EXECUTIVE SUMMARY

1.0 QUINOLONES

1.1 Norfloxacin is one of the new 4-quinolone anti-bacterial agents introduced in 1984 in the world market. Subsequent to Norfloxacin four more new quinolones compounds also have come into the market. Still Norfloxacin and its successors Ciprofloxacin are able to hold their own market in their clinical use as popular agents for urinary tract infections. The various quinolone anti-bacterial agents are as follows in the chronological order of their introduction :

1. Nalidixic acid
2. Norfloxacin
3. Ofloxacin
4. Pefloxacin
5. Ciprofloxacin
6. Lomafloxacin
7. Enoxacin
8. Sparfloxacin
9. Amifloxacin

1.2 Of these, Nalidixic acid was the earliest introduced in India about two decades back followed by Norfloxacin in 1988 and later Ciprofloxacin was introduced for clinical use. Many other quinolones are already under clinical trials in various parts of the world and many other quinolones are at various stages of developments. The structure of various quinolones which are in clinical use, which are under clinical trials and which are in the laboratory development stages are all given in Fig. 1, Fig. 2, Fig. 3 and Fig. 4 respectively.

1.3 Among all these products, Ciprofloxacin and Norfloxacin are the two products dominating in the present clinical use in the international market. The world market of quinolone drugs was given as US $ 1600 million in 1990 and it is expected to be around US $ 2500 million by 1995. It is said to be around 10% of the total anti-bacterial market as reported in "Scrip-April 1990". As for the Indian market, the total quinolone market is said to be around Rs. 940 millions, of which Norfloxacin market is claimed to be Rs. 270 millions. The market survey of anti-bacterials, including antibiotics and quinolones, has been given as Rs. 5800 millions, of which for quinolones is around Rs. 940 millions, nearly 16% of the total anti-bacterial market. This projection is considerably less than the international picture, most probably due to the later introduction of these products in India and also due to lesser availability and higher price of the formulated drugs. Table 1 shows the market trends of the quinolone drugs introduced in this country since 1985.

TABLE 1

MARKET TREND FOR QUINOLONES IN INDIA

(Rs. in lakhs)

Year	Ciprofloxacin (% increase)	Norfloxacin (% increase)	Nalidixic Acid (% increase)	Ofloxacin (% increase)
1985	-	-	320.57	-
1986	-	-	513.66 (60.2%)	-
1987	-	6.88	627.78 (22.22%)	-
1988	-	740.12 (99%)	625.73 (-0.3%)	-
1989	518.44	1270.68 (71.69%)	642.84 (2.73%)	-
1990	255.643 (39.3%)	255.252 (100.88%)	850.96 (32.38%)	197.31
1991	3080.02 (20%)	3132.40 (22.72%)	973.35 (14.4%)	332.81 (68.6%)

(The figures in bracket is the percentage increase over the previous year).

Source : ORG - Baroda

2.0 STRUCTURE OF THE INDIAN INDUSTRY

2.1 In India, Ranbaxy Laboratories Ltd., New Delhi has first introduced Nalidixic acid production, about two decades back, followed by Norfloxacin in 1988. Norfloxacin and Ciprofloxacin are being made by M/s. Ranbaxy Laboratories, New Delhi; Dr. Reddy's Laboratories, Hyderabad and M/s. CIPLA Ltd., Bombay in the organised sector, while many other SSI units also make them in smaller quantities. The licensed capacities and Letters of Intent of various quinolone drugs are given in Table 10 in Chapter 3. The total production of Norfloxacin is about 70-80 tonnes per annum. The projected growth for these three quinolone drugs is given as about 16-20% per annum.

3.0 NORFLOXACIN -- SPECIFIC ADVANTAGES

3.1 Among the quinolone drugs introduced for clinical use in the market, Norfloxacin demonstrates a much wider *in-vitro* anti-bacterial spectrum and a greater potency than the parent compound, namely Nalidixic acid. Its antibacterial activity against most gram-negative pathogens in enhanced in comparison to Nalidixic acid. It is similar in

activity to Enaxacin and slightly less potent than Ciprofloxacin. Moreover, the main advantage of Norfloxacin over Nalidixic acid, lies in the fact, that it is active against *Pseudomonas aeruginosa* and on some of the gram positive organisms also. Norfloxacin is as effective as spectinomycin in *Gonorrhoea*, since resistance to Norfloxacin developments is yet to be established. Due to these properties, Norfloxacin has a distinct advantage over the presently used quinolone antibacterials and even over co-trimoxozole and many other antibiotics.

