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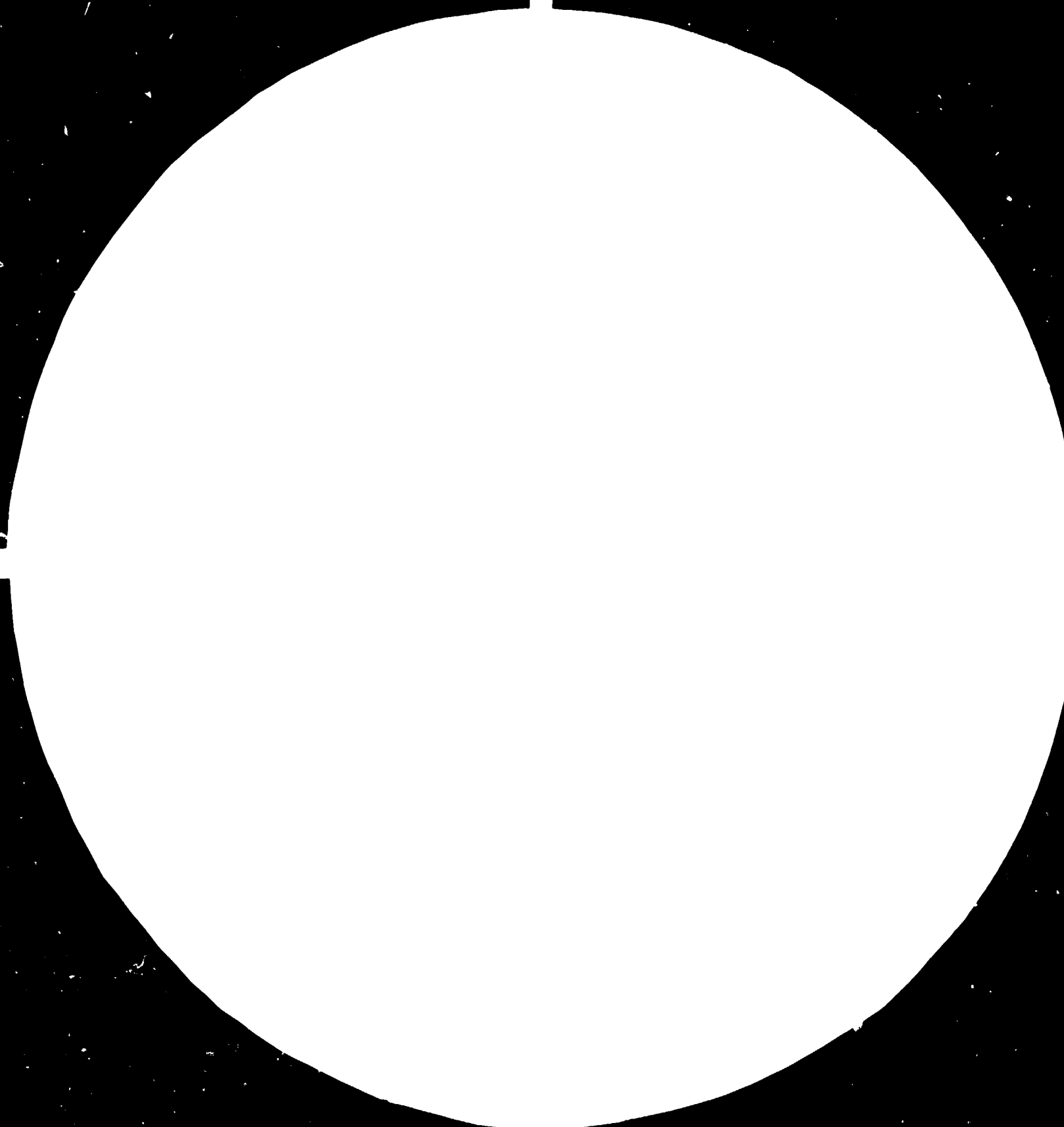

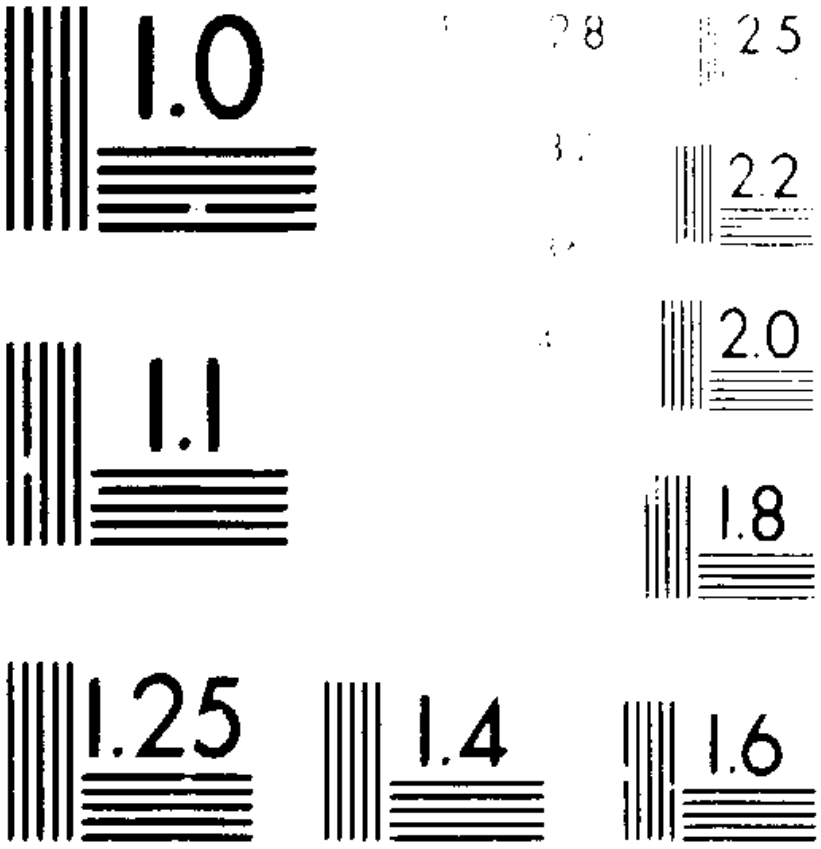

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India.

DEVELOPMENT OF TECHNOLOGY FOR PRODUCTION OF BIOCHEMICALS, PHYTOCHEMICALS AND STEROID HORMONES

DP/IND/83/021

INDIA

Terminal report*

Prepared for the Government of India
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of L. Pillich,
Pharmaceutical Industry Development Adviser

United Nations Industrial Development Organization
Vienna

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TABLE OF CONTENTS

EXPLANATORY NOTES

General

Value of the local currency: 1 U.S.$ = Rupees 10.42

Crore = 10,000,000 (ten million)

Organization

CDRI	CENTRAL DRUG RESEARCH INSTITUTE - LUCKNOW
CIMAP	CENTRAL INSTITUTE OF MEDICINAL & AROMATIC PLANTS - LUCKNOW
CIPLA	CHEMICAL, INDUSTRIAL & PHARMACEUTICAL LABORATORIES LIMITED - BOMBAY & BANGALORE
CSIR	COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH - NEW DELHI
OPPI	ORGANIZATION OF PHARMACEUTICAL PRODUCERS OF INDIA
PIRDC	PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT CENTRE
R & D	RESEARCH AND DEVELOPMENT
UNDP	UNITED NATIONS DEVELOPMENT PROGRAMME
UNIDO	UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
WHC	WORLD HEALTH ORGANIZATION

Technical abbreviations

16-DPA	16-DEHYDROPREGNENOLONE ACETATE

ACKNOWLEDGEMENTS

It is my duty to express my deep appreciation for the valuable assistance and information received from the concerned institutions, especially from CDRI, THEMIS CHEMICALS LTD. and UNICHEM LABORATORIES LTD., which is hereby gratefully acknowledged.

ABSTRACT

At the request of the Indian Government, possibilities for the further development of the Indian Pharmaceutical Industry in the field of biochemicals, phytochemicals and steroid hormones have been investigated.

In context of this objective, the present status of the R & D activity of pharmaceuticals has been analysed through a perusal of the work carried out in different research institutes and industrial units. It has been stated, that due to the effective collaboration of the Indian scientists, technologists and industrialists, the Indian Pharmaceutical Industry has achieved a high level of self-reliance and production capability in a wide variety of drug manufacturing technology and the climate for further development of the national pharmaceutical industry is advantageous. In order to increase the effectiveness of the R & D activity, recommendations have been made for the development of some existing research institutes, involving to a certain extent the support of the UNDP. The proposals related to the indigenous development of the R & D activity include also the assistance India can provide to other developing countries through establishment of International Training Centres.

The development, utilizing available raw materials, have been investigated through selection of technologies advantageously adaptable in India. Recommendations have been made for the development of indigenous manufacture of drugs in the field of biochemicals, phytochemicals and steroid hormones, which can be produced economically. The policy of the development of these products as well as the possibilities of securing the postulated requirements for production and the conditions for the acquisition of adequate technology has been discussed.

INTRODUCTION

The Indian Government requested UNIDO to entrust a Pharmaceutical Industry Development adviser with the investigation of possibilities for augmenting the development of technology for the production of biochemicals, phytochemicals and steroid hormones by the Indian Pharmaceutical industry in the National Sector, utilizing available raw materials. For this purpose, Mr. L. Pillich, UNIDO expert, had been delegated to India in a mission of three months.

The background of the Indian Government's request was that the Indian Pharmaceutical Industry had over the years acquired/developed technology for and undertaken production of a large range of synthetic drugs and some important antibiotics. However, there is still inadequate or no production of some synthetic drugs involving high technology, a large number of biochemicals, particularly those required for diagnostic and research purposes, hormones like insulin, some phytochemicals, cortico and contraceptive steroids and their key intermediates. Even where there is production of such items, it is predominantly in the hands of transnational companies.

Development of know-how for these high technology items would lead to their indigenous production to the extent feasible and thereby the country would achieve self-sufficiency in their production, and ultimately these products could be exported.

The CSIR laboratories, particularly Central Drug Research Institute, Lucknow, National Chemical Laboratory, Pune, Regional Research Laboratory at Jammu and Hyderabad are concerned with development of appropriate technology in the area of pharmaceuticals and transfer of know-how to industry for commercial production. The Biochemicals Unit of CSIR is also engaged in production of Research Biochemicals. Some units of the industry also have well equipped R & D laboratories and a high level of expertise. Among these CIPLA, UNICHEM and THEMIS Group, have promoted the development of technology and production of the above mentioned type of products.

