EXECUTIVE SUMMARY

1. Insulin is the hormone secreted by the β cells of the Islet tissue in the tail of the pancreas of all animals. Insulin is required by the body for the utilisation of glucose by all cells for energy and cellular respiration.

2. In the absence of insulin, the disease **Diabetes mellitus** will set in leading to increased blood sugar levels and if it is not controlled by insulin treatment in insulin dependent diabetics, the patients will develop various complications and can die within eighteen months of the onset of the disease. Hence insulin is a very essential drug and all these years, it was being manufactured by isolating it from the cattle and pig pancreas. Recently biotechnological methods have been developed for producing highly purified insulins and the human insulin.

3. According to WHO reports, the insulin dependent diabetic population is increasing by 3 to 5% a year in the world. The various studies at All India Institute of Medical Sciences, New Delhi, Diabetes Research Centre, Madras etc., reveal that on an average of nearly 5% of the Indian population has impaired glucose tolerance. Fortunately nearly 95% of these are non insulin dependent. Based on all these studies nearly 3 in 1000 in urban India can be considered as insulin dependent diabetic with greater family aggregation of diabetics. Thus on the whole the diabeties incidence is high and in keeping with the world trend, it is increasing. The assumption that the incidence is prevalent among affluent people is no longer valid. The Gujarat and Orissa studies have identified malnutrition also as a factor for diabetic incidence.

4. Based on all these factors, a detailed evaluation of the insulin demand projection had been published in Industrial Researcher in April 1986. These experts have projected the insulin requirement of India by 1989-90 to be around 4413 MU.

5. Against such a requirement projection, The Boots Company (India) Ltd. had been sanctioned a capacity of 2780 MU with an installed capacity of 3475MU at present.

6. Recently, from 1985, Synbiotics (Baroda) has been permitted to import highly purified insulin from Novo,Denmark and re-vial that for marketing in India. They are at present importing and marketing nearly 20 MU of insulin vials per annum. The product even though costly, is required for those cases developing reactions to the conventional insulin and in cases where insulin resistance is developing due to antigenic effects.

7. M.J. Pharmaceuticals (Gujarat) import about Rs. 3 to 4 lakhs worth of bulk insulin from Eli Lilly and Co., USA., to be vialed in India and exported to USSR. This quantum of insulin will not be available for the Indian requirements.

8. Under these circumstances the actual manufacture is around 3475 MU as against requirement of 4413 MU by 1989-90. There is also about 20 MU of the highly purified insulin imported. Thus there is still a demand gap of 918 MU. This gap is likely to grow wider and wider with the demand increasing by nearly 12-15% per year according to the study in Indian Researcher.

9. The technology used by the Boots Company (India) Ltd., is the conventional process of extracting insulin from frozen pancreas of slaughtered animals. Since the Indian slaughtered animals are not specially bred for meat, they are malnourished and often not healthy, with the result the efforts to produce insulin from their pancreas proved to be uneconomical. India today does not have any organized slaughter house, where specially bred animals are slaughtered and the important organs removed, preserved and processed scientifically. Therefore, the Boots Company has to import the pancreas in a frozen state from U.K. and then process it locally. Approximately 10,000 kg of pancreas will be required to produce 1 Kg. zinc insulin crystals.

10. Since the number of slaughtered animals in the developed countries is related to their meat demand, the availability of the pancreas, and therefore the insulin from that natural source has a considerable limitation. This naturally has created a world-wide insulin shortage. India without an organized meat packing industry for meeting its meat requirements by specially breeding the animals for slaughtering, will have to depend entirely upon the developed countries for their frozen pancreas needs. This is going to be a big limiting factor for insulin production in future by this conventional technology in India.

11. Fortunately, a breakthrough has occurred in the insulin production technology, through the development of Biotechnological techniques. Even before the breakthrough for the development of human insulin by biotechnological techniques, technological developments did take place to purify insulin to reduce its antigenicity. This lead to the preparation of purified and highly purified insulins like (i) single peak (SP) insulin and single component (SC) insulin of Eli Lilly, (ii) mono-component insulins of Novo, (iii) highly purified and rarely immunogenic (HP & RI) insulins of (Nordisk) and (iv) Desphe Beta insulin of Hoechest. These insulins were prepared from the conventional porcin and beef insulins, by purifying them through chromatographic and electrophoretic techniques. This is the second phase in the development of insulin production technologies.

12. Even with these highly purified insulins certain allergic reactions were noticed, because the pig and cattle insulins are structurally different proteins from human insulin. The primary structure of the insulin is a monomer protein chain consisting of 51 aminoacids in two chains A and B, with a molecular weight of 6000 Daltons.

