EXECUTIVE SUMMARY

0.1 INTRODUCTION

0.1.1 Paracetamol is an important antipyretic and analgesic agent with weak anti-inflammatory effects. Paracetamol has been around as a drug for more than thirty years. Paracetamol, being a safe and low priced analgesic, is quite popular world-wide. Medical opinion throughout the world is in favour of using Paracetamol, either by itself or in combination, over the established drug 'Aspirin', due to its lower side effects.

0.2 MANUFACTURING PROCESS

0.2.1 World over, the following four routes have been established for the manufacture of Paracetamol :

* Phenol Route
* Para Nitrochloro Benzene Route
* Nitrobenzene Route
* Para Hydroxyacetophenone Hydrazine Route

The first three routes have been employed since quite long. The first plant based on the fourth route (i.e. P-Hydroxyphenone Hydrazine) was set up in 1990.

0.2.2 All the routes primarily lead to the manufacture of Para Aminophenol (PAP) of which Acetaminophen (APAP), i.e. Paracetamol is a derivative.

Various processing steps by these steps by these routes are depicted in the Figure 2 in Section 2.2.1 of Chapter 2.

0.2.3 Comparative evaluation of the salient features of the various routes is given as follows :

Comparative Evaluation of Various Paracetamol Manufacturing Technologies

Sr. No.	Particulars	Phenol Route	PNCB Route	Nitrobenzene Route		Para-Hydroxy acetophenone Hydrazine Route
				Electrolytic Reduction	Catalytic Reduction	
1.	Type of Process	Batch	Batch	Continuous	Continuous	Continuous
2.	Major Inputs	Phenol, Sodium Nitrite, Sulphuric Acid, Ammonium Sulphate, Acetic Anhydride	PNCB, Iron Powder, Acetic Antydride	Nitro Benzene, Sulphuric Acid, Ammonia, Acetic Anhydride	Nitrobenzene, Hydrogen, Ammonia, Acetic Anhydride	Para-Hydroxyphenone Hydrazine, Acetic Anhydride
3.	Catalyst	Not Required	Not Required	Not Required	Very Expensive Platinum Catalyst, which can be regenerated	Not known
4.	Yield	Lower	Lower	Much Higher	Higher	Much Higher
5.	Control of Operation	Manual/Semi Automatic	Manual/Semi Automatic	Automatic	Automatic	Automatic
6.	Solid Waste	Nil	Iron Sludge	Nil	Nil	Nil
7.	Liquid Effluents	Yes	Yes	Yes	Yes	Yes

Table Contd.

Table Contd.

Comparative Evaluation of Various Paracetamol Manufacturing Technologies						
Sr. No.	Particulars.	Phenol Route	PNCB Route	Nitrobenzene Route		Para-Hydroxy acetophenone Hydrazine Route
				Electrolytic Reduction	Catalytic Reduction	
8.	By-Products	Dilute Acetic Acid	Dilute Acetic Acid, Sodium Salt of Para Nitro Phenol	Dilute Acetic Acid, Aniline	Dilute Acetic Acid, Aniline	Not known
9.	Utilities	Steam, Power and Chilling plant ice consumption is likely to be high.	Steam, Power and Chilling Plant	Steam, Power and Chilling Plant Steam and Electricity consumption likely to be high	Steam, Power and Chilling Plant	Steam, Power and Chilling plant.
10.	Manpower requirements	60	50	30 Highly skilled manpower	30 Highly skilled manpower	Not Known
11.	Hazards/Probl-ems	Nitros compound explodes even at moderate temperature	Hydrolysis of PNCB is highly exothermic	Corrosion Problems	Fire and Explosion hazards due to hydrogen leakage	

Table Contd.

Table Contd.

Comparative Evaluation of Various Paracetamol Manufacturing Technologies						
Sr. No.	Particulars	Phenol Route	PNCB Route	Nitrobenzene Route		Para-Hydroxy acetophenone Hydrazine Route
				Electrolytic Reduction	Catalytic Reduction	
12.	Minimum Economic Plant size	20-25 TPM	20-25 TPM	300 TPM	300 TPM	500 TPM
13.	Level of Investment for MES Plans	Rs. 1.0 Crores	Rs. 1.0 Crores	Rs. 30.0 Crores	Rs. 30.0 Crores	Rs. 300 Crores
14.	Acquisition of Technology	Easy	Easy	Difficult	Difficult	Very Difficult
15.	Unit cost of Production	Highest among all routes	Higher but lower than Phenol routes	Higher than PHAP route but lower than phenol and PNCB routes	Higher than PHAP route but lower than phenol and PNCB routes	Lowest
16.	Advantages	Ease of operation Lower investment	Ease of operation Lower investment	Lower cost of production Continuous process	Lower cost of production Continuous process	Lower cost of production Continuous process

Table Contd.

