EXECUTIVE SUMMARY

0.1 THE PRODUCT

Trimethoprim is a broad spectrum anti bacterial agent. It is a structural analogue of the pteridine portion of hydrofolic acid, as a competitive inhibitor of dihydrofolate reductase, the final enzyme in the pathway to tetrahydrofolic acid.

0.2 PROPERTIES

It is a white or yellowish white, odourless or almost odourless crystalline powder (or crystals) with a very bitter taste.

Trimethoprim is active in vitro against a wide variety of Gram-postive and Gram-negative organisms. In particular, it is active against Streptococcus pneumonia, Streptococcus pyogenes, Haemophilius influenzae, Cornybacterium diptheriae and E. Coli. It has no activity against Clostridium, Mycobacterium or Treponema and is relatively inactive against Brucella species. Trimethoprim is commonly used in combination with sulphamethoxazole but because of the side effects of the combination, Trimethoprim is increasingly used on its own.

Trimethoprim has been shown to be effective in the treatment of acute urinary tract infections in doses ranging from 100 mg twice daily for 5 days to 200 mg twice daily for 7 days. As Trimethoprim has been shown to be concentrated in sputum as well as in urine, it is of particular use in respiratory tract infections. It has been shown to be equally as effective as co-trimoxazole in a variety of chest infections, with fewer side effects. Another study has shown Trimethoprim to be more effective than co-trimoxazole in the treatment of pneumonia.

Trimethoprim alone is available as tablets and suspension for oral administration and in the injectable form for parenteral administration, all being available in varying doses. In India however, Trimethoprim is only available in combination with sulphonamides (mostly Sulphamethoxazole and infrequently,

Sulphadiazine). In Russia it is also available in combination with Rifampicin in the form of tablets.

0.3 PROCESS OF MANUFACTURE

The manufacture of Trimethoprim involves three distinct stages; starting from Gallic Acid which is converted into 3, 4, 5 Trimethoxy benzaldehyde and which in turn is converted into Trimethoprim.

Manufacture of Gallic Acid is commenced by extracting tannic acid from imported tara powder and hydrolyzing it to obtain Gallic Acid which is crystallized to obtain the final product.

Manufacture of 3, 4, 5 Trimethoxy benzaldehyde commences with methoxylation of Gallic Acid with Dimethyl sulphate to obtain the intermediate product 3, 4, 5 Trimethoxy benzoic acid. This is reduced to the benzaldehyde with the help of hydrazine hydrate and potassium ferricyanide.

The subsequent manufacture of Trimethoprim begins by reacting Morpholine with Acrylonitrile to give beta morpholine acrylonitrile, which is made to react with 3, 4, 5 Trimethoxy benzaldehyde to give an intermediate product which on reacting with aniline and hydrochloric acid gives the penultimate product. This is further treated with Guanadine Nitrate to yield the final product Trimethoprim.

0.4 HISTORICAL DEVLOPMENT

Trimethoprim was synthesized as part of a research program exploring the activites of folate antagonists as antimetabolites initiated by the Wellcome Research Foundation in 1942. The active metabolite in which PABA participates was revealed when the structure of folic acid (pteroglutamic acid) became known in 1946. In the then current milieu, it was inevitable that attention would turn promptly to the preparation of antimetabolites to the new structure. The importance of the 4-amino group was emphasized by Hitchings et al in 1945 who had been studying the antimetabolic effects of modifications of the functional groups of the natrual pyrimidines. They had recognised that antagonism

to folic acid in the growth of Lactobacillus casei was a property of nearly all 2, 4-diamino pyrimidines and their condensed systems. This gave rise to a number of compounds useful in antimicrobial chemotherapy.

In 1947, two laboratories independently announced their discoveries that 2, 4-Diamino pteridines were powerful inhibitors of the activity of folic acid. The 4-amino derivative of folic acid itself, amiopterin provided what was probably the closest possible analogy to the parent vitamin. The announcement of the potent inhibitory effects of aminopterin as well as it's growth inhibitory properties in mammalian systems paved the way for the development of methotrexate, one of the most widely used antitumour drugs available today.

The second series of announcements of 1947 concerned 2, 4-diamino pteridines, which lacked the paminobenzoyl glutamic acid moiety. Several such compounds were reported to inhibit the growth of various bacteria. The focus was on 2, 4-diamino pteridines and quinazolines, many with rather massive hydrophobic substituents in the PABG region.

