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## **CHAPTER 9**

# **MANUFACTURING OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) AND PLANT DERIVED PHARMACEUTICALS**

### **9.1 INTRODUCTION**

This chapter outlines the current status of API manufacture world-wide and in South Africa, including current developments and future trends. This chapter also includes a review of the current status of the manufacture of plant-derived pharmaceuticals and APIs, again worldwide and in South Africa. It was not the original requirement of the study to cover Active Pharmaceutical Ingredients and this was noted in Chapter 1 of this report. However, it has become highly apparent during this investigation that there is a complementary and supportive relationship between pharmaceutical manufacturing and production of the active ingredients used for the finished products.

### **9.2 OVERVIEW**

In order to grow production in the formulation sector of the pharmaceutical industry, it is necessary to become export-focused, as the size of the local market is limited to 0.6% of the world total, which is too small to sustain a vibrant and growing manufacturing sector. It is clear that for a viable and sustainable export-based downstream pharmaceutical industry to develop, a similarly viable upstream Active Pharmaceutical Ingredient (API), also referred to as bulk actives, manufacturing sector needs to exist. The manufacturing of API's forms part of the broader **fine chemical** industry, which includes other intermediates and functional chemicals such as pesticide actives, dyestuffs, etc. The fine chemical sector is typified by technologically advanced, multi-step chemical synthesis, compared to the relative lower technology based on formulation employed by the downstream sector. API's typically account for around 50% of the value of the total fine chemical sector, making them the most significant sub-sector.

Historically, the business of bulk actives manufacture has been almost ignored in South Africa, largely because of the active ingredient's relatively small contribution to the overall price of a drug, the small market and the costs of regulatory compliance. An estimate is that bulk actives average between 10 and 15 percent of the cost of a finished dosage, with bulk actives for some patented drugs as low as 7 percent of the total.

The South African API industry consists mainly of one FDA approved facility, Fine Chemicals Corporation (FCC) in Cape Town. FCC is manufacturing a range of products, mainly from imported feedstocks or intermediates. Other non-FDA manufacturing include vaccines by the State Vaccine company, lactulose by Illovo Sugar and a Naproxen project by the Atomic Energy Corporation. Recent closures in this sector include aspirin production by Hoechst/Noricell (was FDA approved), as well as phenolphthalein by Mikrochem. The South African API industry is lacking a serious approach to the development of competitive advantages, integrated with the development of the downstream sector

The value of the South African API market is estimated at R2-2.5 billion per annum, consisting of both patented/licensed API's and generics. In contrast, sales of local manufactured API's into this sector is only around 2%, with imports accounting for the balance. This is symptomatic of the total fine chemical manufacturing sector in South Africa. In a typical well-developed economy fine chemicals account for around 15-20% of chemical sector output, whilst in South Africa it is around 1-2%.

Globally the API business has had a low profile in that bulk active is a highly fragmented market. A handful of major drug companies produce their own material. Others contract this work out to independent fine chemical manufacturers with approved facilities. In the generics sector, most bulk active product is produced in Europe (notably Spain and Italy), the traditional centre of bulk active manufacture. There is now a major trend towards India, China and South East Asia.

Generics are the real area of opportunity for bulk active manufacturers. Name brand makers generally lose about 40 percent of their market when a drug comes off patent. After losing

patent protection the drug innovator will often choose to outsource bulk active manufacture if it is cost effective.

Currently, the market for new generic drugs is good, with a strong pipeline of products coming off patent in the next 10 years. This healthy outlook has caused some name brand makers to come up with creative arrangements to claim part of this business. Among possible solutions is the securing of a position in bulk actives manufacture.

Pharmaceutical companies have been moving out of the chemical manufacturing side of their business and have focussed on their core therapeutic manufacture. For many companies, the capital costs of improving their plants and the increasing threat of environmental liability have already made contracting bulk production, or outsourcing, a more attractive option.

Another source of business for independent bulk active makers is coming from drugs developed by small, start-up pharmaceutical firms who have no experience in scale-up and production. In the past, bulk manufacturers would take over a product that a large pharmaceutical company had been producing for years. The newer drugs come with a manufacturing process that has only partially been developed and is then improved in-house by the bulk manufacturer.

What these point to is a realignment of roles within the pharmaceutical industry as all participants seek to focus on the area where they can do what they do best, in the most cost-effective manner. With shrinking revenues, traditional drug companies may be increasingly forced to choose between investing capital in manufacturing facilities or spending their earnings on new products development.

Another potential source of earnings comes from the Supplementary Patent Certificate (SPC) legislation now being discussed in Europe. If European companies are prevented from working on the key ingredient of a drug they would be able, thanks to the SPC, to synthesise material to as near the finished product as was allowed, then transport it to the US. This would globalise the bulk actives industry far faster than would otherwise be likely.