The project is expected to promote the efforts to develop know-how for above products utilizing indigenously available raw materials. This know-how will be ultimately translated to production by the national sector of the pharmaceutical industry, including units in the public and private sector, and to a limited extent by the Biochemicals Unit of CSIR.

The mission started on 1st January 1984 and was completed on 31 March 1984.

The objective of the project is the development of technology for the production of biochemicals, phytochemicals and steroid hormones by the Indian Pharmaceutical Industry in the national sector utilizing indigenously available raw materials.

I. RECOMMENDATIONS

A. Increasing the effectiveness of R & D activity

1. Significant increase in the ratio of engineers and technologists possessing industrial experience is recommended within the staff of the CDRI.

2. Progressive encouragement - moral and financial - of the scientific and technical staff of the CDRI is recommended in the implementation of economical industrial processes.

3. Supplementing the pilot plant equipment of CDRI is recommended, with the equipment specified in the list enclosed under Annexure No. 2.

4. A detailed technological prescription is recommended to be followed in the elaboration of new manufacturing processes, according to Annexure No. 3.

5. Establishment of a technological unit of the CDRI is recommended in the vicinity of the pharmaceutical industry area (i.e. Bombay), with the financial support of the Indian Government and the sponsorship of Industrial Units.

6. Establishment of an International Training Centre for Bulk Drug Technologies is recommended in the frame of CDRI, at Lucknow, with the financial support of the Indian Government and the contribution of UNDP.

7. Establishment of an International Training Centre for formulation of pharmaceuticals in the Bombay College of Pharmacy is recommended, with the mutual financing of the Indian Government, the Industrial Units and the UNDP.

8. It is recommended that the CDRI should start with genetic engineering research activity in order to train qualified staff for the growing demands of biotechnology.

B. Concerning Development of Technologies

9. The hastening of the construction and functioning of up-to-date slaughter houses in the big cities of the country is recommended.

10. Local production of HEPARIN is recommended applying new technology characterized by preservation of the at present unused raw material.

11. Local production of PANCREATIN for therapeutic use is recommended through the organization of up-to-date collection of the pancreas.

12. Evaluation of the existing technology of CHOLIC ACID derivatives is recommended, giving preference to the production of DESOXYCHOLIC ACID and CHENODESOXYCHOLIC ACID.

13. The popularisation of some processes worked out in the CDRI is recommended among the small industrial units.

14. Optimisation of the existing production of HUMAN CHORION GONADOTROPIC HORMONE has been discussed.

15. Indigenous production of ALBUMIN and GLOBULIN from human blood is recommended, primarily for export.

16. Collaboration with a foreign company, e.g. BEHRINGWERKE GmbH, West Germany, is recommended for the development of BIOCHEMICAL REAGENTS, ANTIGENS and CLINICAL DIAGNOSTIC KITS.

17. Taking into consideration the local conditions, a development policy for the production of steroid hormones in India is recommended.

18. The revision of the existing industrial technologies for processing of medicinal plants is recommended in order to reduce the loss of organic solvents and to increase the yield.

19. The local cultivation of a new plant VOACANGA AFRICANA has been recommended and its seeds have been handed over for cultivation.

20. The investigation of the utilisation of BALANITES AEGYPTIACA is suggested on the basis of the UNIDO document No. IF/INT/77/021, which has also been handed over.

21. Collaboration with foreign research institutes is recommended, in the further detailed pharmacological investigation of about 400 medicinal plants, whose biological activity has been established in the systematic investigations at CDRI.

22. The selection of the drugs of essential importance for India is recommended, with the simultaneous designation for the development of their processes.

II. ANALYSIS OF THE PRESENT STATUS

Many research institutes and industrial units dealing with the development of the pharmaceutical industry have been visited (Annexure No. 1) and a number of scientists as well as technologists, industrialists and state officials concerned with pharmaceuticals have been consulted. Based on the compiled information, the present state of the Indian Pharmaceutical Industry in the national sector can be set down as follows.

India, in spite of the tremendous efforts made in the interest of raising the public health and nutritional level, is still faced with many communicable and non-communicable diseases. The mortality rates for women and children are still high, almost one third of tne total deaths occur among children below the age of five years, infant mortality is around 130 per thousand live births. Only 31% of the rural population have access to potable water supply and 0.5% enjoy basic sanitation. Diarrhoeal diseases, blindness, leprosy, tuberculosis and other tropical diseases still have a high incidence. The high rate of the population growth, lack of safe drinking water, poor environmental sanitation, poverty and ignorance are hindering the efforts made in the interest of amelioration of public health.

Though the rapid growth of drug consumption achieved in the last 30 years (shown below), the actual per capita consumption is far below the real need of the population.

Year	Consumption per capita*
1950-51	Rs 0.45
1960-61	Rs 1.61
1973-74	Rs 6.56
1979-80	Rs 17.58

*OPPI reports

In the last 15 years, the Indian Pharmaceutical Industry has achieved a significant growth in the production of pharmaceutical products. With this striking progress, the rate of the production of bulk drugs rose above the increase in the production of formulations.

Year	Production of bulk drugs	Production of formulations
1965-66	Rs 18 crores	Rs 150 crores
1975-76	Rs 130 crores	Rs 560 crores
1978-79	Rs 200 crores	Rs 1050 crores
1981-82	Rs 275 crores	Rs 1300 crores

The indigenous production of bulk drugs supplements the major needs of the formulations produced in the country. Nevertheless a good part of the

bulk drugs are also imported to augment indigenous production. The following are the imports of bulk drugs into the country during the last four years.

Year	Imports (c.i.f.)
1978-79	Rs 800 million
1979-80	Rs 938 million
1980-81	Rs 1120 million
1981-82	Rs 1360 million

In India, currently there are in operation more than 5000 units in the drug industry, 135 of them belonging to the organized sector. Sectorwise value of the production of bulk drugs in 1980-81 was as follows:

Public sector	RS 63 crores	little growth during the last 3-4 years
Foreign sector	RS 53 crores	
Indian organized private sector	RS 98 crores	pronounced growth during the last 3-4 years
Indian small scale sector	RS 26 crores	
Total bulk drugs	RS 240 crores	

The Indian Government in appraisal of the situation of the public health, took many measures in order to speed up the development of the national pharmaceutical industry. The most effective steps in this respect were the enactment of the new PATENT LAW in 1970 (which became operative in 1972-73) and the announcement of the NEW DRUG POLICY in 1978, which gave a tremendous impetus to the Indian pharmaceutical industry.

The main features of the PATENT LAW as applied to drugs are:

1. Term of the patent to lapse, seven years after the date of filing and five years after the date of sealing, whichever is less.

2. Patent can be filed for a process only, not for a product.

3. Every patent is to be endorsed with a licence of right, effective three years after the expiry of the patent.

The major objectives of the NEW DRUG POLICY are:

- to develop self-reliance in drug technology,
- to provide leadership role to the public sector,
- to encourage the growth of Indian sector,
- to ensure that drugs are available in abundance,
- to make drugs available at reasonable price,
- to keep careful watch on quality of drugs.

Due to the active collaboration of scientists, technologists and industrialists, the Indian Pharmaceutical Industry has achieved a high level of self-reliance in a wide variety of drugs. Recent major achievements in bulk drugs manufactured by the National Sector are:

Ampicillin	Lorazepam
Amoxycillin	Mebendazole
Clofazimine	Methyldopa
Diazepam	Metoprolol
Diloxanide	Metronidazole
Doxycyclin	Propranolol
Erythromycin	Salbutamol
Ethambutol	Sulfamethoxazole
Furazolidone	Terbutaline
Glybenclamide	Tinidazole
Ibuprofen	Trimethoprim

Nowadays, the conditions of the development of the national pharmaceutical industry can be characterized by the following favourable climate:

- Due to the systematic efforts to promote higher education, a considerable pool of well-educated scientists, technologists and engineers is available in the country.

- Many research institutes dealing with the development of pharmaceuticals are functioning in the frame of the Council of Scientific and Industrial Research as well as in the bigger industrial units. These research organizations are provided with up-to-date library, advanced instrumentation and partially equipped pilot plants.

- The infrastructure for industrial development in India has reached a high state, the equipment required for the industrial processing of pharmaceuticals is produced locally and experienced maintenance organizations can assure their continued functioning.

- Many indigenously produced basic chemicals are already available in India, which makes possible the extensive production of intermediates, leading to the phased development of the vertical processing (manufacturing) of bulk drugs.

- Due to the incentives offered by the Government, an increase in the industrial entrepreneurship took shape, which resulted in the intensification of the R & D activities in the field of pharmaceuticals.

The exploitation of this potential requires an increasing degree of systematic organization and effective coordination of the research and development activity of the pharmaceutical industry.

The organization as well as the field of activity and its efficiency is very different in the institutions visited, occasionally presenting parallelism in the work.

III. EVALUATION OF THE FINDINGS

The Central Drug Research Institute, Lucknow, embracing the broad spectra of the research on chemo- and immuno- therapeutic agents and related basic oriented research as well as standardisation of process know-how for drugs, intermediates, fermentation chemicals and biochemicals, is the nationally recognized centre for the development of pharmaceuticals. Highly qualified staff of scientists, library facilities at the 'National Information Centre for Drugs & Pharmaceuticals', 'Regional Sophisticated Instrumentation Centre' and up-to-date experimental animal house are the salient strength of the institute which has achieved remarkable results in the past few years in basic research as well as evolving new technologies on a laboratory scale.

The bottleneck of the Institute's activity in the area of process development of established drugs, appears to lie in the practical realisation of the scaling up of the processes standardised in the laboratory. Some of the reasons hindering the exploitation of this activity apparently are:

1. Inadequate exposure and experience of the staff to industrial problems, for a keen a[illegible]aisal of the likely impediments.

2. Prevailing insufficient equipment facilities in the pilot plant for scaling up the processes worked out on a kilogram scale.

3. Lack of effective interaction with the pharmaceutical industrial units, owing to the remote location from the pharmaceutical industry centres.

The pharmaceutical research activity of the Regional Research Laboratory, Jammu - although it represents only a minor part of the very extensive and broad development programme of the Institute - is wide-spread, including phytochemical screening, microbiological processing of steroid hormone derivatives, synthesis of new molecules, pharmacological and pharmacokinetic studies, applied botany, applied mycology, tissue culture as well as chemical engineering and design. The equipment of the Institute is up-to-date, but the diverse working programme containing certain overlappings is hampering its exploitation. In this Institute, the concentration of the research work is recommended through limiting the working programme.