Another milestone observation was made at this time ; Because these compounds had been conceived as analogs of the pterin part of the molecule, it seemed logical to test them in conjunction with sulphonamides, analogs of the omitted part of the folic acid molecule. However, the important discovery that led to Trimethoprim was that simple 2, 4-diaminopyrimidines scuh as the 5, 6-dimethyl derivative or the diamino analog of thymine actually inhibited the growth of L. casei owing to interference with the utilization of folic acid, rather than thymines or purines. This was rapidly followed by publications of the potent antimalarial activities of 5-aryloxy—2, 4-diamino pyrimidines, and then 5f-benzyl and 5-aryl—2, 4-diamino analogs, and then by the discovery that some of these compounds (notably benzyl pyrimidines lacking 6-substituents on the pyrimidine ring) were more active against bacteria than plasmodia. The effort to optimize these results led eventually to Trimethoprim. However, what put Trimethoprim into perspective as a candidate antibacterial agent, was the announcement of the tremendous specificity of

Trimethoprim for bacterial dihydrofolate reductase, coupled with equally astonishing specificity of a dihydrotriazine for mammalian enzyme and of pyrimethamine for plasmodial enzymes.

Although Trimethoprim was patented in 1958, been in the public domain since 1959 and available to the public since 1968, in combination with sulphamethoxazole as a broad spectrum antibacterial agent, it still stands almost alone in this field as a species-specific dihydrofolate reductase inhibitor. It was preceded by its close relative Diaveridine which found its utility as an anticoccidial agent, and was followed by Ormetroprim which again found its use in the latter category. Still later another very close relative, Tetroxoprim has been introduced in combination with Sulphadiazine as an antibacterial competitor.

0.5 INDIAN INDUSTRY

The Drugs and Pharmaceuticals industry has made impressive progress during the last four decades, after independence in 1947. Among the developing countries, India has achieved the status of having a sound and reliable bulk drug production industry which caters substantially (46-48%) to the needs of its own formulations industry. Almost all the kinds of forumations needed by the medical profession are manufactured within the country, and only a portion, below 1% is being imported.

The total consumption of bulk drugs has been on the rise. The production of formulation has also steadily increased ; however, imports of finished formulations have remained practically stationary. Nearly 360 bulk drugs are consumed in the country (to make about 20,000 formulations) and of these the majority are produced within the country.

The production of Trimethoprim started early when Burroughs Wellcome (India) put up their plant, way back in the seventies. Since then many more manufacturers have come up, all based on the same technology brought to India by Burroughs Wellcome. Nonetheless, Burroughs Wellcome remains the largest producer of Trimethoprim in India. Two other major producers of Trimethoprim are Standard Organics Ltd. and Inventa Chemicals Pvt. Ltd. each of which has an installed capacity of 150 TPA.

The present installed capacity of Trimethoprim in India is more than 1305 TPA. Trimethoprim, being an antibacterial drug has tremendous export prospects, especially in developing countries who can ill afford the costlier substitutes like Cephalosporins, Quinolones and other such classes of antibiotics. Thus from an export turnover of Rs. 10.9 lacs of Trimethoprim in 1986-87, it has jumped to Rs. 23.88 crores in 1992-93. The demand was perceived as around 2000 TPA in 1993 and is estimated to rise to 4500 TPA by the year 2000.

Similarly, the production of 3, 4, 5 Trimethoxy benzaldehyde was placed at around 300 TPA as against a demand of 1800 TPA in 1993 and 4000 TPA by the year 2000. In case of Gallic Acid the production was 120 TPA as against a demand of 700 TPA in 1993 and 1500 TPA by the year 2000.

0.6 TECHNOLOGY STATUS IN INDIA

The manufacture of Trimethoprim involves three stages, viz; manufacture of Gallic Acid from Tara Powder, manufacture of 3, 4, 5 Trimethoxy benzaldehyde from Gallic Acid and finally the manufacture of Trimethoprim based on 3, 4, 5 Trimethoxy benzaldehyde. While most of the manufacturers of Trimethoprim are having the technology of Stage III, that of stages I and II is not very prevalent.

The manufacture of Gallic Acid in India started in 1988 when Venkateshwara Labs was set up in Pondicherry. Since then a few more manufacturers have also come up, all making a product of acceptable quality. One big manufacturer of Trimethoprim, Standard Organics Ltd. is making its own Gallic Acid but for captive consumption only.

Manufacture of 3, 4, 5 Trimethoxy Benzaldehyde started in early eighties with Seamless Coporation putting up their unit with indigenous know-how. Recently Alpha Drug India Ltd. have come up having foreign colloaboration with Fuso Chemicals (Japan) who have provided the technical know-how for the product. Since then a few more manufacturers have also come up for the manufacture of 3, 4, 5 Trimethoxy benzaldehyde.

While the original technology for Trimethoprim was brought to India by Burroughs Wellcome India Ltd. it has slowly percolated down to numerous manufactures who manufacture Trimethoprim starting from 3, 4, 5 Trimethoxy Benzaldehyde. The technical capability of Indian manufacturers of Trimethoprim is quite good and at par with international standards, both in terms of product qualisty as well as yields. However one major point of concern here is that most of the raw materials required for the manufacture of Trimethoprim are being imported, in part or in full. This leads to a tremendous outflow of foreign exchange given the widespread usage of this product.