Table Contd.

Comparative Evaluation of Various Paracetamol Manufacturing Technologies						
Sr. No.	Particulars	Phenol Route	PNCB Route	Nitrobenzene Route		Para-Hydroxy acetophenone Hydrazine Route
				Electrolytic Reduction	Catalytic Reduction	
		Easy availability of technology	Easy availability of technology			
		Less operational skills required	Less operational skills required			
17.	Major drawbacks	Higher cost of production	Higher cost of production	High capital investment	High capital investment	High capital investment
		Batch process	Batch process	High operational skills required	High operational skills required	High operational skills required
		H_2S emissions causes inconvenience to workers	Corrosion problems			
		Unreacted phenol in effluents difficult to remove	Explosion hazards		Fire and explosion hazards	Closely guarded technology.
		Explosion hazards				

0.3 WORLD INDUSTRY STATUS

0.3.1 Market

The total world market for Paracetamol bulk drug is estimated to be about 1,10,000 tonnes per annum, with Europe and North America accounting for nearly 40% of the total market.

The world market for Paracetamol is growing at an average growth rate of 5-6% per annum. Increasing global demand for Paracetamol is primarily attributed to the growing third world market. The growth of Paracetamol market in countries like USA and Japan is due to incorporation of Paracetamol in cough and cold drug formulations. World over, Paracetamol continues to effect the market share of Aspirin. However, Paracetamol in turn, is facing competition from newer drugs.

0.3.2 Major Players

USA, Germany, Turkey, China and India are the leading producers of Paracetamol bulk drug. However, most large producers are in USA. The major players in the world Paracetamol bulk drug market are :

* Hoechst Celanese Corp., USA
* Mallinckrodt, USA
* Rhone Poulenc, USA
* Sterling Organics, UK
* RTZ Chemicals, UK

0.4 INDIAN INDUSTRY STATUS

0.4.1 Market

Manufacture of Paracetamol, in India, started in the late 1960s. Till the late 1970s, the domestic consumption was hardly about 700-800 tonnes per annum. During this phase, 'Aspirin' and 'Analgin' were widely used as analgesic/antipyretic agents.

The domestic market for paracetamol has grown substantially in the last decade. The current (1992-93) domestic market for paracetamol has been estimated to be around 8000 tons. A growth rate of 10% per annum has been envisaged in the domestic consumption during the next decade, considering population growth, increasing urbanisation and increasing medical facilities in the rural areas.

The current export demand for paracetamol, which is about 2400 tons, is likely to grow at an average annual growth rate of 15%, considering the tremendous opportunities for exports.

Based on the above, demand for paracetamol has been estimated to reach about 12,850 MT and 22,900 MT by 1994-95 and 1999-2000 respectively.

0.4.2 Installed Capacity and Production

At present, there are more than 60 units, both in the orgnised and other sectors, in India, manufacturing paracetamol. The total installed capacity for paracetamol bulk drug manufacture in the country is about 18,000 tons per annum.

The domestic production of paracetamol has increased from about 580 MT in 1980-81 to almost 10,400 MT in 1992-93.

0.4.3 Exports and Imports

Exports of paracetamol have been reported in the last few years. Exports were made to Germany, United Kingdom, Malaysia, Bangladesh, Sri Lanka, etc.

The manufacturers are convinced that the quality of paracetamol produced by them meets international standards. Thus, they do not face major problems in exporting the products, at least as far as quality is concerned. India, reportedly, has an edge over China in terms of quality and Indian products command a premium over Chinese drugs.

The exports of paracetamol during 1992-93 from India were estimated to be about 2400 MT.

Exports of paracetamol is likely to grow at an average annual growth rate of 15% considering the tremendous scope that exists for export of paracetamol. However, this will be possible only if Indian producers can continue to compete with large international producers of paracetamol both on the price and quality fronts. Adoption of nitrobenzene route by few manufacturers abroad has already threatened manufacturers producing paracetamol by phenol/PNCB routes, as the former route has proved to be most cost-effective. The domestic industry must assess the strategic implications of the new technology and take necessary actions to meet such competition effectively.

Since 1989-90, no imports of paracetamol have taken place. This is due to the fact that a large manufacturing capacity already exists in the country. Further import of paracetamol seems unlikely in the future.

