome of the current process to restructure the regulation of pharmaceuticals in South Africa, one can assume that the use of prescribed generic drugs in the private sector will increase substantially. The main contributing factors for this are the encouraged generic substitution and an increased focus on costs in privately managed healthcare facilities as demand for quality secondary and tertiary health care from the private sector increases. It is estimated that the demand for generic medicine will increase by around 20% in 1998 and between 35% and 45% in 1999 and 2000. This will result in a decline in ethical drugs of around 2% per annum until the year 2000.
- ◆ Deregulation of the distribution chain, and in particular, the opening up of pharmacy ownership to non-pharmacists (Pharmacy Amendment Act) is likely to result in an increase in demand for OTC's at the expense of prescription drugs. Conservative estimates suggest an OTC share of the private sector pharmaceutical market of around 45% by volume by the year 2000. Furthermore, there is an expectation that pharmacies will be rapidly "absorbed" into the retail shopping chain network. However, this impression is wrong in that an applicant for a new license would have to prove that a real need exists in the community, which is generally not true for the areas where retail stores operate.
- ◆ The rate of generic consumption in the public health sector is expected to accelerate due to the implementation of the Essential Drugs List (EDL), which largely lists generics, as well as the encouragement of generic substitution. It is estimated that the demand for ethical drugs will decline by around 15% in 1998, and 30% in 1999, 40% in 2000.

4.2.7 RESEARCH AND DEVELOPMENT

Using an average development cost of nearly R2 billion per NCE and recognising that even the major global players are barely averaging 1 NCE every two years, the development of New Chemical Entities (NCE's) on a sustainable basis by local companies is clearly not viable (Ref 16). Local R&D levels are extremely low compared to that of global players.

Pharmacare is involved in basic research into delivery systems, but not NCE's. Adcock has invested R5 million in sponsoring local research into a TB vaccine and other projects. The total R&D budget of these two major local manufacturers is around R85 million per annum (Ref 16). However, some limited results have been achieved, including:

- The State Vaccine Institute became only the second laboratory in the World to develop Rabies Vaccine using human cells.
- AECI Bioproducts identified but could not commercially develop the process to manufacture a major anti-inflammatory, Naproxen, by means of an isolated biological enzyme.
- The CSIR licensed a plant based anti-obesity drug to international partners.

It is averred that the focus of local manufacturers focus would have to be upon the clinical development of known entities through conducting local clinical trials. This would imply selectively developing new formulations and dosage forms of known entities and targeting the discovery of entities that can readily be licensed to international third parties with the funding for clinical trials (Ref 17). In this context South Africa is regarded as a priority base for clinical trials, with major multi-nationals spending up to 6% of global research budgets for clinical trials in South Africa. Due to this interest in South Africa clinical trials could be used as a base of departure for investigating further manufacturing opportunities.

4.2.8 INDUSTRY COMPETITIVENESS

The competitiveness issues in the industry can be summarised as follows (Ref 17):

4.2.8.1 Overall

This is a fiercely competitive industry with no individual company totally dominating the market. The largest market shares are held by two local companies - Adcock Ingram (ethical) and SA Druggists (generic). However, the leading position of the South African companies could be under threat should multinationals (that previously had agreements with local companies to produce drugs under licence) re-enter the South African market. Further

plant rationalisation and closures by multi nationals due to global restructuring, could, on the other hand, enable domestic companies to increase their market share.

4.2.8.2 Distribution

Wholesalers have been affected by increased competition from smaller regional players who offer limited product lines and generally do not carry high overhead costs incurred by full-line wholesalers. Big distribution groups such as International Healthcare Distributors (IHD) have put further pressure on independent wholesalers. Inefficiencies and over-regulation of the distribution network at the retail level, have resulted in the exclusion of non pharmacists, medical insurers and medical aid schemes from selling scheduled drugs directly to the patient and using bulk buying power to effect the required savings. Pharmacies, on the other hand, have been hit by increased competition on two fronts : the selling of OTC's by supermarkets as well as the selling of prescription drugs by dispensing doctors. The proposed SA Medicines Regulatory Authority Act (No. 132 of 1998) aims to create a more level playing field and prices could be more controlled in the future. Large pharmacy chains will not be able to negotiate bulk discounts, which would have given them a competitive advantage over smaller players. This could result in smaller orders, which could lead to more deliveries and higher prices eventually.