On analyzing the structure of Indian manufacturers, it is observed that the majority of the companies are operating at a very low level of operations. The average installed capacity for most manufactures is 5 to 25 TPA, are either private limited or proprietorship concerns (all being in the private sector exclusively) and most of them are based in Western India region.

0.7 TECHNOLOGY ABSORPTION AND GAPS

It is relatively easy to absorb the Gallic Acid part of the technology, Indian companies have, by and large, been successful in achieving good efficiencies. The manufacturing process itself is quite simple in fact and most of the units have stabilized their production. However, the main raw material, Tara Powder, is totally imported presently. The main disadvantages are that Tara Powder is an expensive product having erratic supply therefore requiring larger inventory.

3, 4, 5 Trimethoxy benzaldehyde is the crucial intermediate for the manufacture of Trimethoprim. This intermediate is encountered whichever route of synthesis is taken using any starting material, be it gallic acid, para-cresol, para-nitro toluene, vanillin, veratraldehyde etc. Although all the plants today are based on Gallic Acid as the starting material, newer processe are being tried out to replace the Gallic Acid with synthetic derivatives.

Trimethoprim technology has been absorbed to a great extent and the current yields and product quality are as per current

international standards. However, one area which attracts attention is the high import component of raw material requirements that go into the manufacture of Trimethoprim, Most of the materials like 3, 4, 5 Trimethoxy benzaldehyde, Morpholine, Dimethyl Sulphoxide, Acrylonitrile, Aniline, Guanadine Nitrate etc. are being imported at present in varying degrees of import intensity.

0.8 CONCLUSIONS

In conclusion, therefore it can be said that the technology for Trimethoprim manufacture starting from 3, 4, 5 Trimethoxy benzaldehyde is more or less at par with international standards. The same goes for the manufacture of Gallic Acid also. However, in case of 3, 4, 5 Trimethoxy benzaldehyde, while the techonlogy for most of the units is less efficient than international standards, they are able to make their product of acceptable quality. However, inspite of the presence of acceptable technologies of both the intermediates of Trimethoprim, i.e. 3, 4, 5 Trimethoxy benzaldehyde and Gallic Acid, the installed capacities of both are on a very low level and therefore the imports of these two vital ingredients are still at appreciable levels.

Even in the case of Trimethoprim, while the total production is almost fulfilling the demand for the product, the production is highly fragmented and hence awareness of international market opportunity and technological upgradation taking place around the world, is lacking.

Another fact which emerges out is that most of the manufacturers of Trimethoprim are not making their own 3, 4, 5 Trimethoxy benzaldehyde and most of the manufacturers of 3, 4, 5 Trimethoxy benzaldehyde are not making their own Gallic Acid. Hence, the cost of production in India is high due to the existence of multivendor environment from Tara Powder to Trimethoprim.

No technology import of Trimethoprim, 3, 4, 5 Trimethoxy benzaldehyde or Gallic Acid is required. India is self sufficient in the terms of the technology as well as the product and is in fact quite capable of exporting these technologies. However in case a

novel route of synthesis is offered, which promises substantial savings in terms of cost of production or promises to replace imported raw materials with those available indigenously etc., it should be freely allowed to be imported.

As the present production of Trimethoprim is already too fragmented, new manufacturers should be discouraged to enter the field and at the same time present manufacturers should be encouraged to increase their production capacities. They should take initiative in working towards greater import substitution coupled with greater export promotion efforts, as this will have a direct bearing on their own profitability and in improving their international as well as national competitiveness.

0.9 RECOMMENDATIONS

i) No further import of technology, unless it be for a totally novel route giving rise to several proven improvements, is necessary.

ii) Import substitution and the possibilitly of manufacturing the raw materials which are being largely imported, like acrylonitrile, dimethyl sulphoxide, 3, 4, 5 Trimethoxy benzaldehyde, morpholine, sodium metal, guanadine nitrate and aniline — should be taken up on a priority basis by Indian manufacturers.

iii) There is no further scope for new manufacturers of Trimethoprim.

iv) The following research and development activities need be taken up by the manufacturers :

- Recovery of Solvents
- Stabilisation of pale cresol route
- Setting up effluent treatment plants
- Development of alternate routs using alternate raw materials.

v) Export promotion activities need to be stepped up. Participation in trade fairs, contacting potential users in other developing countries, arranging trade relations with merchant exporters and arranging long term supply agreements with established traders, are some of the steps that could be taken.

vi) Manufacturers would initiate projects aimed at import substitution/export boosting. They should take up studies in order to appraise themselves of the latest technology trends, market and export potentials.