EXECUTIVE SUMMARY

1.0 PRODUCTS

Streptomycin and Rifampicin are potent antibiotic drugs. Streptomycin is broad spectrum drug effective against both gram positive and gram negative bacteria. However, its major use is as an anti-TB drug. Rifampicin also is used extensively as an anti-TB drug but it is also used in treatment of leprosy. As both the diseases are rampant in India, their importance can not be over emphasized.

Streptomycin is available in its sulphate form. It is poorly absorbed from the gut and hence is normally available in injection form. Normal dose is 0.5 to 1.0 gm of the base, given daily. Streptomycin is normally given along with other anti-TB drugs. Streptomycin is especially useful during initial phase of a therapy as it is very effective against rapidly multiplying bacilli.

Rifampicin belongs to napthoquinol ansamycins known as ansamacrolides. It is an antibiotic characterised by an aliphatic bridge connecting two non-adjacent position of an aromatic nucleus. It possesses a chemical structure completely different from those of other known antibiotics. It consists of an aromatic moiety of the napthoquinone type with a long aliphatic chain spanning the aromatic system. Unlike most antibiotics which show a striking loss of activity when their chemical structure is changed even within narrow limits, rifamycin (the group to which rifampicin belongs) appear to have a common skeleton which tolerates series of substitution without losing its antimicrobial properties.

Rifampicin is a bactericidal drug and is a first line drug used in treatment of tuberculosis and leprosy. Its possesses the ability to eliminate semi-dormant or persisting organism.

2.0 MANUFACTURE

Streptomycin is manufactured by fermentation process. The process comprises three major steps :

1. Inoculum preparation.
2. Fermentation.
3. Extraction, recovery and purification.

Streptomycin griseus is the micro-organism whose strain is used for the purpose of manufacturing streptomycin. First step is the preparation of inoculum from the stock culture of the strain. The inoculum is transferred to a germinator, where total quantity of biomass is increased. This biomass is sent to the first of a series of fermentors in which medium has been introduced. Fermentation process is an aerobic submerged type fermentation. Sterile air is introduced through spargers. Fermentation takes place in controlled environment with suitable media ingredients consisting of carbohydrates, soybean flour, corn steep liquor, sodium sulphate etc. Other chemicals like antifoaming agents are also added. Fermentation usually takes about 200 hours.

Broth, after harvest, is filtered, diluted and passed through Ion Exchange Resin columns where streptomycin is adsorbed. Streptomycin is eluted from resin column as streptomycin sulphate. It is further treated with sodium hypochlorite, EDTA, activated carbon and de-ashed in resin column to remove impurities.

Purified streptomycin sulphate solution is concentrated under vacuum and dried under aseptic conditions.

3.0 DEVELOPMENTS

The research efforts directed exclusively towards streptomycin are meagre since 1970. Since research requires sustained commitment of money and manpower, major developments for any antibiotic have come from advanced countries. With negligible requirement, production has stopped in these countries and so have the research efforts

However, major development did take place in first two decades of its discovery.

Strain Selection

At the beginning in 1940s, strains were of very poor quality and yields were about 50 units per ml of broth. These strains were steadily improved to give yields of as high as 25,000 units per ml. Yields of 16-18000 units per ml became common. Further research could have yielded higher potency as in the case of penicillin.

Second major area was development of strains where no streptomycin-B is produced. Streptomycin-B is an undesirable product. If present, it could lower overall efficiency by 10-15% and increase the cost of production.

Fermentation

Fermentor size has increased substantially making larger batches possible. Material of construction has improved. Close loop process control and complete automation have resulted in finer control and reduction in number of batches lost. Process time has reduced by more than 50 % and media quality has improved. All these have helped in improving the yields and in reducing the manufacturing costs.

Extraction & Recovery

Major changes have taken place, Ion exchange resin columns have replaced traditional solvent extraction. Number of steps have been reduced and savings made in expensive solvents. Extraction efficiency of upto 10% have been achieved.

