EXECUTIVE SUMMARY

1. Products

Product(s) : Ampicillin Anhydrous, Trihydrate & Sodium.

Use : Ampicillin is a broad spectrum Antibiotics.

2. Demand and Production

(Tonne)

Market Size	1990-91			1996-97 (Estimated Demand)
	Demand* Tonne	Indigenous Production	Imports	
- 6-APA	500	500	NIL	760
- Ampicillin	750	750	NIL	1097
- Ampicillin Sodium	80	N.A.	N.A.	167

* Includes Export Demand

Indigenous Availability

- 6-APA : A large number of plants have been set up. Import is not required. Self sufficiency is achieved.

- Ampicillin : A large number of plants have been set up. Import is not required. Self sufficiency is achieved.

- Ampicillin Sodium : Indigenous production reported. Production is believed to be small but growing.

3. Manufacturing Process

- 6-APA : Chemical Process and Enzymatic Process

At present, enzymatic process is superior and economical. It is likely to remain so in

the future unless major technical advances occur for the chemical process.

- Ampicillin : Acid Chloride Process and Danes' Salt Process.

  Presently acid chloride process is universally preferred. New advances in Dane's Salt Process are reported. However it requires chemicals which are suspected carcinogens.

4. Raw Materials

Major raw materials required are Potassium Penicillin, Enzymes and D(-) Alpha Phenyl Glycine Chloride Hydrochloride. These raw materials account for more than 65% of manufacturing cost.

5. Advances and Current Research

The process are well standardized. Research can be broadly classified as :

A. Operational Research :
   (a) To improve efficiency of conversion by various means like fine tuning operating parameters, use of newer chemicals, etc.
   (b) Reduction in Residence Time.
   (c) To develop better enzymes and research on immobilized living cells.

B. Fundamental Research :
   (a) Enhance the effectiveness of ampicillin by combining with substances like Clavulanic Acid.
   (b) Use of Genetic Engineering Technology.

6. Indigenous Capability

Manufacturing : Self sufficiency is largely established except for Sodium Ampicillin. Technology for both 6-APA and Ampicillin is indigenously

available. Technology may not compare with the best in the world but is good enough.

Raw Materials	:	Major raw materials are not fully indigenously available.
Enzymes	:	Recently HAL/NCL has developed immobilized enzymes. But they require perfection. Fermetapharma Biodil has set-up an enzyme manufacturing plant.
Research :		
(a) Operational	:	Quite good but not enough efforts applied.
(b) Fundamental	:	Weak.

7. Recommended Measures

Import of Technology	:	Technology for sodium ampicillin may require import. Otherwise technology import is not necessary unless new developments take place.
Manufacturing	:	Efficiencies are on lower side in many plants. Especially enzyme efficiencies require improvement. Research in this direction is essential.
Raw Materials	:	A major weakness. Intensive efforts required to develop indigenous, efficient production.
Enzymes of Biotechnology	:	Recent efforts are not sufficient. Dawn of new era of biotechnology must compel us to enhance our research efforts tremendously in this field. Discussions between the Government, research institutions and industry must lead to defining new relationship, more commitment on the part of all of us to initiate and support the research effort.
Medical Research	:	Research in the area of antibiotics is extremely insufficient. A major thrust is necessary.

8. Introduction

Ampicillin is an antibiotic drug. It is effective against gram positive and gram negative bacteria. It is a semi synthetic Penicillin derived from penicillin. Its major advantage over penicillin is its broader spectrum of activity.

Ampicillin is used in gastrointestinal tract infection, genitourinary tract infection, meningitis, respiratory tract infection, septicemia and soft tissue infection. It is a drug of first choice against streptococcus faecalis (bilial tract and intestinal infections), Haemophilus influenzae (respiratory tract infections) and proteus mirabilis (urinary tract infection).

Ampicillin is available in three different forms, viz., ampicillin trihydrate, ampicillin anhydrous and ampicillin sodium. Ampicillin trihydrate is the most widely used form. It is taken orally and is stable in acid environment. Ampicillin sodium is given as an injection. It does have minor side effects or allergic reaction like skin rashes, irritation of mouth and tongue, nausea, vomitting, etc. Specifications for quality of ampicillin are laid down in Indian Pharmacopoeia (1985).