In the Regional Research Laboratory, Hyderabad, as a result of extensive research work by a small team, valuable new molecules have been synthesised and a new drug successfully introduced in the market. The Institute is in possession of an excellently equipped pilot plant, providing outstanding facilities for scaling up the processes worked out on a laboratory scale. Unfortunately, this significant advantage which would be highly useful to the drug industry is only slightly exploited, since the pharmaceutical research activity represents only a small part of the immense developing programmes of the Institute. Profitable exploitation of the excellent pilot plant facilities and of the technological experience of the staff is recommended in the interest of the speedy development of the pharmaceutical industry.

The activity of the National Chemical Laboratory, Pune, in the area of drugs and drug intermediates, is restricted to the synthesis of known drugs,

following new approaches in respect of raw materials, intermediates and reaction conditions. The accomplishment of this objective is realised by the financial support of the industry, sponsoring well-identified projects to develop process of 'high technology' for specific drugs. This Institute has especially been successful in establishing close collaboration with industrial units. Though the pharmaceutical research activity represents only a small segment of the Institute's total programme, a series of new, economical technologies have been worked out and industrialised, for the production of drugs which are either exclusively imported or insufficiently produced in the country. The prospective research programme for pharmaceuticals of the Institute is oriented towards development of new methodologies in organic synthesis and capability development. The present activity as well as the proposed programme of the Institute merits intensive support especially if the industrial exploitation of the scientific findings of this Institute is to be realised.

Among the Institutes engaged in drug research, CDRI has the most appropriate facilities to accomplish the whole gamut of the very complex activity of the development of pharmaceuticals. While the Institute is well-equipped to undertake and effectively carry out the different facets of research associated with new drug development, the technological activities of the Institute need to be augmented. To this end, a significant increase in the ratio of engineers and technologists, possessing industrial experience and an appropriate way of looking at the practical realisation of scientific findings, is essential. It is recommended that engineers and technologists of the Institute should work for a considerable period in industrial factories to acquire an industrial bias.

An essential prerequisite for productive work is systematic moral and financial encouragement of the scientific and the technical staff in the implementation of economical industrial processes.

With the aim of increasing the effectiveness of the pilot plant of the CDRI, a list of equipment to be supplemented has been worked out (Annexure No. 2), and a draft (scheme) of detailed technological prescriptions to be applied for the elaboration of new manufacturing process has been prepared (Annexure No. 3). In the interest of enhancing the practical exploitation of the research achievements, it is suggested that the technological activity of the Institute should be transferred to the vicinity of the pharmaceutical industry. For this purpose, the establishment of a Technology Extension Centre of the Institute would be desirable, within easy reach of Bombay, with the financial support of the Indian Government, and the sponsorship of the Industry. It is recommended that CDRI, in collaboration with the experts of the pharmaceutical industry, should prepare a detailed proposal for the establishment of this Technological Extension Centre.

In the interest of helping other developing countries to attain self-reliance in bulk drug technology, an International Training Centre for Bulk Drug Technologies is recommended within the frame of CDRI, at Lucknow, with the financial support of the Indian Government and the contribution of the UNDP. In case UNDP should accept this proposal, CDRI is ready to prepare a detailed project report for the establishment of this Centre.

In concurrence with the above proposal, the establishment of an International Training Centre for Formulation of Drugs is suggested within the frame of Bombay College of Pharmacy (Kalina, Bombay). This College is a pioneering institution of pharmaceutical education in India, imparting training to about 240 students annually, to provide trained pharmacists for the pharmaceutical industry and the country's public health services. The College founded in 1957 by the Maharashtra State Branch of the Indian Pharmaceutical Association - has a built-up area of 50,000 sq. ft., including library, lecture halls, auditorium and well equipped laboratories, erected through the aid of donations from the major pharmaceutical laboratories in Bombay. The sponsoring industrial companies also undertake the training of students in their industrial units, laying thereby the foundation of their orientation to an industrial way of thinking. The College is in possession of a free land of 50,000 sq. ft. suitable for the construction of the necessary buildings. The teaching staff of the College is highly qualified, possessing the requisite aptitude, to train the candidates of other developing countries in the field of formulation of drugs, as well as imparting knowledge of the public health services. The construction of the International Training Centre could be financed, jointly by the Indian Government and the pharmaceutical industry, with the support of the UNDP. If UNIDO accepts this proposal, the Bombay College of Pharmacy will prepare a concrete proposal for the evaluation of the costs of the establishment and its recurring expenditure. Details of equipment with cost and space required for the Centre for Formulation are shown in Annexure 4.

The above two training Centres would contribute to the efficient development of the Indian Industry and through the training of technologists of the other developing countries, would give substantial aid to the establishment of the pharmaceutical industry in these countries.

The research facilities available at CDRI make the above Institute admirably suitable, both for carrying out research as also imparting training to scientists from developing countries, in the areas of biotechnology and genetic engineering - an area, which UNIDO has been trying to promote in recent years, and which holds immense possibilities and potentialities for pharmaceutical production. It has an excellent animal house with a number of inbred strains of animals available, including Balb C mice; good histological research laboratories, a peptide synthesis laboratory, pilot plant and fermentation facilities, with fermenters varying in size from 5 litres to 1500 litres and with good capability of growing both yeasts and bacteria. CDRI in its own research programme, has been developing facilities for hybridoma techniques and gene cloning, but if these facilities could be upgraded with some aid by UNIDO, CDRI could play a very useful role without any loss of time, in accepting and training scientists from developing countries in different aspects of biotechnology. If UNIDO is agreeable to this, in principle, CDRI would be prepared to submit a proposal for this.

IV. DEVELOPMENT OF TECHNOLOGIES

The investigation concerning the development of technologies utilising available raw materials, resulted in the following conclusions:

A. Biochemical products

Since, in India, the development of up-to-date slaughtering technology is on the way, the exploitation of animal glands for the production of pharmaceutical products shows an upward tendency. It is therefore suggested that erection of additional up-to-date slaughter houses in all the major cities be considered. On the basis of the investigations of the slaughtering technology of the DEONAR ABBATOIR, BOMBAY, it was found that significant numbers of animals are continuously slaughtered (about 700 buffaloes and bulls, 6500 sheep and goats per day) and with the existing facilities, adequate collection of animal glands is feasible. Taking into account that additional slaughter houses are under construction in Calcutta, Goa and Hyderabad, planning for the indigenous production of the following products is recommended.

Production of HEPARIN, starting from MUCOSE and SEROSE obtained from the casing of the small intestine of buffaloes, bulls, sheep and goats, by applying a new technology for preserving the HEPARIN content of the raw material through heating and drying on the spot in the slaughter house. The indigenous production of HEPARIN is all the more desirable, because the collection and casing of small intestine is already organized, but the raw material for HEPARIN is not being utilised. The main points of the technology, the advantages of the process and details for the acquisition of the know-how - eventually through compensation against the supply of crude HEPARIN, has been discussed; the suggested technology being a patented process of Gideon Richter Limited, Budapest. A brief description of the process is indicated in Annexure 5.

The production of PANCREATIN is recommended, since, through the slaughtering technology actually applied at the DEONAR ABBATOIR, it is feasible to collect the pancreas of the slaughtered animals, in a proper state, corresponding to the requirements of the pharmaceutical processing, through the installation of refrigeration facilities in the cooling-room of the slaughter house. Actually the pancreas of the slaughtered animals is only partially collected and is used in the leather industry. Since this utilisation requires inferior grade, it can be met by pancreas collected under more adverse slaughtering conditions. The details of the technology for the production of pancreatin, corresponding to the requirements of the pharmacopoeia, has been discussed and can either be developed at CDRI or the know-how obtained through foreign collaboration. A brief description of the process is given in Annexure 6.

Indigenous production of INSULIN cannot be recommended, since the slaughtered animals are mostly undernourished, therefore their pancreas having a low INSULIN content, cannot be economically processed. The achievements of biotechnology in the future, is likely to solve the insulin production through genetic engineering, therefore the development from animal sources in India is not viable.

The development of the local production of CHOLIC ACID derivatives can be recommended, since the raw material, viz. the bile of buffalo, sheep and goat can be easily collected applying conservation techniques. The flow sheet for the technology of production of DESOXYCHOLIC ACID and CHENO-DESOXYCHOLIC ACID has been discussed. A brief outline of the process is shown in Annexure 7.

At CDRI, the processes for the production of several biochemical products derived from animal glands and other byproducts, have been developed. PEPTONE from buffalo meat, PEPSIN produced from the internal lining of buffalo stomach, TRYPSIN from buffalo pancreas, PROTEIN HYDROLYSATE from oil seed cake and bacteriological ingredients like PANMEDE, TRYPTON and PROTEOSE PEPTONE. These processes lead to products corresponding to quality requirements, are feasible and seem to be economical. Nevertheless, with the exception of peptone and protein hydrolysate, they are not yet realised on a commercial scale. On the basis of the estimation of the cost of production and the calculation of the profitability, the popularisation of these processes is recommended, particularly among the small industrial units.

The utilisation of raw material of human provenance for production of pharmaceuticals offers a particularly advantageous potential in India. The high growth of population can provide abundant raw material for the production of hormones isolated from urine of pregnant women. The manufacture of CHORION GONADOTROPIC HORMONE is already being carried out at the Unichem Laboratories Limited. Possibilities for optimising of the at present applied technology, as well as the further extension of the production, have been discussed.

The ALBUMIN produced from human blood is much in demand on the world market, therefore it could be a potential export item for India. The γ-GLOBULIN as a byproduct of albumin is more and more applied in 'component therapy' in the form of SUPERIMMUN γ-GLOBULIN manufactured from the blood of immunised donors. The local production of both the abovementioned products preferred in the Western countries is recommended in India, in spite of the fact that production of albumin and γ-globumin starting from human placenta is already in operation in the country. The organization of the system of donors and the flow sheet of the technology have been discussed, in addition the provision of procuring the know-how of the process is suggested, advantageously as compensation for the supply of intermediates from HUMAN LABORATORIES, BUDAPEST. A brief outline of the process is indicated in Annexure 8.

The development for the production of BIOCHEMICAL REAGENTS, different ANTIGENS used in the diagnosis and immunotherapy of allergic disorders and some CLINICAL DIAGNOSTIC KITS has been started at the CSIR CENTRE FOR BIOCHEMICALS, DELHI. Since the clinical applications of these products is rapidly growing, a high speed increase of the demand is expected, therefore the development in this field is recommended. Besides, the local research which has to be carried out suitably in the frame of the genetic engineering activities of the CDRI, the launching of a collaboration with a competent foreign company, e.g. BEHRING WERKE, W. Germany, would be advisable. This could be amalgamated in the future, with the activity of the INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY to be established in India with the support of the UNDP.

