EXECUTIVE SUMMARY

0.1 PRODUCTS

0.1.1 Penicillins are antibiotic substances belonging to the family of related substances having various side-chains fused to a ß-lactam thiazolidine ring system. These are powerful anti-microbial substances extensively used in the treatment of many infectious diseases. Of these, penicillin-G and penicillin-V are the two penicillins that were produced by submerged aerobic fermentation techniques for the first time in the pharmaceutical industry in 1944, opening "the antibiotic era".

0.1.2 From the large-scale fermentation point of view, only pencillin-G which has the benzyl side-chain and penicillin-V, which has the phenoxymethyl side-chain are of importance. Penicillin-G and penicillin-V are produced by a highly aerobic submerged fermentation process, using carefully selected strains of the mold Penicillium Chrysogenum Thom., under aseptic conditions. The process and technology for both are the same, except for the use of precursor side chain phenylacetic acid in the case of penicillin-G and phenoxy acetic acid in the case of penicillin-V. Both these penicillins can be manufactured in the same plant.

Though Penicillin G and V are still important pharmaceutical drugs for the treatment of various infectious diseases, their use as drugs is decreasing, since the newer semisynthetic penicillins and cephalosporins are being used more and more. Therefore, the future demand for Penicillin G/V will be mainly as raw materials for the manufacture of 6-APA, 7-ADCA and 7-ACA, the demand for which is steadily increasing.

0.2 PROCESS

0.2.1 The process consists of preparing the inoculum from the stock culture of the special strain of the organism, increase the quantum of the biomass (vegetative culture) in a germinator (which has usually 8 to 10% volume of the fermentation medium), then transfer it to the medium in the fermentor proper for fermentation under properly controlled environmental conditions by feeding various nutrients, additives for pH control, addition of the precursor solution at a proper

rate, etc., and then harvest the broth at the end of the fermentation cycle, which is around 120 to 140 hours in the short cycle system or 180-240 hours in extended cycle system. The harvested broth then goes through the recovery process. All the four Indian penicillin manufacturing companies still follow more or less the same conventional recovery process, namely first filtering the broth, extracting the penicillin with a solvent (butyl acetate at acidic pH), the penicillin from the "rich solvent solution" next transferred back to aqueous phase as "aqueous rich extract", purification with active carbon treatment followed by butanol addition and azeotropic distillation, crystallisation, filtration and drying of the first crystals.

0.3 DEVELOPMENTS

0.3.1 The process mainly consists of three important stages: (i) a proper high yielding strain selection and preparing stock cultures, (ii) fermentation proper, and (iii) the recovery process. The economics of the entire process depends upon the efficiency in each of these three stages and hence the entire technological development that have taken place all these four decades from 1944, centre around these three stages. Major breakthroughs in all these three areas have taken place in the period 1973 to 1976, the impact of which is now exploited successfully by most of the international manufacturers.

0.3.2 Initially in the forties, when the penicillin technology was developed, these strains were giving very low yields of 10 to 20 units per ml. These strains were steadily improved to yield nearly 30,000 to 36,000 units per ml. of the broth during extended cycle of nearly 200 hours by 1973-76 period. By 1986-87 various international manufacturers have started using strains yielding about 60,000 units per ml of broth in 200 hours cycle. Of late some of the International manufacturers have started using strains of 80,000 units/ml. with improved cycle time.

0.3.3 In fermentation proper also from the original small fermentors of 5,000 to 10,000 litres, most of the manufacturers have gone to more than 200,000 litres size fermentors. Along with the increase in size of the fermentors, the in-depth knowledge on the importance of control of environment in the fermentors by evolving a good regime of nutrient feeds, understanding of biosynthetic mechanisms, etc.

many major manufacturers have developed sophisticated instrumentation for analysis and control of the fermentation conditions interlinked with computerised process control system. These developments have resulted in not only improving the yields, but also reduced the manufacturing costs considerably.

0.3.4 In the area of recovery of the product from the fermented broth also considerable developments took place over the last fifteen years. They not only helped in increasing the overall recovery from 60% to nearly 92%, but also in reducing many steps in the recovery process, which again has helped in the economics of the manufacture. More active R&D work is in progress for still higher recoveries.

0.3.5 Thus, in all these three areas of the technology, tremendous developments have taken place during the last 15 years leading to the Penicillin-G prices coming down significantly, in spite of cost of many of the inputs going up very much. The total penicillin-G and V bulk production in the world is estimated to be 15,000 tons (24000 MMU) in 1985-86, with a projection of 17,700 tons (28000 MMU) for 1990 and 27,000 tons (43000 MMU) by 2000 A.D. Penicillin-G is the world's largest produced antibiotic by fermentation process and is expected to remain so for a long time.