9. Process for Manufacture

Ampicillin is manufactured from penicillin in two steps. In first step 6-amino penicillanic acid is produced from penicillin G/V. While in second step 6-amino penicillanic acid is converted to ampicillin trihydrate.

10. First Step of Manufacture

6-Amino penicillanic acid (6-APA) can be manufactured either by enzymatic process or by chemical process. At present both processes are industrially employed.

11. Enzymatic Process

Immobilized enzymes are used to deacylate penicillin molecule. An enzymatic reactor can either be a fixed bed reactor or a continuously stirred tank reactor. Raw material can either be potassium salt of pencillin-G or potassium salt of penicillin V. Both raw materials have been industrially used. The product from reactor is filtered and crystallized. Crystals of 6-APA are washed with suitable solvents and then dried and packed.

12. Second Step of Manufacture

Process for the manufacture of ampicillin trihydrate from 6-APA is either based on using D(-) alpha phenyl glycine chloride hydrochloride or D(-)

alpha phenylo glycine Dane's Salt. However at present acid chloride method has become the standard.

6-APA is silylated in the presence of a catalyst in suitable solvent. Silylated 6-APA is condensed with D(-) alpha-phenylo glycine chloride hydrochloride in presence of a base. The aqueous layer is hydrolysed with alkali solution. Ampicillin trihydrate crystals are formed, is centrifuged, washed with suitable solvents and then dried at 40°C.

Ampicillin anhydrous is made by dissolving ampicillin trihydrate in a suitable solvent (e.g. is proply alcohol) and crystallizing ampicillin anhydrous.

For making ampicillin sodium, sodium hydrozide solution is added to the ampicillin trihydrate. The solution is filtered and distributed in lyophilizators. Dried powder of ampicillin sodium is sieved and packed.

13. Historical Development

Ampicillin was first discovered in 1961. However it was only in 1965, the first commercial process was developed.

Penicillin, the first antibiotic, was discovered in 1929. In 1940, a commercial process for its manufacture was developed. Its shortcomings, like its narrow range of spectrum, resistance developed by pathogenic bacteria, allergic side reactions, soon became apparent.

6-APA, the central molecule of penicillin was first isolated in 1950. It was in 1959 that a viable process for its manufacture was developed. It was also discovered that by substituting the side chain of penicillin by amino group, its effectiveness against gram negative bacteria is substantially enhanced. It was then, that ampicillin was discovered. Later on more such semi synthetic Penicillins, like amoxycillin, have been discovered.

In 1965 the first commercial process, using Dane's Salt, was established. Initially the efficiencies were low. In 1973 the acid chloride process was established. Today the acid chloride process has become a standard.

Soluble enzymes were used for the manufacture of 6-APA. Efficiency was low and the production cost was high. Later, a chemical process was developed. It was sturdier and more efficient. Howere, it required handling of many hazardous chemicals. Immobilization of enzymes was first reported in 1969. Its use made enzymatic process very attractive as the production cost came down and the process became simpler.

Today enzymatic process based on immobilised enyzmes has become a standard.

14. State of Art Technology and Current Research Areas

Processes for the manufacture of 6-APA and ampicillin are now well standardised. Enzymatic process for 6-APA manufacture and acid chloride method for manufacture for ampicillin are used at most places. Chemical process for 6-APA is also employed. However that route is not preferred due to its many disadvantages.

In the enzymatic process, the reactor efficiency of 97% and recovery efficiency of 91-93% are considered good. Any one of the variety of immobilized enzymes are used. All are considered good though some may be more sturdy to varying operating parameters. Both fixed bed and continuous stirred tank reactors can be used. For smaller plant capacity, continuous stirred tank reactors are preferred. Research is going on to find better enzymes and enzyme supports. Immobilization of whole cells is also being tried, though commercial scale production is not yet established. Fluidized reactors are also under investigation.

For the post enzymatic reactor operations, solvents, solvent recovery etc. are all well established. However recovery of second crop of 6-APA is practiced at some places only. Good plants are highly automated and use sophisticated instruments. These give better control on efficiency and product quality. 97% assay is considered good. However Meiji Seika of Japan guarantees even 99% assay (though its cost could not be ascertained).