Another possibility is that a significant portion of bulk active production may move out of Europe to the developing world, to countries such as India, China and Africa. This is a trend that is affecting the major pharmaceutical companies in terms of their own production, in a move that is called offshore manufacturing.

### **9.3 TRENDS IN API MANUFACTURING**

#### **9.3.1 INCREASING IMPORTANCE OF OFFSHORE MANUFACTURING**

A number of pharmaceutical companies are moving towards some form of offshore manufacturing. Offshore manufacturing can be roughly defined as those manufacturing activities which take place in a country outside the home base of a company, and whose ends are primarily to serve the non-domestic market. Offshore manufacturing has grown in importance to be a major part of the world manufacturing industry in a number of sectors, including consumer electronics, textiles and toys.

Fully 80% of pharmaceutical demand lies within an area comprising less than 15% of the world's population. As the untapped potential markets increase their purchasing power, pharmaceutical manufacturers will need to address these markets. Offshore manufacturing could present savings to the manufacturers, allowing them to make the most of the new markets.

A number of factors have increased the importance of offshore manufacturing:

- There is no longer a desire on the part of management to control the entire value chain and to be fully integrated into manufacturing and discovery. Companies can look at outsourcing parts of the manufacturing process or relying on outside suppliers. This has become known as the "Corporate Hollowing-out Syndrome".
- Relaxation of trade and tariff barriers have meant that the movement of goods across borders has become easier, allowing market forces to play their part in decisions on manufacturing sites.

- The variation in the cost of critical manufacturing inputs (especially labour) is large when taken on a worldwide basis. Relocating facilities to low wage areas can save a significant amount of manufacturing costs.
- With improvements in logistics, the cost of transporting product around the world is reducing, making it cost effective for the manufacturers.

### 9.3.2 CURRENT PRACTICE

There are four principal locations for offshore manufacturing at present – Puerto Rico, the Bahamas, Ireland and Singapore. The drive towards using these locations is primarily the tax and/or investment granted to companies locating in these areas. However, the short-term nature of these government grants means that companies that have taken advantage of them have not followed a sustainable long-term strategy. If tax credits are revoked or removed, the manufacturing plants that have been set up offshore may no longer be profitable.

A more sustainable policy looks at the whole area of **maximising competitive advantage**. The combination can be very compelling: cheap raw materials; economies of scale through the building of world-scale production units; and competitive differentiation such as siting near end-user markets create competitive advantages for the companies that employ them.

Primary API manufacturing can well benefit from offshore siting. There is scope for significant economies of scale, making it effective for companies to manufacture active compounds in one (or a few) place only – in world-scale units, rather than scattering it about the world. One example is Glaxo, which manufactures a significant proportion of its ranitidine needs in Singapore.

API manufacture is characterised by the low cost attributable to labour, while depreciation (of the large fixed asset base) is a large factor.

### 9.3.3 FUTURE DEVELOPMENTS

In the case of drugs with patent protection, the factors mentioned above suggest that there will be a relocation of primary manufacturing facilities to the most suitable locations. Suitability will be defined by the presence of **favourable government policies, the quality of infrastructure and logistics**. In this respect Singapore may emerge as a front-runner, threatening the dominance of the four countries mentioned above. It will be necessary to develop a development strategy for API production in South Africa that will be competitive with those developed by these countries.

For chemicals which are freely available, the forces that drive towards internationalisation will mean that companies will purchase from the most competitive location rather than the nearest. The importance of China, India and other Southeast Asian countries will increase as they are used more and more as sources for active ingredients for both generic and OTC pharmaceuticals.

In fact, a large number of European and US generic producers source their bulk active ingredient needs from India and the Far East. Compounds used in antibiotics such as lincomycin, caffeine and theophylline used in cold preparations and painkillers such as dextropropoxyphene are already often sourced from these areas.

As healthcare needs change in these countries, they will need production of actives for the treatment of chronic disease. This will ensure that the range of pharmaceutical bulk products produced in the countries will broaden significantly. As the range widens, so the value-added that companies can derive from the manufacturing process will increase. The process will be accelerated by conformance to TRIPS in these countries, improving technology transfer and the ease of setting up new plants/manufacturing in the country.

Bearing these factors in mind, the pharmaceutical industry must contemplate moving outside of its traditional areas of influence. Moving primary production to the most competitive sites will create a bridge between the mature markets and those yet to be developed. This trend must be exploited to develop the South African API sector.

These movements will have to be based on a careful analysis of the long-term benefits of a move, rather than the short-term cost benefits created by government surpluses and the like. For example, there may be regulation of the free repatriation of profits. Such regulation forces manufacturers to think in a longer time scale than simple profit maximisation, as the manufacturer must be certain that the country is worth investing in.