0.5 DOMESTIC TECHNOLOGY STATUS

0.5.1 Currently, paracetamol is being produced in India only by phenol and PNCB routes. Of these two routes, the PNCB route is more popular. The equipments are standardised. The end-product conforms to IP specifications. The end-product from few manufacturers conform to BP/USP specifications. Many companies have claimed that their product assay is consistently above 98%. It is, however, felt that some manufacturers do not have proper quality control checks. Their product quality may barely meet IP standards and may contain higher percentage of impurities.

0.5.2 The yield obtained by various domestic manufacturers varies widely (i.e. from 70% to 95%). The batch time for processing is also found to be varying significantly from unit to unit.

0.5.3 Research and development efforts by domestic manufacturers are concentrated on improving end-product quality, improving yield and reducing cost of production. R&D work to develop other routes, i.e. Nitro Benzene and PHAH, are insignificant, as of now. Exports are however underway to improve the situation.

0.5.4 The technology to manufacture paracetamol thought Phenol and PNCB routes is very well established and is available from indigenous sources. It seems that the technology based on these two routes has been absorbed quite well.

0.5.5 Paracetamol manufacture via Nitro Benzene route is yet to start in the country. Although some efforts in this direction were made, they have not been successful.

0.5.6 Except few quality control equipments, most of the equipments required for the manufacture of Paracetamol through Phenol and PNCB routes can be fabricated locally.

0.5.7 Continuous efforts are being made by domestic manufacturers to enhance process efficiencies and to reduce batch processing time. With these efforts, significant improvement in the process yields and considerable reduction in batch processing time has been reported by a few domestic manufacturers.

0.5.8 These improvements were made by incorporating sophisticated equipments, enhancing automation level in the process, using better quality raw materials and devising better plant and equipment layouts.

0.6 TECHNOLOGY GAPS

0.6.1 Several areas of technology gaps have been found to exist in the

Indian paracetamol industry. Gaps have been observed not only between the industry in India and abroad, but also within the various domestic units.

0.6.2 Technology Gaps within the Indian Paracetamol Industry

Various gaps within the domestic industry has been identified in several areas and are as follows.

TECHNOLOGY GAPS

WITHIN INDIAN PARACETAMOL INDUSTRY

Sr. No.	Area	Remarks
1.	Scale of operation	Plant capacity varies for 50-100 TPA to 700-1000 TPA, hence economies of scale also vary significantly.
2.	Yield and raw material consumption	Wide variations in the yield and raw materials consumption have been observed among the various units using the same route (i.e. 20-30% variation in case of phenol route and about 10-15% variation in case of PNCB route). These variations are due to type of equipments and controls employed, quality of raw materials used etc.
3.	Raw material quality	Quality of Phenol, PNCB, Activated Carbon and Hydrogen are not consistent and vary from source to source.
4.	Product quality	Variations in end-product quality have been observed among several units. Very few quality conscious manufacturers have put in an extra efforts to establish quality that conforms to IP, BP and USP standards.

Table Contd.

Table Contd.

Sr. No.	Area	Remarks
5.	Degree of Automation	Level of automation in various processing steps have been found to be differing significantly among the various units. Only a few better equipped units have a higher degree of automation (i.e. as high as 100%) in reaction, filtration and pulverisation sections. Majority of the units have either lower degree of automation or manually controlled process.
6.	Choice of equipments	Wide variations have been observed in the type of equipments employed for the same process step. Some domestic manufacturers use wooden vats while some use M.S. reactors. Some of the manufacturers do not get reactors properly designed and some purchase them second hand. In the case of filtration, some use conventional filter press, while some use sophisticated centrifuges and Neutsche filters. In the case of drying, some manufacturers use conventional tray dryers, while some use fluidized bed dryers, vacuum dryers. For separation and drying operations, some manufacturers have dedicated sets of equipment for each important process stage, whereas some of the manufacturers use the same equipments.

0.6.3 Technology Gaps Between Paracetamol Industry in India and Abroad

Several areas where gaps exist in the domestic paracetamol industry in comparison to the industry abroad have been identified as follows :

COMPARATIVE TECHNOLOGY STATUS ANALYSIS			
Sr. No.	Particulars	India	Abroad
1.	Use of Technology	Phenol and PNCB are the only routes established in India.	Apart from Phenol and PNCB, other routes such as Nitrobenzene route also is use.
2.	Scale of operation	Most units below 500 TPA capacity.	The average plant size is not less than 1500 TPA.
3.	Quality of inputs	Quality of inputs not consistent. Batch to batch variations have been reported. The desired quality of Nitro Benzene required in Nitro benzene Route to manufacturer paracetamol is not available indigenously. Also noble metal catalyst required in the process is not available indigenously.	Quality of inputs are fairly consistent. Desired quality of raw materials are available easily.
4.	End product quality	Majority of domestic manufacturers obtain fairly good and consistent quality, however few match the BP/USP standards which are quite stringent.	Quality standards have been adhered to strictly.
5.	Yield	Average yield obtained by domestic manufacturers is quite low compared to manufacturers abroad, because of lack of sophistication in each processing step, lower degree of automation etc.	Higher yields have been attained due to the use of sophisticated equipment and higher degree of automation.