Chemical process for the manufacture of 6-APA is also used, even by the best companies. They give higher efficiencies than enzymatic process. Process is also sturdier as it is not as sensitive to the quality of penicillin raw material. Overall efficiencies of 90% can be achieved. However, currently, enzymatic process is deemed superior to chemical process. Chemical process requires much higher investment, has much higher land requirement, involves handling of many hazardous chemicals, generates toxic waste. As against that, enzymatic process does not require large investment, has less land requirement, does not involve handling of hazardous chemicals and does not gnerate toxic waste. Thus, though chemical process is sturdier, is less sensitive to operating parameters and more efficient, overall, its shortcomings outweigh its advantages.

For ampicillin, efficiencies of conversion of 1.65 kg. per kg. of 6-APA, are standard. It is reported that conversion efficiency of 1.70 has been achieved

at certain plants abraod. Good plants are completely automated and are closed circuit process and can give consistent quality of 99% assay and more. Cost of a good plant could be about Rs.20 million for a 100 TPA plant. Presently research is going on to improve the conversion efficiency and minimise the batch time. Work on finding better sylylating agents is one area of research.

Combining ampicillin with enzyme inhibitor like calvulanic acid for the drug formulation has been reported. Research is also centred on direct enzymatic manufacture of ampicillin.

15. Structure of Indian Industry

Indian drug industry is well developed for the manufacture of many bulk drugs and ampicillin is one of them. At present India is self sufficient and technologically at par with the best in the world.

Indian ampicillin industry is unitwise small and in fact many units are in small scale sector. These small units also manufacture other drugs in the same plant. Almost 55% of the domestic production is contributed by small scale units. Production during 1990-91 was reported to be 750 tons. Imports are almost nil. Exports of about 250 TPA are reported. Demand has been growing at 6-10% per annum. Demand is expected to grow at 6% per annum to 1097 tonnes in 1996-97. Apart from this, ampicillin sodium, whose manufacture has only recently started, is having expected demand of 80 tonnes in 1990-91. Its demand is expected to grow to 167 tonnes by 1996-97. But the working group on Drugs and Pharmaceuticals for the 8th Five Year Plan has, however keeping in view the factor of obsolescence and substitutability, estimated this demand to be only 694 TPA.

Major units for the manufacture of ampicillin are Ranbaxy (production 100 TPA), Gujarat Lyka Organics (production 50-60 TPA), Lawande Pharmaceuticals, Cepham Laboratories, Pharma Chem, Kopran Chemicals, Cadila Laboratories, and Armor Chemicals. Most units are in northern and western India. Capacity of many small units is in the range of 10-25 TPA per unit.

Many ampicillin manufacturing units make their own 6-APA. As late as 1985, large quantity of 6-APA was imported. However at present sufficient manufacturing capacity for 6-APA has been established. Two large plants, Max India (100 TPA) and Gujarat Lyka Organics (35 TPA) have been well established. Besides, quite a few ampicillin manufacturers have started manufacturing 6-APA for their own cative consumption. It is observed that they have been quite successful, though not as efficient. Present domestic

production capapcity exceeds 1000 TPA, sufficient for present domestic needs. Most plants are based on enzymatic process. Enzyme was imported till recently.

16. Technology Status of Indian Industry

For this section, industry can be broadly divided in two groups : manufacture of 6-APA and manufacture of ampicillin from 6-APA.

For the manufacture of ampicillin, Indian technical ability is well developed. The industry can manufacture a quality product, comparable to international standards. There are no major technology gaps.

Manufacture of ampicillin in India started in late 1970s. Alembic chemicals, Cepham Organics and Ranbaxy Laboratories started production based on indigenous in house development of technology. Meanwhile HAL started manufacturing ampicillin, based on a foreign collaboration with American Home Products. IDPL also entered into a foreign collaboration with Farmfin, Italy. However, major growth took place due to diffusion of technology. Today almost 90% of production comes from units which have no foreign collaboration. And these units are producing quality product, which are even being exported.

One major undeveloped area is the supply of raw materials. Two major raw materials (Constituting about 80% of total manufacturing cost) are 6-APA and D(-) alpha phenyl glycine chloride hydrochloride. 6-APA is being manufactured in India but is costly. While India has no manufacturing base for the acid chloride.