In a bid to reduce costs, nine multinationals set up International Healthcare Distributors (IHD) to be the sole distributor of their products to retailers. Upon formation of IHD the multinationals announced a 5% reduction in the catalogue prices of all their drugs. Each of the multinationals individually announced a further reduction on most of its drugs ranging between 5% and 18%. A second direct distribution chain, Project NASA, is currently being negotiated by five multinationals and Pharmacare, a division of Aspen Pharmacare Holdings Ltd. However these distribution chains have been accused of anti-competitive behaviour by independent drug wholesalers and pharmacists, and they have lodged a complaint with the Competition Board (now Competition Commission). The complaint was aimed at manufacturers who have or intend establishing direct distribution channels that intrude on the wholesalers' traditional domain. The report by the Competition Board was published in May 1999.

4.2.8.3 Economies of Scale

Many domestic pharmaceutical plants were built during the sanctions era to supply the local market. These plants are equipped with outdated technology and are too small to supply the international market. Due to the size of the local plants, the production volumes are so small that the unit costs are up to five times higher than those of Asian producers. With the global competitiveness drive to reduce manufacturing costs, companies are maximising output to ensure lower production cost. But the older, less sophisticated facilities locally are unable to produce the high volumes required.

In order to become globally competitive, new investment in high-volume, high-technology plants is required, which in turn requires substantial levels of exports due to the relative small domestic market. Against this scenario, multi-nationals are restructuring manufacturing to limit production to few, large competitive and strategically located manufacturing plants. Imports from these operations are very competitive against locally manufactured products.

4.2.9 RAW MATERIALS

Raw materials and more specifically API's (Active Pharmaceutical Ingredients) are a key factor in determining competitiveness aspect in the pharmaceutical industry. APIs are classified in the chemical sector as fine chemicals. Fine chemicals are typically high unit value downstream chemicals made in small (or smaller) quantities, utilising multi-step batch processing. Whilst the South African basic or upstream chemicals industry is fairly well developed, the downstream fine chemicals sector as a whole is totally underdeveloped. Local API production is limited to a few sites, including:

4.2.9.1 Fine Chemicals Corporation (FCC)

FCC's product portfolio consists of more than 30 APIs, which include both plant-derived substances (alkaloids of opium, ergot and vinca; scopolamine and their derivatives) and synthetic chemicals, such as azathioprine, fluphenazine, paracetamol, thioridazine, trifluoperazine and warfarin sodium. Over 50% of FCC's production is exported, the main

foreign market being the USA. FCC has FDA accreditation for products exported to the USA. FDA does not accredit a site, it approves each manufacturing practice (for each product) and quality assurance system. The design and execution of production lines and individual production units (equipment etc.) are part of accreditation requirements. FCC is not the only institution in SA having its manufacturing practice accredited by the FDA - CSIR's pilot installation producing medicinal plant extracts is the second.

4.2.9.2 Human Vaccines

SA has two manufacturers of human vaccines: SA Vaccine Producers (Pty) Ltd (SAVP) and the State Vaccine Institute (SVI). Both are the property of the State and both fall under the Department of Health (DoH). For technical and economic considerations, the production of vaccines at SAVP will cease as from the end of March 2000, and the production at the SVI from the end of this year. However, the core staff will be retained, pending the outcome of the sector's planned restructuring. The production of anti-sera that is profitable and technologically advanced will continue.