World Production Status

All the above developments took place before 1970. World production has considerably reduced since then. Presently, People's Republic of China and India are the leading manufacturers in the world .

4.0 STATUS OF PRODUCTION AND TECHNOLOGY IN INDIA :

4.1 India, today, is a major producer of streptomycin. (Production has almost stopped in all the major developed countries). Indigenous demand is fully met from indigenous supply.

4.2 Actual production for the last few years is reproduced below :

Year	Licensed capacity tonne	Production tonne
1983-84	425	238
1984-85	425	235
1985-86	425	188
1986-87	425	203
1987-88	425	248
1988-89	425	244

Consumption has stagnated and is likely to decline in years to come. There is a considerable export market. However, Indian price of about Rs.1100 per kg. is way above the international price. More potent drugs like rifampicin which are now available, are likely reduce the demand for streptomycin. Even most optimistic scenario (assuming no major further development) puts the demand for streptomycin at no more than about 300 tonne in 1995. Conversely, demand could be as low as 85 tpa in 1995. Thus, there is little incentive for further research and development. Major manufacturers in India are:

1. Hindustan Antibiotics Limited, Pune, (HAL)
2. Indian Drugs and Pharmaceutical Limited, Rishikesh (IDPL)
3. Synbiotics Ltd., Baroda (SL)

Out of the above companies, only HAL and SL are major producers. Both plants are based on foreign technologies and are quite old.

No major and substantial research has emerged in India. Other than manufacturers, there are hardly any organizations engaged in research in streptomycin. Manufacturers have done considerable work. This work though not fundamental in any sense, has helped reduce the cost of

manufacture by replacing costly inputs by cheaper inputs. On the whole, technology at SL appears to be better than that at HAL.

5.0 PROCESS DESCRIPTION

Manufacturing process of rifampicin consists of two stages, viz :

i) Fermentation of *Nocardia mediterranei* (a micro-organism) to yield rifamycin B;

ii) Synthesis of rifamycin-B to rifamycin-O to rifamycin-S to rifamycin SV to rifampicin.

5.1 Fermentation

Fermentation is carried out using a mutant micro- organism of *Nocardia mediterranei* under aseptic conditions. The micro-organism is grown by feeding the nutrient media. The whole fermentation cycle is completed in 160 to 200 hours. Rifamycin-B is separated from the mycelium by extraction and filteration. In general, industrial fermentation technology is very difficult to master. Rifamycin fermentation is even more difficult and complex since the behaviour of the micro-organism could not be fully understood nor have all the conditions been identified which would give an optimum yield.

5.2 Synthesis

Rifamycin B, in presence of sodium persulphate, is oxidised to rifamycin-O. Rifamycin-O is hydrolysed with sulphuric acid and tetra-hydrofuran to give rifamycin-S. rifamycin-S is first treated with t-butyl-amine and manganese-di-oxide and then reduced and hydrolysed by ascorbic acid and sulphuric acid to yield 3-formyl-rifamycin-SV (3FRSV). The penultimate stage of rifampicin consists of reacting 3FRSV with 1-amino-4-methyl piperazinamine, and other solvents to give rifampicin.

The synthesis stages, though not simple, are not as difficult as the fermentation stage, as fermentation of Rifamycin and the yield obtained (or say the efficiency) is nearly the same. Thus fermentation yield is the most critical stage which determines the overall process efficiency.

One of the most important parameters for determining the quality of the product is the bulk-density of the (uncompacted) product. Higher the bulk density higher is the bio-availability of the drug. Higher bulk density is obtained by proper crystallization.

6.0 INDUSTRY STATUS

There are four main regular manufacturers (fermenters) of rifampicin in the world, viz : Lepetit (Italy), Ciba-Geigy (Switzerland), C.K.D., (S. Korea), Youhan (S. Korea). Besides the above, Proter (Italy) is also a regular manufacturer of Rifampicin intermediates.

In addition to the above main manufacturers there are number of other manufacturers in the world who do not manufacture rifampicin regularly, like CIECH (Poland), Pharmachim (Bulgaria), Cipan (Portugal), Ferpharma (Switzerland).