0.4 STATUS OF PRODUCTION AND TECHNOLOGY IN INDIA

0.4.1 India's demand for penicillin-G is also going up steadily both for pharmaceutical formulations and also for its use as the raw material for 6-APA and 7-ADCA. The projected demand up to the end of the Year 2000 A.D. is given in Table 5. Penicillin-V has only a limited growth. The present need of penicillin V is around 20 to 30 MMU per annum. However, in the opinion of some of the foreign experts as in Novo, the Penicillin V prices are coming down in line with Penicillin G price. The enzyme for conversion of Penicillin V to 6-APA/7-ADCA is remaining quite costly and hence Penicillin G still will remain the preferred raw material.

0.4.2 As compared to the world's production of about 15,000 tonne (24000 MMU), the licensed capacity, actual production and imported quantity in India for seven years from 1982 are given in table 1.

Table 1 : **Production & Import of Penicillin***

Year	*Licenced Capacity (MMU)*	*Actual Production (MMU)*	*Imported** Quantity (MMU)*
1982-83	637	424	2.57
1983-84	637	435	16.22
1984-85	637	402	81.92
1985-86	891	521	281.92
1986-87	891	541	196.60
1987-88	891	509	379.90
1988-89	891	661	651.40

All the present manufacturers have now been permitted to increase their capacity to 1000 MMU.

* Data collected by the study Team.
** SRC Bulletin.
Central statistical organisation report.

The indigenous production during 1984-85 has reduced due to import of penicillin-G and even penicillin-V to some extent by the 6-APA manufacturers, who have been permitted to use 60% of the imported penicillin-G because the indigenous penicillin-G is costlier by more than 100%. This aspect has to be considered carefully, when deciding about the country's demand for different penicillins and licensing new capacities.

0.4.3 There are four Indian manufacturers for penicillin-G and they are:

i) Hindustan Antibiotics Ltd., (H.A.L.) Pimpri, Pune (Maharashtra) — Public Sector

ii) Indian Drugs & Pharmaceuticals Ltd., (I.D.P.L.) Virbhadra, Rishikesh (U.P.) — Public Sector

iii) Alembic Chemical Works Co. Ltd., Baroda (Gujarat) — Private Sector

iv) Standard Pharmaceuticals Ltd., Serampur (West Bengal) — Private Sector

H.A.L. and Alembic Chemical Works manufacture penicilin-V also in the same plant.

0.4.4 They are all now producing a total of about 660 MMU of penicillin-G per year. Penicillin-V production is between 20 and 30 MMU per year according to the market needs.

0.4.5 Hindustan Antibiotics Ltd. (H.A.L.) acquired their technology and the strain in 1954 from W.H.O. with the aid of U.N.I.C.E.F. Licensed capacity was increased to 200 MMU per annum in collaboration with M/s. Toyo Jozo Co., Japan in 1976. The strain is yielding an average of 36,000 units/ml. As they are the members of Panlab International, U.S.A., they have received four strains capable of yielding more than 50,000 units/ml. On the product recovery side, they are using the routine extraction process and have about 70% overall product recovery. They manufacture 15-20 MMU of penicillin-V also per annum. Their present licensed capacity is 1000 MMU/Annum.

0.4.6 The Indian Drugs & Pharmaceuticals Ltd. (I.D.P.L.) acquired their technology from U.S.S.R. in 1967. The strain used by them originally was not giving yield equivalent to that of H.A.L. and so recently they have acquired the high yielding strain from H.A.L. The performance appears to be around a yield of 30,000 to 35,000 units/ml. The overall recovery of the final product also appears to be around 70 to 75%. Their licensed capacity of 414 MMU per annum is now increased to 1000 MMU per annum.

0.4.7 The Alembic Chemical Works Co. Ltd. acquired their high yielding strain in 1979 from M/s. Meiji Seiko Kaisha Ltd., Japan. They have to their credit development mostly through their own R&D efforts. They have been active in development of penicillin-V technology and manufacture nearly 15 to 20 MMU per annum. Their licensed capacity has increased to 1000 MMU per annum.

0.4.8 Standard Pharmaceuticals Ltd., which was acquired by M/s. Synbiotics Ltd., Baroda (a company of the Sarabhai Group) got their penicillin know-how and the strain from M/s. E.R. Squibb & Sons, U.S.A. Their yield is also around 36,000 units/ml. with an overall recovery of 65-70%. Their licensed capacity of 147 MMU per annum is now increased to 1000 MMU per annum.