B. Steroid hormones

These days the world production of the large assortment of steroid hormone derivatives has come to a particular phase. While during the past decades, the main raw material base for the production was DIOSGENIN, isolated from the wild Mexican Dioscorea, the drastic increase of its price compelled the big steroid producing companies to search new raw materials and new technologies. Due to the intensive research activity considerable progress has been achieved, in the field of the production of steroid hormones. The total synthesis and efficient new microbiological processes for the degradation of the side chain of natural steroids have been worked out. Consequently, new economical raw materials came to the fore, like SITOSTEROL, STIGMASTEROL, CHOLESTEROL, HECOGENIN, SOLASODIN, etc. to rival diosgenin. Since the variety of the raw materials used has been increased and further achievements are likely in the development of the technological processes, the production of steroid hormones has to be developed in a very flexible way, being adaptable to the prevailing requirements.

In India, the cultivation of DIOSCOREA FLORIBUNDA is being carried out on a large scale and the processing of DIOSGENIN as well as the production of key steroid intermediates is being carried out on an industrial scale. However, it is to be noted that due to the high cost of farming, the cultivation of dioscorea cannot be competitive with the wild one, which is simply collected, e.g. in China. In different research laboratories of the country, intensive R & D development has been started in different fields of steroid hormones. The fact that in India, in principle, all steroid raw materials can be available and the health care of the country requires a large assortment of steroid compounds, seems to motivate the wide-spread research activity which is going on, but it has to be taken into account that the effectiveness of the development can be warranted only by organized concentration of the efforts. Consequently, the recommended policy for the development of the steroid hormone industry in India can be characterized by the following directives:

- The self-sufficiency should be achieved by realisation of profitable global currency balance, with a positive approach as high as possible, instead of aiming for the local production of the whole assortment of steroid derivatives.

- The economy of the rich potential of steroid raw materials in India should be carefully investigated, in order to select the most promising sources and the development has to be concentrated.

- The R & D activity should be aimed on the development of the production of those key intermediates and steroid products of vital importance (contraceptives and basic corticoid hormones) which can be economically produced in India.

- The production of the above items should be realised in large quantities, which besides covering the local demand, also assure the export value needed to purchase the missing steroid derivatives, as well as to acquire the necessary know-how stages, on the basis of compensation agreement with companies which are in want of raw materials.

The potential raw material richness of India raises some problems of the abundances. DIOSGENIN as the traditional key intermediate for the production of steroid derivatives can be isolated from many locally available plants.

DIOSCOREA FLORIBUNDA
DIOSCOREA COMPOSITA
HYBRID OF D. FLORIBUNDA & D. COMPOSITA
KALLSTROEMIA PUBESCENS
COSTUS SPECIOSUS
BALANITES ROXBURGHII
TRIGONELLA FOENUM GRAECUM

The development of all these plants is figuring more or less in the programme of different laboratories, leading to undesirable overlapping (from time to time contradictions) and dilution of the efforts. It is desirable that the chances of the economical feasibility of all these plants should be reviewed with the participation of competent experts and the further developments should be concentrated on the most promising resources.

Considering the pending situations of the steroid industry as explained above, the possibility of the exploitation of additional raw material sources has to be investigated.

STIGMASTEROL and SITOSTEROL can be isolated from the deodorizing sludge in the refining of sunflower oil or soyabean oil, as a byproduct of Vitamin E. Since the production of both sunflower oil and soyabean oil are taking shape, it is suggested that the economics of the processes applied to the isolation of these sterols should be investigated. The salient features of these processes have been discussed. A brief description of the process is shown in Annexure 9.

An alternative source of SITOSTEROL is the sugar-cane press mud, plentifully available in India. Since the sugar-cane wax is containing only about 10% sterol mixture, the promise of the profitable exploitation of the latter is the utilization of the former. The investigation of this source is advisable.

CHOLESTEROL which again seems to be a promising raw material for the production of steroid hormones, can be obtained economically either from wool grease or from fish oil. As both raw material sources are abundantly available in India, the possibility of their exploitation is suitable for investigation. The chances of acquisition of a related know-how has been discussed.

The research programme at CDRI, envisaging the development of processes for the production of essential steroid hormones, is in accord with the suggested policy of development. At the Regional Research Laboratory, Jammu, overlapping research work is going on in the field of microbiological transformation of steroid compounds, the elimination of it is recommended.

In the range of the contraceptives, priority has to be given for the production of NORETHISTERONE starting from 16-DPA and D-NORGESTREL by total synthesis. In the group of corticoids, the production of HYDROCORTISONE and PREDNISOLONE has to be in spotlight. With these products - although the research work by CDRI has already achieved significant partial results, the difficulties of scaling up have to be considered. The solution of the problem can be

recommended in the frame of cooperation-agreement with companies which are in want of steroid raw material and need steroid key intermediates.

The indigenous production of other steroid hormones is recommended to be postponed, partially because it would take too much capacity at the expense of the essential products, and partially because the demand of the country can be covered through cooperation-agreement against exported intermediates. Some sources of technology for possible collaboration for local production of some of the above biochemicals and steroid hormones are indicated in Annexure 10.

C. Phytochemical products

The extremely rich flora of India is offering many plants already exploited as well as a lot of dormant potential for the utilisation of other plants available in the country.

Concerning the plants already processed on an industrial scale, the revision of the processes under operation is recommended considering the following points of view:

- Whether the loss of organic solvents used for the extraction, can be reduced by the application of automatised counter-current extractor, operating in a closed system. The advantages of the process and the mode of the acquisition of the equipment has been discussed.

- Whether the use of organic solvents can be saved applying high-pressure technology for the isolation of the active ingredients. The possibilities of carrying out this type of investigation have been discussed.

- An assessment of the efficiency of the industrial processes already under operation is recommended and if their yields are not satisfactory, optimising the technology is advisable, either in indigenous research laboratories or in the frame of foreign collaboration. The implications of the latter have been discussed.

The series of the medicinal plants already exported from India has to be investigated from the point of view of the possibilities of exporting intermediates of higher value instead of the dried crude herbs. This would, besides increasing the value of the items, lead to the standardisation of the quality, the want of which is often the cause of significant devaluation of the goods.

The local cultivation of a new plant VOACANGA AFRICANA has been recommended and its seeds have been handed over to the Central Institute of Medicinal and Aromatic Plants, Lucknow. The seeds of the fruits of this tree contain about 2% TABERSONIN, which is much in demand as a starting material for the synthesis of VINCA ALKALOIDS.

The fruits of BALANITES AEGYPTIACA seem to be a new and promising source of diosgenin. A UNIDO document entitled 'BALANITES AEGYPTIACA, AN UNUTILISED RAW MATERIAL POTENTIAL READY FOR AGRO-INDUSTRIAL EXPLOITATION, No. TF/INT.77/021' - which has been handed over - represents an exhaustive

survey for the utilisation of this plant. It is recommended that taking into account the above economics of its exploitation should be investigated.

At the CDRI, during the last three decades, nearly 2,000 Indian medicinal plants have been systematically investigated with the aim of discovering new drugs. The ethanolic extracts of all botanically authenticated plants were screened through nearly 100 biological tests and further research work has been carried out with the plants in which the activity was of a significant order. Based on this broad biological screening, more than 400 plants manifested different biological activities. From the promising plants, many active ingredients have been isolated and the chemical structure of most of them identified; several types of novel structures have been found.

The immense research work, which has been done in the frame of this multifold examination of medicinal plants, has resulted in interesting findings of high scientific value. The proving of the eventual therapeutical application of these valuable research achievements need prolonged and costly investigations. It is advisable to investigate the organization of this work in the frame of a collaboration with foreign research institutes involved in the same field.

In order to increase the efficiency of the development of the Indian pharmaceutical industry in the National Sector and to achieve self-sufficiency, a potent organization and coordination of the R & D activity of the country is required. In the interest of this objective, it is recommended that an expert committee of prominent clinicians, researchers and industrialists should scan the international drug armamentarium, determining the drugs of essential importance for the country and deciding in the meantime which institute should carry out the necessary research work for each technology and which company should shoulder the industrial realisation of different products.

Annexure No. 1

LIST OF THE VISITED INSTITUTIONS

1. CENTRAL DRUG RESEARCH INSTITUTE, LUCKNOW
   Dr Nitya Anand, Ph. D., F.N.A., Director and his collaborators

2. CENTRAL INSTITUTE OF MEDICINAL & AROMATIC PLANTS, LUCKNOW
   Dr Akhtar Husain, Ph.D., Director

3. INDUSTRIAL TOXICOLOGY RESEARCH CENTRE, LUCKNOW
   Dr G.B. Singh, M.D., Director and his collaborators

4. NATIONAL BOTANICAL RESEARCH INSTITUTE, LUCKNOW
   Dr G.S. Srivastava, Ph.D., Asst. Director

5. REGIONAL RESEARCH LABORATORY, JAMMU
   Prof. K.K. Kapoor, Chairman, Industrial Survey, and his collaborators

6. COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH, NEW DELHI
   K.N. Johry, Head, International Scientific Collaboration

7. CSIR CENTRE FOR BIOCHEMICALS, NEW DELHI
   Dr S.V. Gangal, Ph.D., Scientist

8. V.P. CHEST INSTITUTE, UNIVERSITY OF DELHI, DELHI
   Prof. T.A.V. Subramanian, Ph.D., F.R.I.C., Head, Biochemistry Division

9. WORLD HEALTH ORGANIZATION, NEW DELHI
   Dr B.B. Gaitonde, Regional Adviser

10. UNICHEM LABORATORIES LTD., BOMBAY and HYDERABAD
    A.V. Mody, Managing Director, and his collaborators

11. THEMIS CHEMICALS LTD., BOMBAY, VAPI and HYDERABAD
    S.D. Patel, Chairman, and his collaborators

12. CHEMICAL, INDUSTRIAL & PHARMACEUTICAL LABORATORIES LTD., BOMBAY and BANGALORE
    Dr Y.K. Hamied, Ph.D., Managing Director, and his collaborators