The size of private market for vaccines in SA is negligible. The size of public sector demand is determined chiefly by the number of new-borns, which is 1,1 million per year. Children Immunization Programme (CIP) accounts for nearly all the vaccines purchased by the state. The cost of purchasing vaccines for CIP quadrupled from 25 million Rands per year in 1998 to over 100 million in 1999, due to the introduction of vaccination against *Haemophilus Influenza B* (HiB). While five years ago all vaccines for CIP, except one (measles) were made domestically, currently all, except one (BCG, an anti-TB vaccine) are imported.

The state of vaccine production in SA was subject of a cabinet memorandum in May 1999. A project is under way to upgrade SA vaccine production to the best international standards, in strategic alliance with a foreign partner.

It is noteworthy that in certain areas academic research on vaccines in SA is among the world's most advanced and has potential for commercialisation.

4.2.9.3 Naproxen

AECI attempted to develop this commercially but without success.

4.2.9.4 Lactulose

Lactulose is manufactured by Illovo Sugar. Lactulose is not strictly an API, but it acts as an osmotic laxative

Without access to competitive API's it will be extremely difficult for off-patent medicine producers to be sustainable competitive players in the domestic and export markets. The global non-captive API market is estimated at \$9 - 10 billion, of which two-thirds are generic API's. The generic sector of the market is growing at 8 - 10% per annum globally (Ref 5).

For an API producer to be internationally competitive, sales of minimum \$50 million are required (Ref 5), which is well above the capabilities of any of the existing players in South Africa. However, a number of possible synergistic events are currently unfolding which could create a platform for a vibrant and competitive API manufacturing sector.

- Firstly, the CSIR has recently taken over the AECI R&D facility at Modderfontein, which includes significant human and equipment capabilities in process development of fine chemical and microbiological synthesis. With the correct focus this group could develop on a syndicated basis as a major strength for the industry to obtain competitive API manufacturing technologies;
- Secondly, the ChemCity initiative of Sasol and Gensec, has as goal the development of the fine chemical sector, which currently imports in the order of R5 billion annually (at exchange rate of 6:1 in 1999; APIs estimated at around half of this total). With the pharmaceutical industry being the single most important customer sector, it is critical for a joint approach in development of a competitive API manufacturing sector; and

- Thirdly, a global trend currently amongst major pharmaceutical companies is to outsource their API production function to dedicated fine chemical producers.

By offering an attractive platform in terms of industrial development incentives, competitive raw materials, low production cost sites and an unexplored growing African market, it may be possible to facilitate API production facilities in South Africa. Such facilities would be attractive for multi-nationals to be used as outsourcing API manufacturing facilities. Outsourcing is currently a major trend amongst major multi-national pharmaceutical manufacturers, which are focusing on their core business. However, becoming an outsourced API manufacturer would provide the critical mass to such producers to further manufacture other, off-patent APIs as well.

One of the key issues which has thwarted API production in South Africa in the past was the lack of understanding of the information regarding the market for APIs, both regarding the local and export markets.

4.2.10 SAFETY IN THE WORKPLACE

Safety in the chemical workplace is a very important issue in the pharmaceutical sector, especially due to the sensitive nature of chemical raw materials used in manufacturing processes. The camp standards required from manufacturers have very specific guidelines regarding health and safety aspects, and manufacturers have to comply in order to obtain product registrations. The national occupational health and safety inspection body, NOSA, has also instituted a special rating system for pharmaceutical operations. There has been a greatly increased effort to improve safety in the workplace in South Africa over the past 5 years, as public concern has mounted over environmental damage through chemical spills and pollution and government has become more responsible in terms of regulation and control than was the case in the 1980s. Additionally, organised labour has become more focused and more successful in ensuring a safe working environment.

4.2.11 LEGAL ISSUES

South Africa has experienced a great deal of change over the past 5 years in the health care sector and much of this has been due to government driven changes in the nature and delivery of health care. This section reviews the major legislative changes that have taken place and that are still occurring.

