EXECUTIVE SUMMARY

1. Vitamin-A is a fat-soluble vitamin which was recognised in 1914 as an essential growth factor, the absence or deficiency of which can lead to many diseases or syndromes in man and animals. These diseases are particularly related to the eye, skin and epithetial tissues. The most important disease caused by its deficiency is known as Xerophthalmia and it can progress to night blindness and if it is not treated in time can lead to permanet blindness. In India where malnutrition levels are high, Vitamin-A deficiency remains a major cause of blindness.

2. Vitamin-A, therefore, is a very essential pharmaceutical entity for this country and self-sufficiency in its production must be achieved as early as possible. The apparent requirement of synthetic Vitamin-A for this country has been put at 75 mega million international units (MMU) for 1975 AD and it is expected to be around 240 MMU by 1990 AD. There is a substantial gap even between the apparent demand and production. The gap may be higher if the true nutritional requirement of the population are amended. (One International unit is equal to 0.3 microgram of pure Vitamin-A Crystals. Therefore 1 MMU will be equal to 300 Kgs. of Vitamin-a or equal to 340 Kgs of Vitamin-A acetate.)

3. The demand has been estimated to be growing by 13-15% (compound) per year. This large growing demand has to be met not only by increasing the production of synthetic Vitamin-A, but also by increasing the natural sources of Vitamin-A, such as the fish-liver oils, carrots, green vegetables, etc. The plan should be to have atleast 50% of the demand to be met by these natural sources and the rest by the synthetic commercial production. It may be mentioned here that one molecule of β-Carotene, whch is the yellow plant pigment in many of the vegetables, can provide 2 molecules of Vitamin-A in the intestines of animals and human beings. Hence this natural source also must be exploited to the maximum for meeting the national demand for Vitamin-A.

4. For the synthetic production of Vitamin-A, four synthetic routes have been developed. The first route is based on Reformatsky's reaction, which goes through the addition of ethoxy-acetylene to β-Ionone. This reaction could not lead to a successful commercial process, since many undesirable intermediates also formed leading to poor yield of Vitamin-A. Another is based on Darzen's reaction to synthesise the key intermediate called C_{14} aldehyde. The processes based on this reaction proved to be commercially viable and all the leading Vitamin-A manufacturers in the world such as Hoffmann La Roche, Pfizer, Merck, Sharp & Dome, etc. are following this route of synthesis for their commercial production of Vitamin-A. A third process based upon the use of 2,6,6-trimethylcyclohexanone has also been developed and commercially used by Takeda in Japan and Glaxo in U.K. and in India. Glaxo (U.K) acquired the process from M/s. Distillation Products Industries, USA (a Division of Eastman

Kodak & Co, USA), and transferred the technology to their Indian subsidiary. Even though this process was commercially feasible, it was not able to compete with the C_{14} aldehyde process. The parent company in U.K. abandoned the process recently.

5. A fourth process was successfully developed and commercial production was started from 1964 by BASF, West Germany. This process uses the Wittig's reaction. This reaction involves the conversion of the Carbonyl group (C = 0) to an olefinic grouping C = C providing an important route for the synthesis of long chain olefines as in Vitamin-A side chain. This BASF process can now be considered as the most convenient and technologically the most advanced.

6. In India three companies are manufacturing Vitamin-A, by two different processes. They are (1) Roche Products Ltd., Bombay (started Vitamin-A production from 1962) (2) Glaxo Laboratories (India) Ltd., Bombay (started Vitamin-A production from 1960) and (3) Kerala State Drugs and Pharmaceuticals, Kerala (started Vitamin-A production from 1983-84). The Roche process is based on C_{14} aldehyde as the key intermediate, and they had given their know-how free of cost to the Kerala State Drugs & Pharmaceuticals. Thus, these two companies are using the same technology as acquired orginally from Hoffmann La Roche, Switzerland. Glaxo Laboratories (India) Ltd., got their know-how from their parent company in U.K. This process is based on C_{15} compound as the key intermediate.

   Of these three companies the Roche Process is the best and their share production is the maximum. Their cost of production is however high. The reasons given by them are (1) their local production size is too small to absorb fully the overheads and it also does not permit much of automation in the process. (2) They have been asked to produce Vitamin-A starting from the locally available lemon grass oil, the price of which is not only steadily rising and its quality and availability have become erratic of late, due to the decreased cultivation of lemon grass in Kerala and the cost of steam distillation of the lemon grass has also gone up of late. From Rs. 67.05 per kg. in 1973-74, the price of lemon grass oil has moved upto nearly Rs. 200/- per kg. resulting in the β-Ionone cost going to Rs. 461.29/kg. at present. In 1976 the Vitamin-A cost per kg. used to be Rs. 468.38 for Roche and Rs. 552.03 for Glaxo. As of today the main raw-material (β-Inone) price itself has gone up (or increased) to Rs. 461.29/kg. making the bulk-drug price prohibitively high. Compared to the situation of Roche and Glaxo, who compulsorily, have to make Vitamin-A from Indian lemon grass oil only at a very high cost of raw material, Kerala unit has been permitted to use imported pseudo-ionone as the starting material. The import price of pseudio-ionone is only around Rs. 190/kg including 140% customs duty. All the same among all the three Indian Units, Roche has the best technology and uses it quite efficiently, getting optimal yields at every stage.