13. NATIONAL CHEMICAL LABORATORY, PUNE
    Dr L.K. Doraiswamy, Ph.D., Director, and his collaborators

14. REGIONAL RESEARCH LABORATORY, HYDERABAD
    Dr G. Thyagarajan, Ph.D., Director, and his collaborators

15. BOMBAY COLLEGE OF PHARMACY, BOMBAY
    Dr H.P. Tipnis, Ph.D., Principal, and his collaborators

16. DEONAR ABBATOIR, BOMBAY
    Dr D.N. Gore, B.V.Sc., Chief Inspector, and his collaborators

17. INSTITUTE FOR RESEARCH IN REPRODUCTION, BOMBAY
    Dr (Mrs) Usha Joshi, Ph.D., Deputy Director

Annexure No. 2

EQUIPMENT FOR THE PILOT PLANT

SUGGESTED AS COMPLEMENTARY MACHINERY TO THE EXISTING OUTFIT AT CDRI

		Estimated price (US$)
1.	Glass reactor 50 litres, with flame-proof electric heating mantle and agitator, reflux-cum-distillation assembly, with 20 litres receiving flask and supporting structure. (JENA or QUICKFIT)	30,000
2.	Glass reactor 80 litres, with flame-proof electric heating mantle and agitator, reflux-cum-distillation assembly, with 20 litres receiving flask, 10 litres feeding funnel and supporting structure. (JENA and QUICKFIT)	36,000
3.	Glass vacuum distillation equipment "ROTADEST". Set of 2, 5, 10, 20 and 50 litres. (BUCHI, SWITZERLAND)	56,900
4.	Complete glass assembly with glass rectification column on 200 litres reactor. (JENA or QUICKFIT)	60,000
5.	Glasslined steel reactor with slip-ring stuffing box, flame-proof drive unit, impeller mixer of variable revolution, thermometer with thantal peak, accessories from glass and stainless steel respectively, with teflon stuffing, (condenser with supplementary cooling, reflux divider, distillate cooler with interconnecting piping suitable for reflux and distillation), with two receiver tanks and two feeding tanks able to operate in vacuum, to be provided with compressed air and inertial facility respectively. The mantle of the reactor and the receivers to be provided with deep cooling. Capacity 200 litres. Operation pressure: Shell-full vacuum, jacket 4 kgs.sq. cm. (PFAUDLER).	42,000
6.	Stainless steel reactor (s.s. 316) 250 litres, jacketed, agitated with flameproof drive unit of variable revolution, with teflon slip-ring stuffing box, condenser of s.s. 304, with interconnecting piping suitable for reflux and distillation. Operating pressure: Shell-full vacuum, jacket 4 kgs/sq. cm. (INDIGENOUS).	30,000
7.	Stainless steel reactor (s.s. 316) 500 litres, jacketed, agitated with flameproof drive unit, with internal cooling coil, condenser and interconnecting piping suitable for reflux and distillation. Operating pressure: Shell-full vacuum, jacket 2 kgs/sq. cm. (INDIGENOUS).	40,000

		Estimated price (US$)
8.	Stainless steel cone bottom vessel (s.s. 304) 400 litres, with gate agitator, flame-proof drive unit of variable revolution, provided with limpet coil on the shell, condenser and receiver of s.s. 304. Operating pressure: Shell-full vacuum, jacket 2 kgs/sq. cm. (INDIGENOUS).	35,000
9.	Mild steel reactor 250 litres, jacketed and agitated provided with mild steel condenser (2 sq. metre) and receiver (50 litres). (INDIGENOUS)	15,000
10.	Distillation column (s.s. 304) with grate plates. (GANSONS, BOMBAY).	15,000
11.	Glass liquid-liquid extractor, synthem "RDC" with 80 mm diameter, provided with mixture of variable revolutions, and feeding piston-pump. Capacity: 80-100 litres fluid per hour (CHEMIMAS, BUDAPEST).	16,000
12.	Stainless steel autoclave 20 litres, with flame-proof electric heating mantle and tilting operation. Operating pressure: 100 Atm. (PAAR INSTRUMENT CO., MOLINE, U.S.A.).	30,000
13.	Stainless steel autoclave 10 litres with flame-proof electrical heating mantle and magnetic agitator. Operating pressure: 100 Atm. (BUCHI, SWITZERLAND).	25,000
14.	WESTFALIA-SEPARATOR for liquid-liquid separation Type T.A.I. or S.A.I., Capacity: 100 litres per hour (WESTFALIA, W. GERMANY).	11,000
15.	Filtering-centrifuge Type "COMICONDOR", with 600 mm. diameter basket of s.s. 304, with flame-proof drive unit.	12,000
16.	Sedimenting-centrifuge Type "COMICONDOR", with 600 mm diameter basket of s.s. 304, with flame-proof drive unit.	12,000
17.	SEITZ-FILTER with 20 frames of 200 x 200 mm.	4,200
18.	SEITZ-FILTER with 20 frames of 400 x 400 mm.	11,400
19.	SPARKLER-FILTER jacketed, with 8 plates of 250 mm. diameter and s.s. pump with flame-proof motor.	10,000
20.	SCHENK-FILTER medium size.	14,000
21.	DRUM-FILTER, with 300-400 mm. layering band (GANSONS, BOMBAY).	7,000
22.	DRUM-DRYER 50 litres, in double cone-shaped construction. (GANSONS).	24,000
23.	GRINDING MACHINE Type "ALPINE"	35,000
24.	GRINDING MACHINF Type "MICRO-PULL".	32,600

		Estimated price (US$)
25.	GRINDING MACHINE Type "FITZ-MILL".	26,000
26.	VIBRATING FLAT SIEVE. (GANSONS)	5,000
27.	PULPING PUMP Type "FRIMA".	5,000
28.	DOSING PUMPS Type "BRAUN-LUBBE".	21,000
29.	DOSING PUMPS Type "LEWA".	7,500
30.	DOSING PUMPS Type "HAUKE" in heatable construction	10,000
31.	Stainless steel centrifuge pumps for transport of fluids.	1,800
32.	Manipulation-tanks of 100 litres, s.s. 304, mobile, operating pressure 2 kgs/sq. cm. (5 units).	6,500
	Total	686,900

AUXILIARY EQUIPMENT

Engine house for vacuum	70,000
Engine house for compressed air	50,000
Deep freezing system	50,000
Air conditioning installation	40,000
Miscellaneous equipment	40,000
Total	250,000

Note: Steam and electrical energy supply is available in the CDRI, therefore had not been calculated.

MOUNTING OF THE ABOVE EQUIPMENT

The approximate mounting cost of a pilot plant can be estimated at 50% of the total value of the installed equipment; in the given case this is US$ 470,000.

SUMMING UP OF THE ESTIMATED COST OF THE MACHINERY

Technological equipment	686,900
Auxiliary equipment	250,000
Mounting	470,000
Grand total	1,406,900

SPACE DEMAND OF THE UNIT

Estimation of space demand of the technological equipment:

a) Glass equipment (POS. 1-4, 11)		50 m^2
b) Reactors (POS 5-10, 12-13)		100 m^2
c) Separators, pumps, etc.		30 m^2
d) Grinding, sifting, etc.		20 m^2
e) Miscellaneous		40 m^2
	Total	240 m^2

Space demand of the auxiliary equipment:

Rough estimation	80 m^2

MAIN DIMENSIONS OF AN ADVISABLE BUILDING

a) For technological manipulations

Surface	10 x 24 m
Internal height	6 m (with interposed platform)

b) For auxiliary equipment

Surface	10 x 8 m
Internal height	3,5 m

Annexure No. 3

TECHNOLOGICAL PRESCRIPTION

NAME OF THE PRODUCT

1. Name of the product, utilisation and formulation

1.1 Names

1.1.1. Names in the pharmacopoeias
1.1.2. Name in the literature
1.1.3. Generic name
1.1.4. Name in the plant

1.2 Utilisation

In case of intermediate: which phase of the technology of the end product;
In case of end product: the therapeutic indication.

1.3 Formulation

1.3.1.	"A" tablet	0,... g/tablet
1.3.2.	"B" injection	0,... g/vial

1.4 Synonyms

Identical products at home and abroad.

2. Chemical and physical characteristics of the product

2.1 Structure

2.1.1. Constructive structure
2.1.2. Global structure
2.1.3. Molecular weight

2.2 Physical characteristics

Colour, smell, state, specific weight, melting point, setting point, boiling point, optical rotation and solubility.

2.3 Chemical characteristics

Action against different chemicals.

2.4 Physiological characteristics

Toxicity

2.5 Stability

2.5.1. Stability depending on the air, sunshine, humidity and temperature.
2.5.2. Requirements for stable storage
2.5.3. Expiry time

3. Quality control and quality requirements

3.1 Sampling

3.1.1. Sampling during the manufacture
3.1.2. Sampling of the end product

3.2 Quality control of the raw materials before the manufacture

3.3 Quality control during the manufacture

3.3.1. Quality control to be made within the plant
3.3.2. Quality control to be made in the central (analytical or biological) laboratory

3.4 Requirements of the quality control of the end product

3.4.1. Quality requirements (external characteristics, content)
3.4.2. Biological requirements (activity, side-effects)
3.4.3. Requirements of the formulation (stability)

4. Chemical reaction

4.1 Scheme of the chemical reaction

Indicating the stoichiometric equation and the molecular weights

4.2 Mechanism of the chemical reaction

Known thermodynamical data, if any.

5. Short description of the process

In the text, besides the full name of the used materials, their abbreviations have to be indicated, e.g. HYDRAZOBENZENE (HAB).

6. History of the introduction of the product

6.1 Preparation of the process of manufacture

Names and dates of the working-out of the process and of the scaling up.

6.2 Former processes

Main points of the former technologies, if any.

6.3 Modifications of the process

Main points of the modification of the technology, date of the application.

7. Raw and subsidiary materials

7.1 Specification of the necessary materials

7.2 Quality requirements of the necessary materials with the specifications of the acceptable tolerances

7.3 Storage conditions of the materials

8. Description of the equipment

All machines, equipment and instruments required for the process of manufacture have to be specified in detail, in order of the technology, applying the marking of the technological flow-sheet. The description should make possible the installation of the equipment.

9. Detailed description of the process of manufacture

In the text the detailed description of the process has to be laid down on a technical level, specifying the concrete technical characteristics of the process (^{o}C, Atm., time, etc.). The description has to refer to the markings on the flow sheet and to the data of the diagram of the material flow.

The side reactions, the eventualities of the contamination, the risks of wastage and their prevention have to be pointed out.

The preparation and cleaning of the equipment have to be indicated.