SOUTH AFRICAN PATENTS ACT 57 OF 1978

In terms of the Act a patent may be granted in respect of any invention which involves an inventive step, and which is capable of being used in trade or industry or agriculture. In terms of the Act, a statutory monopoly is given to the patent holder for 20 years, counting from the date of filing an application. A patent excludes other person(s) from making, using, exercising, disposing or offering to dispose of, or importing the invention, so that the patent holder shall have and enjoy the whole profit and advantage accruing by reason of the inventions (sections 45 and 46). However, the Act makes a provision for compulsory licence in case of abuse of patent rights (s. 56). Any interested person who can show that the rights in a patent are being abused may apply to the Commissioner of Patents for a compulsory licence under a patent. The rights in a patent shall be deemed to be abused if:

- (a) the patented invention is not being worked in the Republic on a commercial scale or to an adequate extent, after the expiry of a period of four years subsequent to the date of the application for the patent,
- (b) the demand for the patented article in the Republic is not being met to an adequate extent and on reasonable terms,
- (c) by reason of refusal of the patent holder to grant a licence upon reasonable terms, or if the establishment of any new trade or industry in the Republic is being prejudiced (due to the absence of such a licence) and it is in the public interest that a licence should be granted,
- (d) the demand in the Republic for the patented article is being met by importation and the price charged by the patent holder, his licensee or agent, is excessive in relation to the price charged therefor in countries where the patented article is manufactured by or under licence from the patent holder.

Upon consideration of an application for a compulsory licence, the Commissioner may order (the right holder) to grant the applicant of a licence on such conditions as he may deem fit, including a condition precluding the licensee from importing into the Republic any patented articles.

[Reference: Patents Act, No 57 of 1978, with amendments introduced by Intellectual Property Laws Amendment Act, No. 38 of 1997]

It should be noted that the provision for compulsory licencing under SA Patents' Act is not subject to litigation by the PMA and 41 pharmaceutical companies, which are contesting the Medicines and Related Substances Control Amendment Act (Act 88 of 1997).

When compared to patent laws of several other (especially the developed) countries, South African law has the following salient features, impacting on the production of generic pharmaceuticals:

- there is no provision for “springboarding” (which would be similar or equivalent to the US Hatch-Waxman Act, the so-called Bolar provision), and
- there is no provision for patent extension.

Another characteristic of the SA patent system is that the examination of a patent application by the Office of Patent Registrar is limited to its formal aspects and not to the content. If a patent is granted in SA, this does not automatically mean that the same invention was not earlier patented elsewhere.

South Africa is a member of the Paris Convention (Convention for the Protection of Industrial Property, 1967). A patent filed in SA will automatically enjoy protection in any other member country where a patent application was not filed, for a period of one year. This, however, does not apply to countries, such as India, which are not members of the Paris convention.

The Bolar Provision (The Hatch-Waxman Act): An area of contention is around whether producers of generics can start development of a generic equivalent to the patented product

before the 20 year period elapses. The importance of this is that once the patent expires other producers enter the market very rapidly and the price of the product drops to a fifth or tenth of the patented price within 2 years. If competitors have to wait for expiry of the patent before developing their own product, let alone getting it registered, then they are only likely to get the new product to market after all the profit has disappeared. This favours the original patentee, who will have already been developing a branded version of the patented product as soon as the patent expires. For these reasons an amendment to the Patents Act is currently being considered, which will have a similar effect to the American Hatch Waxman Act. The Hatch Waxman Act became law in 1994 and allows producers of generics to begin tests required for registration before the patent on the original product has expired. These changes reduce the period between expiration of the patent and availability of generic substitutes from 2-3 years to less than 3 months. This should improve the ability of generic suppliers to introduce new generic products in South Africa. In the US the market share of generics grew from less than 20 % in 1994 (when the Act was introduced) to over 40 % in 1996. These so-called Bolar Provisions were now also ruled by the disputes panel of the WTO not to be inconsistent with TRIPS. This will result in them being introduced elsewhere, in particular the EU. It was the EU which complained to the WTO, specifically regarding Canadian Bolar provisions, which strongly favours generics, including stockpiling of production runs before patent expiry. The WTO ruled in favour of aspects such as process development and bioequivalence studies before patent expiry, but against stockpiling (Ref.26)