### **9.3.4 CONCLUSION**

There are opportunities for independent companies to provide manufacturing facilities abroad, in a form of outsourcing. However, it is most likely that the developments will come from within the existing players, as their consideration will be to stabilise returns on existing assets, such as plant, equipment and personnel. In this regard it is recommended that a full-scale strategic evaluation of the development of the South African API sector, within the context of the broader fine chemical industry is conducted. This study should focus upon areas such as:

- Identification of commercially viable intermediates and actives to be manufactured
- Development of strategic linkages and capacity building in skills and technology
- Identification of competitive advantages and disadvantages
- Development of outsourcing and/or JV opportunities with multinational partners
- Upstream implications of the development of intermediates for use in API's and other fine chemicals

### **9.4 MANUFACTURING OF PLANT DERIVED PHARMACEUTICALS AND API's**

The manufacturing of plant derived pharmaceuticals and API's, also referred to as phytomedicines or ethnobotanical drugs, is a topical discussion in South Africa, especially within the context of traditional medicines used by a large section of the South African population. It is however necessary to evaluate manufacturing opportunities from a perspective of market attractiveness and competitiveness, as well as the existing regulatory environment.

It should be realised that certain plant extracts have been part of the formal pharmaceutical environment for a long time already (i.e. opium). The real issue involve products which up to now have not been found to be viable from an efficacy and clinical trial perspective to be used as API's.

#### **9.4.1 SOUTH AFRICAN SITUATION**

South Africa has a wealth of botanical diversity, and approximately 23 000 indigenous plants have been identified to have potential medicinal properties. However, the application of these medicinal plants is mainly outside of the mainstream healthcare arena, and involves mainly the traditional healers and health shops. These products are unscheduled, and therefore not controlled by the MCC.

Several calls have been made in the past to incorporate this sector into the mainstream, especially due to the potential for agricultural and processing job creation, but also due to political undertones to make the industry less Western-based. Some research actions are underway to evaluate API potential for specific products. The CSIR and Pfizer, for example, is evaluating the potential for an anti-obesity drug derived from a plant indigenous to the Karoo. Processing of certain plants, however, would require changes to existing legislation (i.e. Cannabis). Fine Chemicals Corporation (FCC) is currently involved in the extraction of certain plant products for use as API's

#### **9.4.2 GLOBAL SITUATION**

In a global sense phytomedicines was a very hype issue in the 1980's and early 1990's. Great expectations were derived from the untapped bio-diversity potential of areas such rain forests. However, the actual results achieved have been extremely disappointing. The US National Cancer Institute tested 35 000 samples between 1960 and 1982, and only three significant products were discovered (ref. 25). Further collections from 1986 to 1996 have not yielded a single success. Merck, one of the major multinationals, tried unsuccessfully for ten years to find any significant NCE's from Chinese herbal remedies.

Shaman Pharmaceuticals, a major listed USA based company with a focus on phytomedicines, was closed down in 1999. Shaman had teams of scientists and botanists in 30 countries which collaborated with local healers to identify plants with medicinal properties. Shaman made good process in relatively few areas. In diabetes they succeeded in four years to isolate 30 compounds capable of lowering blood-sugar levels for type II diabetes (untreatable with insulin). However, whichever method Shaman was using to identify potential new drugs, these new products still have to pass through the regulatory system. The relative few successes which they had, coupled with the high costs of clinical trials finally forced them to close shop.

The Shaman case study is a valuable lesson in the way in which pharmaceutical research is conducted. Disregarding the emotional issues attached to “natural” products, it must be remembered that although a product is natural, it is not to say it is safe (i.e. snake poison). It is therefore imperative for any natural remedy to be fully evaluated in terms of efficacy and safety, before it is being approved for use as a pharmaceutical product. There is no valid excuse for these products to be excluded from the existing regulatory regimes.

Furthermore, the original thinking behind phytomedicines was that it was an easy way of screening products, since they have been demonstrated to have some medicinal effect. However, modern screening technologies and combinatorial chemistry have enabled multinational pharmaceutical companies to develop literally hundreds of thousands new molecules on a daily basis, as well as screening them for potential pharmaceutical application. In this respect the number of phytomedicine based opportunities is insignificant.

### 9.4.3 CONCLUSIONS

The reality of the phytomedicine situation is that there can be expected to be little commercial opportunity available in the untapped natural remedy field in South Africa. It must also be realised that the serious effort by many organisations over the last 20 years have focused on those areas where **maximum commercial value** could be extracted. This implicates that the products not yet evaluated would probably have a low commercial value,

or a small regional application. From this perspective it is difficult to warrant a dedicated effort into discovering new products, especially if funded by public sources.

However, it can not be discounted that there may still be some significant opportunities out there. In this regard it can be assumed that private organisations will be more geared towards a commercial focus in identifying opportunities. Government support for such research projects should be based upon an intensive scrutiny of the commercial viability of products under evaluation, as well as a clear indication of the efficacy and safety of products.

It is also clear that it should not be allowed for phytomedicines to be introduced outside the existing regulatory environment. There is no technical validation to exempt these products from standard efficacy and safety testing.