In the interest of perspicuity, the division into sections of the text is recommended, e.g.:

9.1 Production of the "A" intermediate

9.2 Production of the "B" intermediate, etc.

9.2.1. Charging
9.2.2. Condensation
9.2.3. Filtration, etc.

10. Control of the processing

10.1 Indication of the characteristics to be controlled in the course of the processing and specification of the data, the recording of which is compulsory (time, temperature, pH, pressure, weights, volumes, specific weight, results of the measurements, identification of the used materials, etc.).

10.2 Organization of the control

The assignment of the workers responsible for the supervision of the operations, influencing the yield and of the dangerous manipulations, has to be determined and their activity has to be scheduled.

11. Experiences of the processing and causes of troubles

11.1 Related to the raw materials

11.2 Related to the equipment

11.3 Related to the technology, yield respectively

11.4 Related to the quality

12. Byproducts, mother liquors, wastages

Their quantity and utilisation are to be indicated.

13. Flow-sheet of the process has to be prepared, using uniform indication for the equipment and technological operations. With each equipment in the flow-sheet, will have to be indicated (on the upper left side) the materials to be charged (quantity and order of addition) and - on the upper right side - the operations to be carried out (with the specific characteristics: time, temperature, pH, etc.).

The flow-sheet has to be enclosed in the Technological Prescription like an Annexure.

14. Diagram of the material flow

Has to be enclosed as a separate Annexure.

15. Measures for the labour-safety, fire-protection and operational safety

15.1 Labour-safety

15.1.1. Dangers due to inadequate treatment or exchange of raw materials
15.1.2. Hazards arising from the mounting and manipulation of the equipment
15.1.3. Hazards of deficient control
15.1.4. Hazards of breakdown

15.2 Fire protection

Prevention of fire which can occur in consequence of hazards under section 15.1.1 to 15.1.4.

15.3 Systematic preventive maintenance

Programme of the periodic inspection of the mishap-perilous equipment has to be worked out.

16. Manpower and time demand of the process

16.1 Manpower and time demand of each operation

Name of the operation	Space of time of the operation	Needed manpower (Number of persons)	Total demand of working hours

16.2 Duration of processing

16.2.1. Duration of time of the process
16.2.2. Duration of time for quality control
16.2.3. Demand of specific working time
16.2.4. Fluctuations in the specific working time

17. Material balance and material factors

17.1 Quantity of the material fed in a charge, the utilized portion and the regenerated fragment.

17.2 The yield of a charge (minimal, maximal, average and theoretical) in kg and in %.

17.3 Material demand of 1-kg product (tabular account) calculated on minimal-, maximal-, average- and theoretical yield.

17.4 Official material-norm

17.5 Tolerance of the wastage

17.6 Fluctuation of the material norm

18. Capacity of the plant

18.1 Capacity of the equipment, calculated per week, per month and per year in case of periodical and continuous processing.

18.2 Capacity taking into account the period of the maintenance.

18.3 Evaluation of the bottle-necks of the technology

19. The calculation of the product

Enclosed under separate Annexure

20. Innovations and rationalisation

21. Suggestions concerning further development of the process

22. Literature

22.1 Bibliography of general literature

22.2 Bibliography of the preparative literature

22.3 Bibliography of the formulation and quality control

22.4 Bibliography of the patent literature

Dateline:

Annexures:

Prepared by: _____ Controlled by: _____

Scrutinized by: _____ Safety-control by: _____

Approved by: _____

Annexure No. 4

EQUIPMENT FOR FORMULATION

S. No.	Description	Material	Capacity	Qty	Total cost * Indian Rupees
1	2	3	4	5	6
A.	TABLETS				
1.	Mechanical shifter (portable type), single desk, with variable meshes 12-120, starter, TEFC motor, 1.8 kW, direct on the line.	S.St.AISI 304	30" dia.	1	27,500/-
2.	Tilting pan, flat lid on top (openable), jacketted.	S.St.AISI 304	63 lit.	1	10,000/-
3.	Planetary mixer, complete with bowl, top disc. agitation assembly, drive mechanism for both, motorized lifting arrangement with drive, TEFC motor along with a spare bowl.	S.St.AISI	380 lit.	1	127,000/-
4.	Comminuting mill, 600-4600 rpm for wet granulation and powdering, TEFC motor 5.7 kW variable screen.	S.St. AISI 304	-	1	45,000/-
5.	Fluid bed dryer, steam heated with steam heater, product container, flame proof vertical motor and with a spare container.	S.St.AISI	100kg/hr	2	255,000/-
6.	Air circulation dryer, steam heated, fibre glass body, insulated, 2 nos. 12" diameter fans with 0.5 HP EPM, trays other accessories, 24 trays of dimensions 32" x 10" x 1.25" of S.St.AISI 304.	MS.S.St. 304	24 trays	1	105,000/-
7.	Multi-mill with motor on a shaft having 12 blades with knife edge and 2 scraper blades TEFC motor, 2.2 kW, variable speed 750-3000 rpm direct on line. The unit should have 6 different perforated screens. All contact points S.St.AISI 304.	S.St.304	-	1	30,000/-

* cost estimates based on ruling prices in India in late 1981 and early 1982.

1	2	3	4	5	6
8.	Oscillating granulator with 1 H.P. TEFC motor.	S.St.304	50kg/hr	1	19,500/-
9.	Drum blender	S.St.304	200 lit.	1	15,000/-
10.	Rotary Tabletting machine 27 stations with suitable TEFC motor, direct on line.	S.St.304	70,000 tabs/hr	2	195,000/-
11.	Rotary tabletting machine 16 stations with suitable TEFC motor, direct on line.	S.St.304	17,000 tabs/hr	2	90,000/-
12.	Coating pan, vibration free, Manesty CP-4, 36" model with variable speed 10 to 30 rpm, drive-EPM 1 H.P. along with SW, hot air blower of 0.5 H.P., EPM to provide thermostatically controlled hot air at 70°C.	S.St.304	36" dia	5	185,000/-
13.	Polishing pan with continuously variable speed reducer 12-36 rpm with worm reducing gear box, with a suitable EPM.	S.St.304/ 316	700 mm	2	42,000/-
14.	Tablet inspection belt with S.St. hopper, magnetic vibrator, conveyor, with adjustable speed.	-	1 lakh tabs/hr	2	30,000/-
15.	Strip packing machine, 4 track model, vibratory feeder, batch printing attachment, special conveyor belt of 3M length with all controls.	-	48000/hr	2	195,000/-
16.	Batch counter with an electro-mechanical system coupled with electronic unit.	-	2000 tabs/hr	2	45,000/-
17.	Tin sealing machine, semi-automatic with 1.5 kWh TEFC motor	-	1000/hr	1	22,400/-
18.	Semi-automatic roll sealing machine for bottles of different sizes and caps of sizes ranging from 12 to 70 mm dia.	-	2000-2500/ hr	1	53,000/-
19.	Conveyor belt, double side, 5 metre length (operating), variable speed with 1 kW TEFC motor.	-	-	2	34,000/-
					1,505,400/-

1	2	3	4	5	6
B.	CAPSULES				
	1. Multimill	S.St.304	36" dia.	1	35,000/-
	2. Shifter	S.St.304	36" dia.	1	27,500/-
	3. Mixer	S.St.304	50 lit.	2	50,000/-
	4. Clearing and sorting machine	-	-	2	75,000/-
	5. Capsule filling machine	S.St.304	3600/min	2	36,000/-
	6. Strip packing machine	-	2400/hr	1	62,500/-
					286,000/-
C.	LIQUID ORALS				
	1. Tank for solution preparation, jacketted, openable lid, dished bottom, bottom outlet, propelled agitator with 0.75 kW TEFC motor.	S.St.316	250 L	1	35,000/-
	2. Tank for solution preparation, openable top lid, flat bottom, propeller agitator with 0.75 kW TEFC motor.	S.St.316	560 L	1	38,000/-
	3. Holding tank, openable flat lid on top.	S.St.316	675 L	3	78,000/-
	4. Centrifugal pump, complete S.St.304 with 0.75 kW TEFC motor mounted on base, covered with S.St.304.	S.St.304	$1m^3$/hr H=30m	1	10,000/-
	5. Filter press, horizontal, 8 plates of 8" dia. Gear type transfer pump with 0.75 kW TEFC motor with suitable starter, mounted on trolley.	S.St.304	500L/hr	1	30,000/-
	6. Bottle washing machine fitted with a tank for soaking the bottles, double ended brushing unit with a suitable TEFC motor, rinsing arrangement.	-	1000 btls./ hr	1	22,500/-
	7. Vacuum filling machine with automatic "return to source" device to prevent overflow. Adjustable device to accommodate different sizes of bottles.	-	1000 lit/ hr	1	22,500/-
	8. Semi-automatic roll sealing machine.	-	2500 lit/ hr	1	33,000/-

1	2	3	4	5	6
9.	Conveyor belt with 1 kW TEFC motor.	-	-	1	25,500/-
10.	Percolator.	S.St.AISI 304	350 lit.	1	18,000/-
11.	Demineralized water unit to give 500 lit/hr. DM water with pH 7.0 and conductivity 14 micromhos/cm, CO_2 free.	St.-rubber-lined	500 lit/ hr	1	30,000/-
12.	Storage tank for DM water.	ST-RL/HDPE	1500 lit.	1	15,000/-
13.	Portable stirrers 170 and 360 rpm with 0.5 HP motors.	S.St.304	63 lit.	1 each	18,000/-
14.	Movable vessels	S.St.304	63 lit.	2	30,000/-
15.	Tank, jacketted	S.St.316/ 304	63 lit.	1	12,500/-
					418,000/-
D.	INJECTABLES				
1.	Distilled water unit to produce pyrogen free distilled water. The unit is complete with still, condenser, steam regulator, strainer, safety valve pressure gauges, etc.	S.St.304	300 l/hr	1	100,00/-
2.	Storage tank	S.St.304	1000 L	1	32,000/-
3.	Centrifugal pump all S.St. 304 0.75 kW TEFC motor	S.St.304	$1 m^3/hr$ H = 20M	1	10,000/-
4.	Solution preparation tank, jacketted, openable top lid, propeller agitator, 0.75 kW TEFC motor, 720 rpm	S.St.316	630 L	1	60,000/-
5.	Holding tank, flat openable top lid, flat bottom.	S.St.316	675 L	1	26,000/-
6.	Solution preparation tank, completely removable top lid, agitator.	S.St.316	63 L	1	15,000/-
7.	Horizontal plate type filter press, 8 plates.	S.St.304	500 L/hr	1	30,000/-
8.	Centrifugal pump with 0.75 kW motor.	S.St.304	$1 m^3/hr$ H=20M	1	10,000/-
9.	Pressure vessels for aseptic filtrations, complete with all accessories.	S.St.304	50 L	1	10,000/-
10.	Pressure vessels for aseptic filtration, complete with all accessories.	S.St.304	100 L	1	16,000/-