0.4.9 Pencillin G/V manufacturing was opened to private sector from the year 1986 and new licenses have been given to private companies with foreign collaboration, as detailed in Annexure III.

0.5 IN-HOUSE R&D

0.5.1 All the four Indian manufacturers do have small R&D set up. H.A.L. and I.D.P.L. have relatively larger R&D set up both by way of financial outlay and physical facilities. All the R&D set up have the same objectives. They are: (i) improving the strain, (ii) indigenisation and proper absorption of the acquired technology, (iii) improvement of fermentation technology, and (iv) improving the product recovery by modifying the extraction procedures.

0.5.2 They all appear to have succeeded in indigenisation of the acquired technology with very little progress in strain improvement, fermentation proper and product recovery system.

0.6 IMPORTS/EXPORTS

0.6.1 The production of 6-APA is around 250 tons in 1985-86 and is likely to grow at 10-15% per annum. Nearly 180 tonne of penicillin-G is considered to have been imported by the 6-APA manufacturers in 1985-86. The projected demand for 6-APA and 7-ADCA/7-ACA by 1990 is 385.5 tonne and 65.2 tonne respectively, with the corresponding total demand of 1525 MMU for penicillin G as a raw material. Regarding exports, since the indigenous price is high, it is not feasible to consider exports of penicillin-G or V even with the present incentives available. Small amounts of formulated penicillin-G products are said to have been exported to Middle East and East African markets.

0.7 RECOMMENDATIONS

0.7.1 Injection of new technology with high yielding strains is an urgent necessity for the four existing units and also for the new units.

0.7.2 Having obtained the new technology and the high yielding strains, the Indian manufacturers should not stop at just absorbing the technology, but should maintain a continuous and concentrated in-house R&D efforts to keep pace with the growth of the technology and improved strains abroad. They must even try to overtake them to gain the lead to acquire a large share of the international market.

0.7.3 For this, it will be advisable not only to use their own limited R&D facilities, but also sponsor specific R&D programmes, particularly for the development of high yielding strains to some of the National Laboratories which are having more sophisticated facilities. A cooperative effort with pooling of resources can yield better results.

0.7.4 Modernisation of the instrumentation systems for the feed-batch fermentation along with computerised process control systems will be essential particularly when the companies start working with higher yielding organisms and larger size fermentors.

0.7.5 Modernisation and proper modifications in the product recovery area is also very urgent. From the present average of 70% overall recovery of the product, a 90% recovery must be achieved quickly. The financial constraints appear to be the main factor for the present manufacturers in implementing improvements in this area.

0.7.6 The wastes from penicillin plants have enormously rich biomass. Instead of processing them in the conventional way at high expenditure, efforts should be made to recover important enzymes and valuable biochemicals from them and also to train the biogas organisms to utilise this biomass to convert it into biogas for energy production. R&D work in these areas is worth considering.

0.7.7 To meet the increased demand projections, Government has already permitted increase in capacities of the existing units and issued new licenses to nine private parties for a capacity of 1000 MMU/annum each. Since the project cost is about Rs. 50 crores for each of the new unit, it can be expected that 2-3 units may impliment the projects with in next 4-5 years. To avoid heavy foreign exchange outflow for the import of Penicillin G/V and capital goods, a cell may be set up to monitor the project execution in time.

0.7.8 The major use of penicillin-G is, as raw material for 6-APA manufacture and since many of the major 6-APA manufacturers complain that the indignous penicillin-G is not pure enough to suit the quality required for their enzymatic process of converting penicillin-G to 6-APA, there is an urgent need to constitute a committee of experts to examine this important problems facing the indigenous production of penicillin-G.

0.7.9 For giving a quick benefit to the existing units to reduce the cost of production of penicillin which is an essential drug, the following could be considered:

i) Providing sugar at levy prices to the present Indian manufacturing units.

ii) Providing electricity at subsidised rate.

iii) Giving reduction in excise duty/import custom duty on the solvents, precursor materials (phenylacetate and phenoxy acetate), and capital goods import.

The above factors can help to bring down the price of indigenous penicillin by nearly 25% since these elements are the major input costs for the Indian mnufacturers.

0.7.10 In view that 1000 MMU/annum penicillin G project is highly capital intensive, involving more time, a capacity of 200 MMU/annum is suggested, for the captive users manufacturing 6-APA/7-ADCA. This will involve less capital expenditure and can be implemented early.