7. In contrast with this, Glaxo has found their technology becoming more and more uneconomical and their technology has become out of date. Their parent

company in U.K. has already discontinued using this process. Glaxo Laboratories (India) Ltd. also desires to give up this process and in June 1987 have sponsored a R&D programme at Regional Research Laboratory, (IICT) Hyderabad to develop a new technology for them. It is learnt from RRL, Hyderabad, that it will take atleast one more year for completing this assignment. Until then Glaxo will be producing a limited amount of Vitamin-A mainly for their captive use.

As for the Kerala Unit, even though they have acquired the know-how from Roche Products Ltd., set up their plant with design planned from their technology and got their technical personnel trained in Roche Products Ltd. at Bombay, they are still unable to get the full efficiency and their yields from the Girgnard reaction step onwards are not quite satisfactory. They are putting in their R&D efforts for improving these yields. That is to say they are yet to absorb the technology fully and satisfactorily.

8. Even though BASF, West Germany, developed their superior quality technology and went into production of Vitamin-A even in 1964, so far no laboratory in India appears to have evaluated the BASF technology. BASF has not been keen on any collaboration or manufacture of Vitamin-A in India so far. It appears that they consider the size of production by this process will have to be around 240 MMU to be economically viable.

9. As it is, one can say at present only Roche Products Ltd., in India has an efficiently operating unit for the production of Vitamin-A and they are also bogged down with the restriction in the licensed capacity and also on the necessity to use the Indian lemon grass oil as the starting material. Thus the present Vitamin-A production status both from technological and commercial viability point of view is far from satisfactory and at this state of operations, the question of reaching self-sufficiency in meeting the growing demand for this vitamin is almost impossible unless many remedial measures are quickly taken.

10. In the light of the above the following recommendations are made.

(i) In view of the national demand being 240 MMU by 1990 A.D. with an annual growth projection of 13 to 15% (Compound), the National demand by 2000 A.D. is likely to be around 720 to 750 MMU per year. Even assuming that nearly 50% of this can be met by natural resources, there will still be a large gap in meeting this level of national requirement by 2000 A.D. Even as of today against a need of nearly 209 MMU, the present indigenous production is about 85 MMU only. It will be necessary to expand the capacities immediately and thereby increase the indigenous production and lessen the requirement gap.

(ii) In addition to increasing the capacities, it will be necessary to allow atleast one more new unit to come up preferably with new technology based on Wittig's reaction, either by collaboration with BASF or by developing a process indigenously.

(iii) Lemon grass oil as a primary raw material is already becoming a bottleneck, by its agricultural production area going down very much and its cost of production also increasing steeply. Further, there is a heavy demand for its export directly and also as β-Ionone. Four units in the country are exporting these in fairly large quantities. In view of this it will be worthwhile to permit all these Vitamin-A manufacturing units to import pseudo-ionone from Europe, where it is sold at around 1 kg for 12 Swiss Francs only. This will enable the final product to come within the reach of an average Indian. The import cost can be made up by increased export of lemon grass oil for which there appears to be a good demand.

(iv) Some of the National Laboratories can be asked to examine the Wittig's reaction in greater detail for the production of not only Vitamin-A, but also Vitamin-E as an offshoot of this technology, to meet the demands for these two vitamins in the country. Many other valuable products useful in the perfumery industry (the Linalools) also can come out of such studies.

(v) Serious study to evaluate processess based on production of Vitamin-A or Vitamin-A concentrates from β-carotene as the main raw material source also should be examined as part of small scale agro-industrial products and develop large cultivation of carrots and other β-carotene containing vegetables. Such units are existing viably in U.S.A.

(vi) Now that Biotechnology is fast developing and since β-Carotene and its hydrolysed product Vitamin-A are capable of being produced by such techniques, such an R&D programme must be considered on national priority for this product also. A biotechnology company by name "Genex Corporation" in Maryland, U.S.A. has a programme for making Vitamin-A and Vitamin-C by Bio-technological routes. This technology is likely to provide a very convenient and highly economical process in near future.

(vii) In near future the availability and cost structure of lemon grass oil is likely to be a problem for Vitamin-A manufacturers in India. It is therefore necessary to develop or acquire the technology to produce β-ionone synthetically early.