1	2	3	4	5	6
11.	Membrane filter holder with teflon gaskets to be used with pressure arrangement along with air escape valve.	S.St.304	-	2	24,000/-
12.	Seitz filter holder for aseptic filtration to be used either for pressure or vacuum filtration.	S.St.304	-	1	15,000/-
13.	Double door leak proof dry heat electro-sterilizer, 760 x 760 x 1200, with 1.5 kW TEFC motor.	S.St.304	-	1	120,000/-
14.	Horizontal rectangular autoclave 600 x 600 x 1200, complete with all accessories and fittings.	S.St.304	-	1	150,000/-
15.	Horizontal rectangular autoclave double door, 1550 x 1220 x 2100, steam heater, complete with all accessories and fittings.	S.St.304	-	2	900,000/-
16.	High speed rotary automatic ampoule washing machine complete with 0.5 HP motor and all other accessories and fittings.	S.St.304	3000/hr	1	42,000/-
17.	Bottle washing machine with suitable TEFC motor and accessories.	-	1000 btl/ hr	1	22,500/-
18.	High speed double stroke automatic ampoule filling machine, 0.5 HP motor, syringes with S.St. drip proof needles, no ampoules, no liquid device to handle 1 cc to 10 cc and with spares to handle 10 cc to 25 cc ampoules.	S.St.304	3500/hr	1	38,000/-
19.	High speed double stroke automatic ampoule filling machine, 0.3 HP motor, syringes with S.St. drip proof needles, no ampoules, no liquid device to handle 1 cc to 10 cc and with spares to handle 10 cc to 25 cc ampoules.	S.St.304	3500/hr	1	38,000/-

1	2	3	4	5	6
20.	Vacuum filling machine.	-	1000 btl/ hr	1	22,500/-
21.	Automatic ampoule labelling machine.	-	3000/hr	1	50,000/-
22.	Conveyor belt, 1 kW motor.	-	-	1	25,500/-
23.	Vacuum vessels for leak test of ampoules and with vacuum gauge.	Steel	100 lit.	1	12,500/-
24.	Semi-automatic roll sealing machine.	-	2500/hr	1	33,000/-
					1,802,000/-

D. OINTMENTS

Complete series of equipment like blender-kneader, filling machine, roll sealing machine, labelling, testing, etc. (tentative) 250,000/-

SUMMING UP OF THE COST ESTIMATION

	Indian Rupees
Tablets	1,505,400
Capsules	286,000
Liquid orals	418,000
Injectables	1,802,000
Ointments	250,000
a) Total cost of the technological equipme.	4,261,400
b) Estimated cost of the auxiliary equipment (30%)	1,278,420
c) Cost of mounting (25% of a + b)	1,385,000
Grand Total - Indian Rupees	6,924,820
equivalent to US$	664,570

ESTIMATED SPACE DEMAND OF THE FORMULATION UNIT

A) TABLETS + B) CAPSULES

preparatory room	35 m^2
weighing room	25 m^2
granulating room	75 m^2
granulate storing	15 m^2
scullery	15 m^2
tableting room	45 m^2
storing of tablets	15 m^2
coating room	50 m^2
selecting room	15 m^2
dragée storing	15 m^2
packing	75 m^2
capsuling	55 m^2
controlling laboratory	15 m^2
transport ways	63 m^2
Total	513 m^2

Recommended dimensions of the needed space:

Surface: 11.4 x 45 m
Height: 3.5 - 4.0 m

C) LIQUID ORALS

weighing room	15 m^2
preparation of solutions	60 m^2
glass washing	15 m^2
scullery	15 m^2
filling room	40 m^2
ion-exchanger	20 m^2
interim storing	45 m^2
controlling laboratory	15 m^2
Total	225 m^2
+ transport ways	63 m^2
	288 m^2

Recommended dimensions of the needed space:

Surface: 5 x 45 m
Height: 3.5 - 4.0 m

D) INJECTABLLS

weighing room	15 m^2
distilled water making	25 m^2
preparation of solutions	25 m^2
scullery	15 m^2
washing and sterilising of ampoules	30 m^2
ampoule filling room	30 m^2
sterilising autoclaves	15 m^2
labelling of vials	15 m^2
optical revision	15 m^2
packing	25 m^2
controlling laboratory	15 m^2
Total	225 m^2
+ transport ways	63 m^2
	288 m^2

The recommended dimensions of the space conform to C).

E) OINTMENTS

Total space demand is 80 m^2

F) AUXILIARY EQUIPMENT

Engine house for compressed air	20 m^2
Engine house for vacuum	20 m^2
Hot water supply	20 m^2
Air conditioning installation	60 m^2
Miscellaneous	40 m^2
Management of the production	40 m^2
	200 m^2

G) STORAGE 500 m^2

H) MAINTENANCE WORKSHOP 50 m^2

SUMMING UP OF THE SPACE DEMAND

Space demand of the productive units (A-E)	1169 m^2
Space demand of the auxiliary units (F+H)	250 m^2
Space demand of the storage (G)	500 m^2
	1,919 m^2

The space demand of the central controlling laboratory, the central management and administration had not been calculated since these can be placed in the already existing buildings.

For the location of the Training Centre for the Formulation of Drugs can be recommended, for instance, the following building:

Surface: 11.40 x 65 m

with 2 floors, internal height 3.5 m in each floor.

On the ground floor can be located the Tabletting, Capsuling and the Auxiliary equipments (A) + B) + F)).

On the first floor can be located the production of Injectables, Liquid Orals, Ointments and Maintenance Workshop (C) + D) + E) + H)).

For Storage the construction of a separate building of light elements can be recommended.

Annexure No. 5

PROCESS FOR THE PRODUCTION OF HEPARINE BY DRYING ON THE SPOT

Raw material: MUCOSE and/or SEROSE of pig, buffalo or goat, gained by the casing of the small intestines.

The principle of the process is to protect the HEPARINE by bonding it to the protein of the mucose by heating. By this method the raw HEPARINE will be stabilized and can be transported, respectively stored for years without any decomposition.

The sketch of the process. The thin suspension of the mucose and serose produced by the casing of the small intestine will be heated by direct steam up to 90°C. The coagulated protein - which contains the bonded heparine - will be filtered and dried. The process is carried out automatically in a special equipment, on the spot of the collection of the raw material, practically in the slaughterhouse.

The dried intermediate has to be extracted in automatised counter-current extractor with saline-alkaline water, precipitated by solution of quaterner-amine and dried in cylinder drier. The produced raw heparine will be purified through one of the well known methods to get heparine purum corresponding to the U.S.P. requirements.

Out of one pig of approx. 100 kg live weight about 120 g dry intermediate can be obtained, which contains 300,000 - 350,000 U. heparine/kg.

For the production of 1 million units heparine U.S.P. approx. 4.5 kg dry intermediate (corresponding to 35-40 pigs) is necessary.

The heparin content of the mucose/serose of buffalo, respectively goat is unknown; has to be investigated.

Advantages of the process

- The raw material - even in thin liquid suspension - can be processed economically, without loss. The process is suited for processing of lungs too. The process does not need refrigerating chain.
- The technology is carried out in closed system; it is hygienic.
- As byproduct cca. 4 kg protein for feed supplement is obtained per M.U. heparine.
- The transport costs are reduced up to 1/5 - 1/8.

The technology is a patented process of Gideon Richter Ltd., Budapest.

Annexure No. 6

PROCESS FOR THE PRODUCTION OF PANCREATINE FROM PIG PANCREAS

The frozen pig pancreas + 10% pig duodenum will be ground, autolysed by 40-42°C during 1.5 hours, filtered, precipitated with acetone, sedimented for 1.5 - 2.0 hours, filtered, washed twice with acetone, filtered again and dryed in vacuum (max. 20°C). The dried product will be ground, afterwards bruised, homogenised, sterilized by STERIVIT GAS, dried and sifted.

The pancreas has to be collected early as possible after the slaughtering, frozen at -20°C within one hour, and stored by -20°C.

The quality of the produced PANCREATINE meets the requirements of the INTERNATIONAL FIP.

The aptness of the buffalo and goat pancreas for the production of PANCREATINE has to be investigated. The facilities of the collection of pancreas by the required conditions has to be investigated too in the frame of the working process of the slaughterhouse.

The above process had been worked out by Gideon-Richter Ltd., Budapest.