Table Contd.

Table Contd.

COMPARATIVE TECHNOLOGY STATUS ANALYSIS			
Sr. No.	**Particulars**	**India**	**Abroad**
6.	Choice of equipment	Equipments used by majority of demestic manufacturers lack sophistication and have lower degree of automation. Some of the domestic manufacturers have installed second hand equipments having dimensions not suitable in their plant capacity.	Selection of equipments is done with great care. Use of sophisticated equipments with higher degree of automation to obtain higher yield and better end product quality.
7.	Plant layout	Majority of domestic units have set up plants without any proper layout designing and planning.	Plant layout is designed with great care considering various factors such as : * convenience in material handling and transport * better space utilisation * future expansion etc.

0.7 RECOMMENDATIONS

0.7.1 A review of the domestic paracetamol industry has indicated that the industry needs to attend to several important pertinent issues. Efforts should be made by the industry and research orgnaisations to upgrade the overall technological status of the industry. The following actions have been suggested to attain this objective.

A major thrust is required for the indigenous development of nitrobenzene route. The Central Electro Chemical Research

Institute (CECRI), Karaikudi has developed a laboratory scale process for the manufacture of paracetamol by electrolytic reduction of nitrobenzene.

Research and development efforts are required to develop the nitrobenzene route based on catalytic reduction of nitrobenzene. A research programme may be undertaken at National Laboratories for the development of necessary catalyst and catalyst regeneration technology.

- A task group to co-ordinate the R&D efforts in this area may be constituted with representatives of research bodies, like NCL, Pune; CDRI, Lucknow; IICT, Hyderabad; representatives of the Paracetamol industry and venture finance institutions.

- With a view to achieve more effective pollution control and cost reduction, research efforts should also be directed at creative utilisation of by-products. The following specific projects were suggested by the industry :

(i) Creative use of iron sludge for manufacture of pigments.

(ii) Development of membrane technology for recovery of paracetamol from the liquid residue.

(iii) Creative use of sodium sulphate, a tonne of which is produced for each tonne of paracetamol.

(iv) Creative use of dilute acetic acid which is another by-product produced in large quantities.

- Need for collective effluent treatment facilities for SSI units have been recognised by the State and Central Governments. Provisions of such facilities wherever feasible, has been encouraged through subsidies. The Paracetamol industry may consider the possibilities of setting up such common facilities, wherever feasible, and avail of the facilities provided by the Governments.

Industry must make efforts to enhance exports of paracetamol. To achieve this objective, industry should overcome certain constraints like stringent quality standards and stiff competition in the international market. The following actions are suggested to overcome these constraints :

(i) Awareness of GMP Standards

The industry must take it up as a mission to train manpower about GMP requirements, provide the requisite infrastructure

and manufacturing facilities and develop an overall quality assurance concept in the organisation. Very few companies realise that elaborate quality assurance and GMP procedures do not really cost much. In order to develop a particular culture and operating method in the plant, the prime requisites are time, efforts and energy. To be internationally competitive, however, both in quality and consistency, GMP awareness must improve.

(ii) Formation of Common "Regulatory Affairs Group" by the Industry

The second major constraint in respect of export of paracetamol bulk drug to many countries, are the formalities of registration/ approval. Each country has certain rules and regulations of registration for pharmaceutical imports and marketing. These formalities involve substantial paper work, record keeping, documentation and sometimes also approval of manufacturing facilities. Such a task may not be feasible for most manufacturers as most of them are operating in the small scale sector. Hence, collective efforts are required by the industry to develop a separate "Regulatory Affairs Group" to handle all regulatory registration aspects.

(iii) Bring About Cost Competitiveness

In order to counter tough competition from other countries like China and Taiwan, the domestic producers need to strive hard to be cost competitive. This is rather difficult in the present type of industry set-up. Most plants are small sized and hence cannot attain better economies of scale. In future, it may be necessary to set up large export oriented units based on continuous process (like Nitro benzene route) for paracetamol manufacture and export.

New capacities may be encouraged through either by expansion or by large size plants to attain better capacity utilisation levels and economies of scale.

Industry must pay proper attention and take suitable steps towards improving safety levels in the plant. Industry should orgnise seminars and training programmes to bring about awareness of various safety aspects.