13. The therapeutically used conventional insulins are derived from pig pancreas

or beef pancreas (often as mixture of both). The insulins of these two species have different aminoacids sequence to human insulin. The pig insulin differs from human insulin in one aminoacid, while the beef insulin differs in three amino acids. These variations make the porcine and bovine insulins more antigenic to the humans. The ideal insulin to be used for the treatment of diabeties mellitus is therefore the human insulin. It is in this context the biotechnological approaches to produce human insulin arose.

14. Between the years 1980-82, while Eli Lilly in collaboration with a biotechnology Research company, Genentech, developed a process of producing insulin by the recombinant DNA technology, while Novo in Denmark and Laboratories Leo in Spain developed and started the human insulin production technology by enzymic modification of the porcine insulin.

15. The recombinent DNA technique consists of the *in vitro* incorporation of the synthetic genes of the A and B chains of the insulin molecule from the β cells of the islets of Langerhans from the human pancreas into a non-pathogenic laboratory strain of E.coli K.12 strain plasmid DNA. This new recombinant plasmid DNA is reinserted into the E.Coli. These bacteria are cloned in culture to get rid of those cells not having the recombinant plasmid. The pure cloned organisms are then persuaded to express the insulin gene, which produces the insulin. The plant for production of this insulin was formally opened on 5th April 1982 at Speke, Liverpool (U.K.)

16. Novo and Leo approached the production of human insulin by enzymic modification of the porcine insulin (Emp insulin). These companies have started manufacturing their human synthetic insulins from 1981-82.

17. Further developments also have occurred in insulin production technology in that Lilly has also produced biotechnologically the human proinsulin (A and B chains linked with C Peptide, which is the precursor of insulin in the pancreas) and by enzymic cleavage producing the human insulin. More recently the process for insulin genetically engineered from yeast also has been developed. These also, are likely to be in the market soon, as new technology for human insulin production.

18. Thus the world over has progressed from the conventional porcine and beef insulin from the pancreas of slaughtered animals to more purified and highly purified insulins and from there has even taken off to develop the technology of converting the porcine insulin to human insulin by enzymic modification and also completely moving away from the limited animal sources to the recombinent DNA techniques for the production of human insulin.

19. As far as India is concerned it is still producing the conventional insulin. Some efforts are being made at the department of Genetic Engineering at Jawaharlal Nehru University, New Delhi to produce the A and B chains by biotechnologi-

cal methods. The work has progressed very satisfactorily and soon they can be expected to have a workable technology developed.

20. The Boots Company (India) Ltd. has been working on purification of the conventional insulins. In short India has no modern insulin technology at production level and is relying on one company using the old conventional technology to meet about 75% of the country's real insulin needs.

21. It is under these circumstances the following recommendations are made.

(a) In view of the steadily increasing demand-supply gap for this essential life saving drug namely insulin, it will be necessary to expand the present production of insulin even by the conventional process. Since at present only one company is engaged in its production, apart from their expansion, even one more unit for the production of the conventional insulins in India will be of a great advantage for uninterrupted production and supply of the drug.

(b) Purified insulins are necessary for cases developing allergy and other hypersensitivity reactions. As of today they are being imported. Boots company (India) Ltd. are developing the technology for these in India. Some of the National Laboratories having strengths in Biological preparations can also take up this area of work on a priority.

(c) The enzymic modification of porcine insulin to produce human insulin is now well established. No R&D work is being done in India on this at present. Apart from the need for human insulin in this country,the development of this type of technology by itself is a technological challenge for the Nation and therefore some National laboratory must consider this project on priority basis.

(d) The production of human insulin through DNA technology is a great breakthrough and this will help in meeting the world requirements of insulin in future, when the cattle and pork pancreas availability in the world will get reduced. The biotechnological process developed by Lilly is in production and this will also undergo major changes soon to improve the process through the proinsulin production and using yeast instead of E.coli. In India R&D work on the production of insulin A and B chains has been progressing satisfactorily at the Genetic Engineering Dept., of Jawaharlal Nehru University, New Delhi. In order to hasten the translation of the technology developed at JNU, it will be worthwhile to have one or two pharmaceutical companies also to participate in taking the process to production technology either by sponsorship of the programme or acquiring the process at a specific stage of the development and get the project through on a time-bound programme. Department of Biotechnology can organise a task-force for a coordinated time-bound programme, since they have the necessary infrastructure and experts for such projects.