In 1988-89 total world rifampicin production is estimated to be between 400 to 500 tonnes. India is the biggest consumer of rifampicin, consuming nearly one-third of the total production.

India manufactures rifampicin only from the penultimate stage i.e. by synthesising 3FRSV to rifampicin (except Lupin which manufactures from rifamycin-S stage). There are six regular manufacturers out of which five are in the unorganised sector :

i) Andhra Citrates (Themis Chemicals)
ii) Avik Pharmaceuticals
iii) Jebco Pharma
iv) Kopran Chemicals
v) Lupin Laboratories (Organised Sector)
vi) Syntho-Rifa

In 1989-90, India consumed around 112 to 120 tonne of rifampicin and the market is expected to grow at the rate of 15 per cent per annum. Demand is estimated at 300 tonne in 1995.

The penultimate stage does not really involve complex ''technology'' (as compared with the fermentation process). The rifampicin intermediate

3FRSV and 1 AMP are imported and the other solvents are procured indigenously. The imported raw materials constitute nearly 90 percent of the total cost of production.

7.0 TECHNOLOGY GAPS

India still does not have the fermentation technology for rifampicin. It also does not have the know-how for the synthesis of the earlier steps, i.e. from rifamycin-B to rifamycin-S/SV.

The penultimate step of the manufacture of rifampicin carried out in India is quite efficient (in terms of raw material consumption and others). But the crystallization technique, which yields a higher bulk density, is not comparable to the international standards. Thus the crystallization technique needs to be improved to bring the present technology at par with the world standards.

Some research efforts have been directed at rifampicin. IMTEC at Chandigarh has developed a new more efficient synthesis step. Themis Chemicals and Cadila Laboratories have done research on fermentation step. However, an integrated approach to the development of the technology is lacking.

8.0 RECOMMENDATIONS (STREPTOMYCIN)

8.1 A comprehensive study on tuberculosis in relation to anti-tubercular drugs should be undertaken to ascertain the industry status, technology availability, cost of production. This may be linked to the efficacy of various drugs. Estimated demand matrix may be generated for each drug especially for streptomycin and rifampicin.

8.2 If the above exercise leads to the conclusion that streptomycin has a future, then major research efforts may be initiated. One of the National Laboratories could be identified as a nodal agency for such efforts. The research should be directed at producing better yielding strains as improvements in strain efficiency could have very large impact on the cost of production. The research should also be directed at improving cycle times, extraction efficiency and identifying cheaper raw materials.

8.3 Co-operation between manufacturers of streptomycin is desirable to plan the research and development programmes. The benefits of any new developments could be shared. There is a definite difference between technologies. Minimizing this difference will reduce total cost to the industry. The markets may be mutually shared so as to help evolve technology sharing mechanism.

9.0 RECOMMENDATIONS (REFAMPICIN)

9.1 Standards for quality should include minimum bio-availability of rifampicin.

9.2 A co-ordinated and concerted efforts should be made to develop rifampicin technology in India. A premier research institute, like IMTEC, Chandigarh, may be designated as a nodal agency. The research programme should be established on a priority basis. This programme should be based on work already done in India.

9.3 Developing a technology for rifampicin may not be possible in the short term. So, import of technology may be necessary. There are only a few technology suppliers and getting the technology may not be easy. However, foreign parties have indicated desire to supply the technology and this opportunity should be availed of.

9.4 Knowledge and experience in fermentation is generally a weak link in Indian technical expertise. Fermentation is increasingly gaining importance for various processes. It is difficult for individual enterprises to commit resources for developing expertise in fermentation processes. It is imperative that a full fledged facility and research programme on fermentation process be established. The research programme on fermentation would not only help in rifamycin fermentation but would also help in gaining expertise in this technology itself which would be useful in developing other fermentation products like the penicillin.

9.5 The Antibiotic industry should introduce automation and control the fermentor parameters through micro- processor. The technique of manual control system should be phased out.