PHARMACY AMENDMENT ACT 88 OF 1997

This act allows for pharmacy ownership by non-pharmacists (including companies), who do not need to be registered as a pharmacist (but registered as an owner) under the Pharmacy Act 53 of 1974 (as amended). However, pharmacies must be supervised by a registered pharmacist. The impact of this is likely to be a decrease in family-owned pharmacies.

MEDICINES AND RELATED SUBSTANCE CONTROL AMENDMENT ACT 90 OF 1997

The original Medicines and Related Substances Control Act was Act 101 of 1965. The Medicines Control Council (MCC) was established under this 1965 Act. Amendments to Act 101 were introduced by Act 90 of 1997 (“The Medicines and Related Substances Control Amendment Act”). The main issues covered by the act were:

- Parallel importation of drugs – would allow the Minister of Health to order the importation of a medicine with the same proprietary name as one already registered with the MCC, allowing the government to buy medicines at lower prices outside South Africa, as well as encourage multinational pharmaceutical companies to align their local and international prices in order to win public sector tenders.
- Dispensing of generically equivalent medicines – would require pharmacists to dispense generically equivalent medicines in all cases, except where it is a higher price than the non-generic one, or if the patient refuses substitution.
- Dispensing of medicines by Non-pharmacists – would allow licensed medical practitioners, dentists and nurses to dispense medicines.
- Contravention of the Patents Act – would allow the Minister, in order to protect public health by supplying more affordable medicines, to prescribe conditions in conflict with the Patents Act (as amended).
- Pricing Committee – establishment of a pricing committee to regulate a pricing system for all medicines, as well as dispensing fees

Contentious parts of the Act included:

- Requirement for re-evaluation of registration of medicines after five years,
- Provision for measures for the supply of more affordable medicines in certain circumstances, at the discretion of the Minister of Health, which included:
 - limitation of patent holders’ rights under Patents Act - i.e the Minister of Health may prescribe conditions in terms of which the provisions of the Patents Act (Act 57 of 1978) shall be suspended,
 - parallel import
 - compulsory licensing.
- Provision for generic substitution of medicines (*Section 22F*),
- Provision for regulating anew the Minister of Health’s power to make regulations,
- Prohibition of bonusing and sampling of medicines.

The MCC publically criticized the Bill (before it became an Act) on the grounds that it compromised the safety of medicines and would severely hamper the MCC in the execution of its function to safeguard the safety, quality and efficacy of medicines.

There was unified opposition against the Act:

- by the PMA, on the grounds that it interfered with the rights of patent holders (the contentious Sections 15C), and it gave the Minister of Health too much power on medicines' regulatory issues (*PMA argued that power should remain with an expert body, i.e that technical, clinical and scientific decisions should not be guided by political considerations*);
- by the NAPM, on the grounds that it compromised the safety of medicines. However, the issue of alleged attempted infringement of IPRs by Section 15C of the Act was not publically commented by the NAPM. Some NAPM members such as Lennon, Apotex and Ranbaxy even expressed their support for the new provisions.
- by the manufacturers of alternative/complementary medicines, because of the introduction of rigid registration criteria, the same as for orthodox medicines.

In January 1998, the Minister of Health established a Review Task Team (chaired by Prof. Graham Dukes* from the WHO and Norway) to review the functions of the MCC and make recommendations. A report was released by the Team in March '98, acknowledging the merits of the MCC and the Inspectorate of Medicines but also identifying their weaknesses and shortcomings. The Report recommended, *inter alia*:

- The present MCC should cease to exist and a new Medicines' Regulatory Authority should be formed.
- The new Authority should be largely financially independent, by charging appropriate registration fees,
- The operation of the Authority should be democratic, with adequate opportunity for appeal against its decisions,
- The Authority should maintain appropriate international contacts so it could benefit from the activities and experience of reputable foreign agencies, avoiding the need to repeat in SA regulatory work which has been undertaken competently elsewhere.