Besides, most plants lack sophisticated instruments and close loop control. However that is just a matter of economy. Though good research laboratories have been set up, innovative research is lacking. Thus, for example, now a new economic process, based on Dane's Salt is reported from abroad and new silylating agents have also been reported. However Indian research has not reached such a level.

For the manufacture of 6-APA, India has attained the technical capability. Sufficient capacity is established to meet the indigenous demand. There are two large plants, two medium sized plants and many small plants. Basic design is known. Local Consultants supply the know-how. Plant and machinery is available within the country.

Some of the raw materials, like penicillin and enzymes have to be imported. Plants are not as well designed as the best in the world. However good quality 6-APA is being produced.

First 6-APA plant was established by IDPL in 1981 in technical collaboration with Farmfin, Italy, Later two plants with foreign collaboration viz. Max India and Gujarat Lyka Organics were set up. Simultaneously HAL set up a plant with self designed and produced immobilized enzymes. Since then many units have set up 6-APA plants.

Most plants are based on enzymatic process. Max India plant has been steadily improving and is reported to have achieved about 85% conversion efficiencies. Most small units have efficiency of around 75%. Enzymatic process is easy to set up but difficult to fully absorb. It is expected to take another 3-5 years before good understanding and control is achieved. However the fact is that, just like ampicillin, the technology is expected to be well diffused.

Ampicillin sodium is manufactured in India in small quantity by very few companies. These few companies have claimed to have developed the process know-how indigenously.

17. Conclusions and Recommendations

Conclusions

Self sufficiency in ampicillin manufacture from 6-APA is achieved. Production is expected to be around 850 tonnes in 1991-92. Growth rate is expected to be 6% per year for next few years for domestic demand and 15% per year for export demand.

Ampicillin manufacture is open to all sectors. Public sector, large private units and small scale sector all contribute to the production. There are about 38 plants. Small scale sector accounts for more than 50% of the total output. Ranbaxy Laboratoreis Ltd. is the largest manufacturer, accounting for more than 100 TPA output. Gujarat Lyka Organics, Cepham Laboratories, Armour Chemicals are some other big units.

Ampicillin sodium has been indigenously manufactured only since last year.

For 6-APA manufacture also, sufficient capacity is established. Two large manufacturers and several others produce full requirement of 6-APA.

Technologically, India is at par with the world in ampicillin manufacture. For 6-APA, technology has been imported by few plants. However, today, technology for enzymatic process is available in India.

There are certain raw materials which are being imported. These include Penicillin, enzymes and compounds of D(-) alpha phenyl glycine.

Recommendations

At present stage of knowledge worldwide, no technology import for either ampicillin or 6-APA is necessary. Technologically there doesn't seem to be any need for foreign know-how. However if there is any significant new development abroad, and such development are not forthcoming to India, such development may be considered for evaluation.

Raw materials constitute a major share of the total manufacturing cost. A large quantity of raw materials are being imported. Three major raw materials being imported are :

(a) Penicillin G/V.
(b) Enzymes.
(c) D(-) alpha phenyl glycine chloride hydrochloride.

Manufacturing capacity of pencillin G is neither adequate nor efficient. Efficiency of producing penicillin is most important. Immediate steps should be taken to improve efficiency of penicillin production. The quality of penicillin G is an important factor for conversion of penicillin G to 6-APA by microbial route. The residual solvent in penicillin G is one of the factors for biocatalyst poisoning. The actual deficiency of indigenous penicillin G may be identified and steps taken to improve the quality so that indigenous penicillin G can be successfully used for the bio-conversion. Ability to manufacture immobilized enzymes is only recently established in two units and not yet proven elsewhere. Technology is non-existent for D(-) alpha phenyl glycine chloride hydrochloride, though three units have been reportedly trying to establish its manufacture.

A major thrust is required for the development of enzyme technology and bio-technology. This is an area where a major technical advance is expected in the future which may immensely benefit the mankind. Research in this area is a sporadic effort. A sustained effort is essential.

There is so much advance in the field of drug research worldwide that the Indian companies seem to be lagging in terms of latest technology. Today they are just entering an era of cephalosporins when fourth and fifth generation cephalosporins are researched. It is very difficult for individual units to have a large research base. National Laboratories could establish active, sustained research activity. These laboratories could play a more active role.