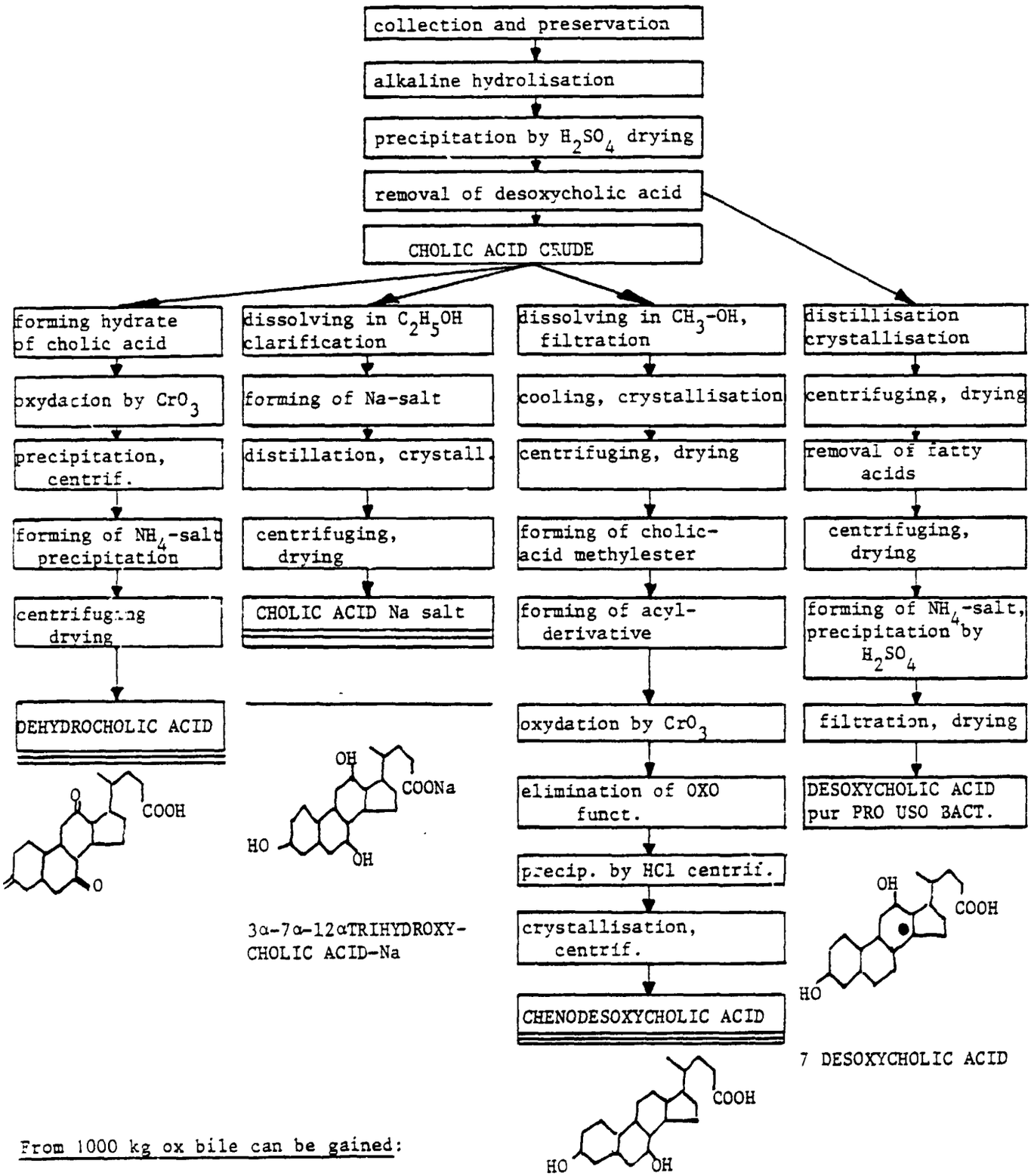
Annexure No. 7

PROCESSING OF OX BILE

From one ox can be collected 120-200 ml bile, which has 7-8% cholic acid content. The cholic-acid content of the buffalo bile and goat bile has to be investigated.

The bile has to be collected in iron drums and preserved with 2% NaOH.

Sketch of the processing of ox bile



From 1000 kg ox bile can be gained:

22 kg	DEHYDROCHOLIC ACID or
33 kg	CHOLIC ACID-Na SALT or
8 kg	CHENODESOXYCHOLIC ACID and
1.8 kg	DESOXYCHOLIC ACID PUR

These processes have been worked out by Gideon Richter Ltd., Budapest.

Annexure No. 8

PROCESS FOR THE PRODUCTION OF ALBUMINE & γ-GLOBULINE FROM HUMAN BLOOD

In human albumine there is a shortage on the world market, the product could be exported in large quantities. Only the albumine produced from human blood is required, the albumine derived from human placenta is not accepted in the western countries.

The γ-globulin applied in the up-to-date "COMPONENT-THERAPIE" is called "SUPERIMMUN-γ-globulin" and can be prepared from blood of immunised donors as a byproduct of the albumine.

The key of the production of these products is the organisation of the adequate, controlled donors. A voluntary donor can produce ~ 400 cm^3 blood per quarter, whereas a paid donor in the case of PLASMAFERESIS (recycling of erithrocytes) is able to furnish 400 cm^3 blood in each 3-4 weeks.

The sketch of the process

The collected blood stabilized with 1/5 volume of ACD has to be centrifuged within 6-24 hours - applying cooling sharpless - and the separated clear plasma has to be frozen by -20 - -30°C, practicably in Al containers of 25-30 litres. In this form the plasma can be stored and transported unlimited, without damage. The isolation of the albumine and γ-globuline is made by gradual fractionation in ethanol by low temperature (-4 - -5°C) varying the pH, temperature and concentration of C_2H_5OH. The precipitated raw product has to be dissolved in water, respectively in physiological NaCl solution, and after filtering through MINIPOR dried by lyophilisation.

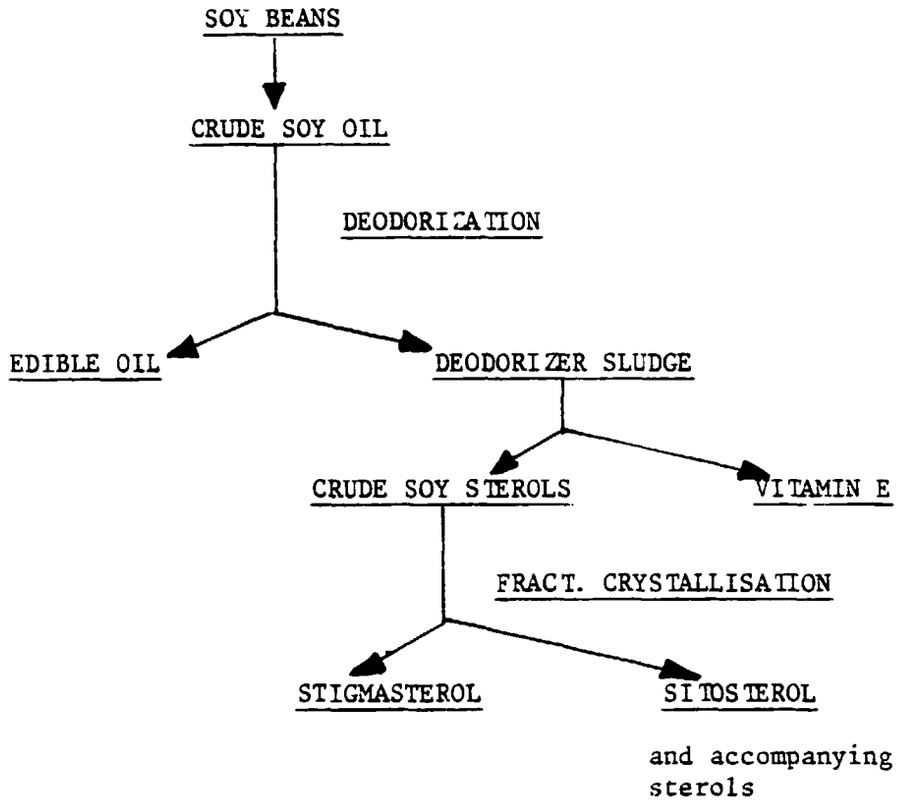
1 litre human blood ≈ 450-500 ml. plasma
1 litre plasma = 24-25g albumine + 4.5-5.0g γ-globuline.

The process is available in the frame of a collaboration with HUMAN LABORATORIES BUDAPEST, through MEDIMPEX. Eventually the know-how can be compensated by supply of albumine or frozen plasma.

Annexure No. 9

PROCESS FOR PRODUCTION OF STIGMASTEROL AND SITOSTEROL

The sketch of process for isolation of STIGMASTEROL and SITOSTEROL from SOY BEANS:



The STIGMASTEROL content of the SOY BEANS can be economically isolated from the DEODORIZER SLUDGE by the process worked out by GENERAL MILLS INC (1), (2) and UPJOHN Co. (3) (4) (5) (6). The main point of the process is the extraction of sterols from the unsaponifying part of the DEODORIZER SLUDGE through a semi-continuous counter-current extraction, applying an azeotrop mixture of halogenated organic solvents or a terner-mixture of halogenated organic solvents and water. The detailed description of the process had been published by F.W. GREINER & G.A. FEVIA (7).

The SOY BEANS yield about 18% CRUDE SOY OIL which contains 0.8% CRUDE SOY STEROLS, out of which about 20% are STIGMASTEROL. From the CRUDE SOY OIL 0.06- 0.12% STIGMASTEROL can be isolated, depending on the effectiveness of the applied process. The yield of UPJOHN Co.'s process is 88%, the purity of STIGMASTEROL is 97%.

(1) S.E. MILLER, C.M. BERRY: U.S. pat. 2.729.655 and U.S. pat. 2.729.656
(2) GENERAL MILLS INC.: U.S. pat. 2.866.797; Ref. C.A. 53, P6657 e (1959)
(3) UPJOHN Co. Brit. 774.466; Ref. C.A. 51, 14211 i (1957)
(4) F.W. GREINER, G.A. FEVIG: U.S. pat. 2.839.544, Ref. C.A. 52 19026 f (1958)
(5) UPJOHN Co.: U.S. pat. 2.905.677; GER. 1.058.509; Ref. C.A. 54 2673 h (1960)

(6) UPJOHN Co.: GER. 1.029.374; Ref. C.A. 54, 23207 c (1960)
(7) F.W. GREINER, G.A. FEVIG: Ind. Eng. Chem. 53, 949 (1961)

Annexure No. 10

SOME SOURCES FOR COLLABORATION CONCERNING THE TECHNOLOGIES RECOMMENDED TO BE DEVELOPED IN INDIA

PANCREATIN

NORDMARK-WERKE GMBH, HAMBURG, WEST GERMANY
ARMOUR PHARMACEUTICAL CO., CHICAGO, ILLINOIS
BIOSYNT (ORGANON) OSS, NETHERLAND
KIMPLAS INDUSTRIAS QUIMICAS Ltda. SAO PAULO, BRASIL
GIDEON RICHTER Ltd., BUDAPEST, HUNGARY

DESOXYCHOLIC and CHENODESOXYCHOLIC ACID

LABORATORICO OPOTERAPICO BRASILIERO Ltda., 06400 BARUERI, BRASIL
ROUSSEL-UCLAF, PARIS, FRANCE
ASCALIA, HAMBURG, WEST GERMANY
POLFA, FELENIA GORA, POLAND
GIDEON RICHTER Ltd., BUDAPEST, HUNGARY
RAFAEL KURLAT Y CIA S.A., MUNRO, BUENOS AIRES, ARGENTINA

ALBUMIN & γGLOBULIN

SCHWAB AND CO., WIENER STR. 93, 2345 BRUNN, AUSTRIA
BIOTEST-SERUM INSTITUTE GMBH, LANDSTEINER Str. DREIEICHENHAIN, AUSTRIA
HUMAN LABORATORIES, BUDAPEST, HUNGARY

SITOSTEROL & STIGMASTEROL resp. CHOLESTEROL

UPJOHN, U.S.A.
VITAMINS Ltd., CHICAGO, U.S.A.

CORTICOID HORMONES & CONTRACEPTIVES

SCHERING A.G., MÜLLER STR. 170-178, BERLIN-WEDDING, W. GERMANY
ORGANON-DYOSINTH BV, OSS, HOLLAND
ROUSSEL-UCLAF, 92080 PARIS LA DEFENSE, FRANCE