- The present Inspectorate of Medicines should continue in place, but with a greater degree of autonomy

Following the release of the Report the Registrar of Medicines, Prof. J. Schlebusch and his deputy, Mr. Christo Bruckner, were dismissed; the decision was made to dissolve the MCC and appoint a new body (later named SAMMDRA); and Prof. Peter Folb resigned as the MCC chairman and was replaced by Dr. Helen Rees. Ms. Precious Matsotso was appointed a new Registrar. A Transformation Task Team (TTT), chaired by Dr. Helen Rees, was formed to take forward work done by the Review Task Team and come up with constructive recommendations for radical improvement in the operations of a medicines' regulatory & registration authority. In July '98 the Team released a report which was intended to become a blueprint for the new regulatory authority (later named SAMMDRA).

SOUTH AFRICAN MEDICINES AND MEDICAL DEVICES REGULATORY AUTHORITY ACT 172 OF 1998

The SAMMDRA Bill was introduced by the Minister of Health (MoH) on 31 August '98 and the SAMMDRA Act (Act 132 of 1998) passed through the Parliament in December 1998. The Act repealed Act 101 and because it repealed the principal act, it automatically repealed the amendments introduced by Act 90 of 1997. Some of the amendments were incorporated in SAMMDRA Act, but others, including the contentious Section 15C, were not. PMA objected to the SAMMDRA Act on the grounds that the Act was poorly worded, contained numerous ambiguities which later could result in court action, had references to points which did not exist in the new Act etc. Due to all these flaws, the new Act was not enforceable. It was also considered that the MoH could overrule the recommendation(s) of a scientific body (SAMMDRA and its Expert Committee). The Virodene case was quoted as an example of the MoH publically supporting, due to political considerations, clinical trials of a hazardous substance, against the recommendations of the MCC and in spite of opposition of a vast majority of SA medical experts and organisations formed to support people with HIV/AIDS.

On 30th April '99 SAMMDRA Act was promulgated and brought into operation with immediate effect. The following problems emerged:

- The MCC ceased to exist but no one was appointed to replace it (SAMMDRA was a “shell”, not a real structure)
- There were no Regulations to the Act i.e. the Act was non-operational,
- The Act repealed the Schedules of Medicines of Act 101 but new Schedules were not yet compiled and published. This created a potential for chaos, allowing *inter alia* to legally import narcotic substances (falling under former Schedule 7) without a permit.

In an attempt to rectify the situation, on 7th May ‘99 the MoH published new Schedules for Medicines. Former nine Schedules (from 1 to 9) were replaced by eight (from 0 to 7). However the new Schedules were published without Regulations to hang on and the Schedules were published without a 3-month period for comments. The industry complained that, due to the extensive range of products made or re-packed in SA, significant lead time was needed for the industry to implement the changes. The same applied to products imported in a ready-for-sale form (packed).

Eight applicants (President Mbeki, the MoH, the DG of the DoH, the Registrar of Medicines, the Minister of Agriculture, the Chairman of the Veterinary Council and the PMA) jointly made an application to the State Attorney to rescind the promulgation of the Act. Acting judge (the Hon. Fabricius) decided that he could not overturn the promulgation as this would constitute an interference of the Judiciary with the Legislation (the judge was not empowered to do so). The applicants appealed the ruling, the appeal was rejected by the Judge, the applicants then appealed to the Chief Justice who allowed the appeal. The appeal was granted and the SAMMDRA Act was declared null and void.