4.0 TECHNOLOGY STATUS AND THRUST AREAS

4.1 All the three Indian companies in the organised sector have developed the processes for Norfloxacin indigenously and are able to compete in the international market and are able to export the bulk drugs and formulations.

4.2 The export figures for Norfloxacin are as follows :

TABLE 2

EXPORT OF NORFLOXACIN

Year	Rs. in Lakhs
1988-89	63.71
1989-90	37.43
1990-91	377.83
1991-92	1064.07
1992-93	836.78

Source : ORG - 1992 Reports

Note : The exports may be affected from 1994 onwards due to product patent problems.

4.3 The three Indian companies have strong in-house R & D setups and they are steadily putting in R & D inputs both for improvement of the process and also for the development of sophisticated formulations.

4.4 Even though these quinolone compounds are likely to grow at nearly 16-20% rate during the present decade, it must be kept at back of the mind that more quinolone compounds are getting introduced both internationally and in India and many more compounds are in the development stage, claiming greater efficacy of a wider range of bacterial infections and lesser side effects. Therefore, further expansions in relation to Ciprofloxacin and Norfloxacin must be taken after careful analysis of the potentials of

ıe new quinolone compounds that are likely to come into the market in the near .ıture. It will be advisable to keep the quinolone product plants in the form of unit process set ups, so that; if necessary, the same plant can be used for newer quinolone derivatives without much capital investment. It will be interesting to note that M/s. Ranbaxy Laboratories has appreciated this fact and got their industrial license expanded to 120 M.T. for the four quinolones anti-bacterials as a total entity. The process details for Norfloxacin is given in the Chapter 2. With a view to compare the various steps in the synthesis and the type of equipment to be used for each step, the synthesis scheme of Ciprofloxacin is given in Annexure 3.

5.0 CONCLUSIONS

5.1 Norfloxacin has proved to be a very broad spectrum anti-bacterial drug, particularly for urinary tract infections, showing superiority over its predecessors like nalidixic acid, pipemidic acid etc. It is closer in activity to cotrimoxozole, amoxycillin etc., but since it has lesser side effects and spares the normal gastro intestinal flora and at the same time acts on the gastro intestinal pathogens all this make the drug very valuable. It has very specific clinical applications with many advantages, hence it will remain a very useful drug. Its clinical use is likely to increase by nearly 16-20% during the next 10 years.

5.2 The indigenous processes used by all the Indian manufacturers are quite competitive and they are making R & D effects on their own. This has enabled them to export the bulk drug and the formulations, which is commendable. However, Indian manufactures and R&D institutions have to give a high priority to development of their own range of quinolones, so that the limitation due to foreign patent, if any, can be overcome.

5.3 New alternative method(s) for the manufacture of norfloxacin should also be explored so that the vast export market to developed countries can be tapped, which at present is not being exploited due to international patent being applicable till 1997.

5.4 There are some manufacturers who feel that chances of exporting norfloxacin are quite bleak as long as major items like 3-cholo-4-fluor aniline, EMME, DMF, pyridine and piperazine have to be imported.

6.0 RECOMMENDATIONS

Based on the study, the following recommendations are made :

6.1 More emphasis to basic research need be given, to explore and discover newer derivatives of fluoroquinolones, to substitute the present range of quinolone derivatives. In order to achieve such objectives, national laboratories, universities and industrial R & D units should work closely an a time bound basis. They should also jointly plan a strategy to modify the present process of manufacture of norfloxacin.

6.2 actively in the D institutions, should give high priority to development of their own range of quinolone antibacterials.

6.3 Drug manufacturers are of the view that in order to maintain and also to increase the export market potential of these drugs, significant incentives may be provided, as is being done in some other countries like China, South Korea, Taiwan and other places for their drug products.

6.4 The overall efficiency of the process followed by Indian manufacturers for Norfloxacin is only about 37%. To maintain competitiveness in the international market, this overall efficiency should be increased atleast to 45-50%, possibly through the efforts of improving the stagewise unit process efficiency by better process and plant engineering designs, coupled with product quality. This aspect is discussed in Chapter - 3.

6.5 The major imported raw materials, namely 3-chloro 4-fluoro aniline and ethoxy methylene malonate diethyl ether constitute about 35-40% of the selling price, which is quite high. This can impede in the long run, the potential to export the product. Therefore, efforts should be made for an import substitution programme, for these two raw materials by manufacturers either by themselves or in collaboration with the laboratories. The possible routes for the synthesis of these two intermediates have been indicated in Annexure 3.

6.6 New alternative method(s) for the manufacture of norfloxacin should also be explored.