The legislation reverted to Act 101 of 1965 (the principal act) with amendments introduced by Act 90 of 1997. However, due to pending court case against some of the Amendments (Section 15C and others) no regulations have been published regarding the Amendments (the Regulations under Act 101 shall apply).

MEDICAL SCHEMES AMENDMENT BILL (1997)

This bill was passed in 1998, also with considerable controversy. The bill effectively reversed the industry deregulation of 1989 by returning to flat community rating, by compelling medical schemes to accept any applicant who can pay the average contribution, regardless of age or health.

PROCUREMENT POLICY

Soon after coming into power South Africa's new democratic government committed itself to the reform of the state procurement system. One of its first measures was the introduction of the interim "10-point plan". This plan sought to change the manner in which the procurement system operated and, among other issues, specifically sought to promote the small, medium and micro enterprise sector, and previously disadvantaged persons. In 1997 a "Green Paper on Public Sector Procurement Reform in South Africa" was released, with the intention of a White Paper and a new bill. To date neither a White Paper nor a new bill have been released for public comment.

PREFERENTIAL PROCUREMENT POLICY FRAMEWORK ACT 5 OF 2000

The intention of the Act is to promote contracting with persons previously discriminated against, as well as promote programmes of the Reconstruction and Development Programme. The South African State Tender Board has set procedures and policies already in preferential procurement requirements for all government tenders. One of the consequences of this Act, however – and not picked up by the public at large – is the change to the existing system of tender price preferences awarded to domestic manufacturers that supply the State. In terms of the 'old' tender price preference system domestic producers were given price preferences over competing imported products in order to promote local consumption and thus local jobs. The 'new' Act will severely impact upon this system as it stipulates total maximum preferences that can be given by any organ of state to suppliers. However, the proposed new preference schedule will only be known once the Minister publishes the new regulations.

TRADE-RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS)

The Uruguay round of the General Agreement on Trade and Tariffs (GATT) negotiations culminated in the signature on 15 April 1994, in Marrakesh, of an agreement instituting the World Trade Organisation (WTO). The WTO came into being on 1st January 1995 and by October 1997 it had 132 members. In deciding to become members of the WTO, States also agree to abide by its rules. A certain number of treaties on trade in goods and services are annexed to the WTO convention and are therefore binding on all members. Among these multilateral agreements is the TRIPS agreement (Trade-Related Aspects of Intellectual Property Rights). The TRIPS agreement establishes minimum standards in the field of intellectual property. All member states have to comply with these standards by modifying, where necessary, their national regulations to accord with the rules of the agreement. South Africa brought its patent law in line with GATT/TRIPS by promulgating the Intellectual Property Laws Amendment Act (Act No. 38 of 1997).

The following Articles of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) have the most profound impact on the pharmaceutical sector:

Article 27 (Patentable Subject Matter) states that patents shall be available for any invention, whether product or process. Furthermore, patents shall be available, and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or produced locally. However, sub-point (3a) of this Article makes a provision for exclusion from patentability by Member states of diagnostic, therapeutic and surgical methods for the treatment of humans and animals.

Article 28 (Rights Conferred) states that a patent shall confer on its owner the following exclusive rights:

- (where the subject of a patent is a product) - to prevent third parties, not having the owner's consent, from the acts of: making, using, offering for sale, selling, or importing for these purposes that product,
- (where the subject of a patent is a process) - to prevent third parties, not having the owner's consent, from the acts of: (a) using the process, and (b) from the acts of making,

using, offering for sale, selling, or importing for these purposes at least the product obtained directly by that process.

Article 31 (Use without Authorization of the Right Holder). This article makes a provision for use of the subject matter of the patent, by the government of a Member country or third parties authorized by the government, without the consent of a patent holder, subject to the following conditions:

- (a) authorization for such use shall be considered on its individual merits,
- (b) prior to such (forced) use, efforts were made to obtain authorization from the patent holder on reasonable commercial terms and conditions and these were not successful within a reasonable period of time. However, this requirement may be waived by a Member country if the case of national emergency or other circumstances of extreme urgency.
- (c) (point “i”) the legal validity of any decision relating to the authorization of such use without authorization of the right holder shall be subject to judicial review or other independent review by a distinct higher authority in that Member country.

Article 33 (Term of Protection) states that the term of protection conferred by a patent shall be a minimum of 20 (twenty) years, counted from the filing date of the patent application. It should be noted that extension of patent protection beyond the mandatory 20-year term is possible in several countries, most importantly the USA, EU and Japan, to compensate the patent holder for the period lost while waiting for registration (regulatory approval) of a drug. Such a provision, however, is not mentioned in the text of the TRIPS Agreement. South Africa’s Patents’ Act does not make a provision for patent extension.

Article 34 (Process Patents: Burden of Proof). An important provision under this article is the reversal of a burden of proof in case of civil proceedings of patent infringement. In case of litigation, a court may order the defendant to prove that the product was obtained by a process different from the patented process. Most pharmaceutical products are protected simultaneously by a product patent and a process patent. Most research efforts and expenses are directed into the discovery of a new molecule - New Chemical Entity (NCE) and proving that it is responsible for a specific therapeutic action and is free from unacceptable side

effects. Once a structure of such a molecule is known, the chemical process (technology) of synthesising it is often relatively simple. Before GATT/TRIPS, patent laws of several countries did not recognize product patents, creating opportunity for “reverse engineering” of new molecules.

Section 7 (Protection of undisclosed information) - Article 39. Sub-point 3 of this article states that data (from clinical trials etc.) submitted by a company to obtain regulatory approval (registration) of pharmaceutical products shall be protected against unfair commercial use. Under US law, a manufacturer of a generic product is not allowed to use data from clinical trials conducted by the originator to obtain regulatory approval. However, the FDA does not require full-scale tests for a generic product.

Articles 65 (Transitional Arrangements) and 66 (Least-developed Country Members). These two articles differentiate the date of commencing applying the provision of TRIPS agreement:

- Developing countries together with countries in a process of transformation from centrally-planned into free-enterprise economies were entitled to a five-year effective delay from entry of the WTO agreement into force (i.e until 1st January 2000),
- Least-developed countries were entitled to a ten-year delay (i.e. until 1st January 2005), which could be further extended upon request,
- All other countries (i.e developed countries) were given one year (i.e until 1st January 1996) to make their national patent laws compatible with GATT/TRIPS.

Article 70 (Protection of Existing Subject Matter). Point 8 of this article states that if a country does not, as of the date of entry of the WTO Agreement into force, make available patent protection for pharmaceutical (and agricultural) chemical products, commensurate with the country’s obligation under Article 27, such a country shall:

- Provide, from 1st January 1995, a means by which applications for patent protection for such inventions can be filed (the “mailbox” provision),
- Provide patent protection as from the grant of the patent and for the remainder of the patent term, counted from the filing date.

CURRENT SITUATION

The original Medicines and Related Substances Control Act (Act 101 of 1965), the principal act, with amendments introduced by Act 90 of 1997, is currently in force. However, due to pending court case against some of the Amendments (Section 15C and others) no regulations have been published regarding the Amendments (the Regulations under Act 101 shall apply). A new SAMMDRA act, with regulations, is due to be submitted to Parliament in mid 2000 although the content of the new bill is not known. Also, the soured relationship between South Africa and the US has eased over the issue of intellectual property rights, with the US stating its support to SA over parallel importing and compulsory licensing, within the context of international frameworks. SA has been taken off the Priority Watch List.

As regard patent law the Patent Act still stands and has been amended but there has been no provision for springboarding under SA patent law as has been done in the US. Generic manufacturers therefore have to wait for patent expiry before commencing development, a situation aggravated by the excessively long (up to 3 years) registration time for new products. This obviously continues to favour the patentee. It is suggested that licensing arrangements relating to the acquisition of raw materials could reduce the market entry period for local generic producers.