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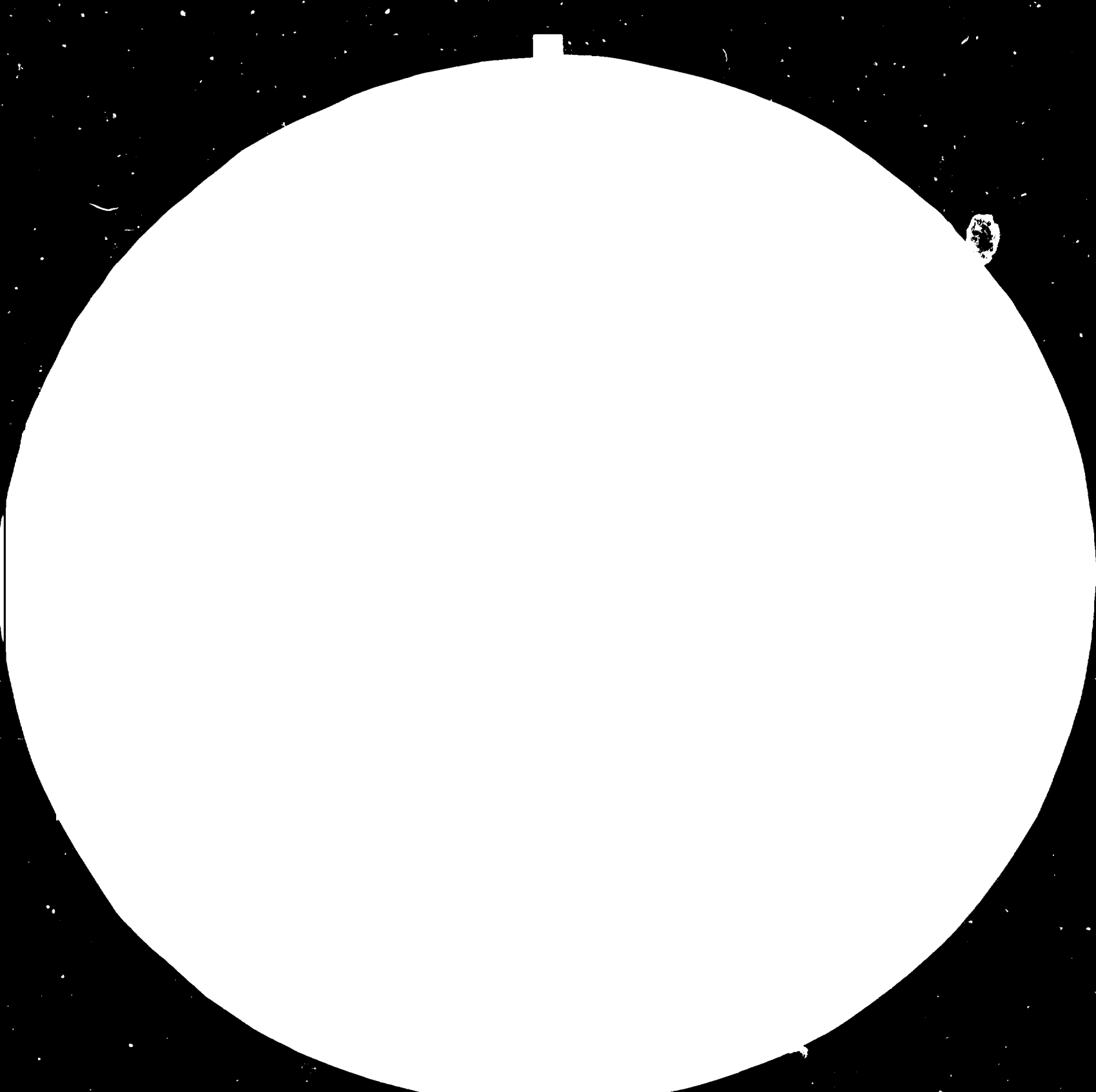

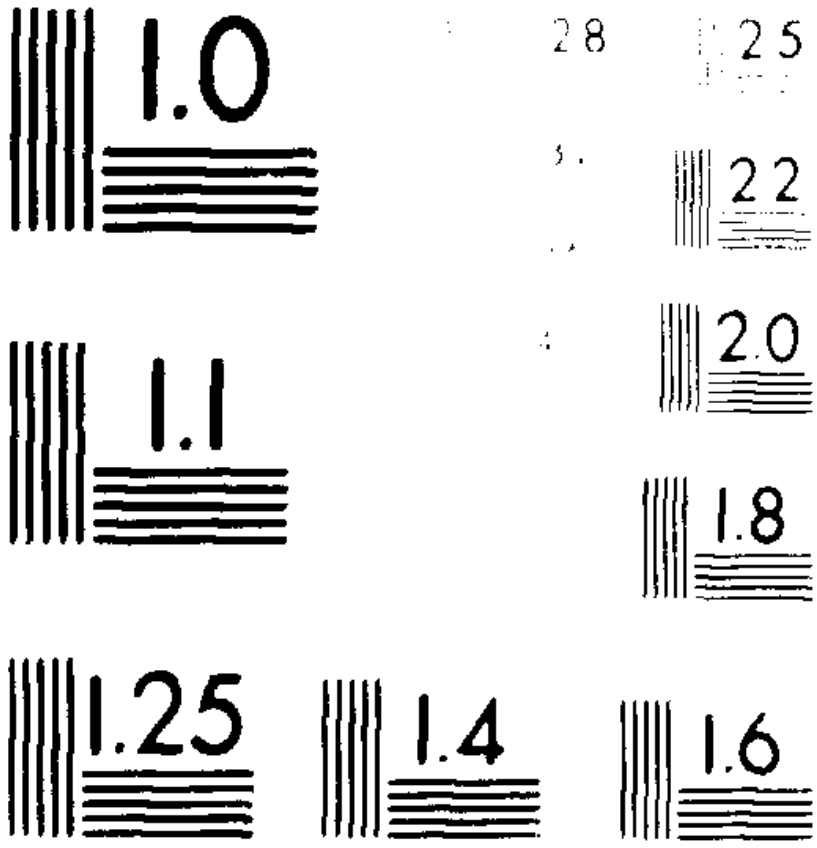

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13441

DP/ID/SER.B/434
4 January 1984
English

Nepal.

# STRENGTHENING THE ROYAL DRUGS RESEARCH LABORATORY

DP/NEP/80/003

NEPAL

Terminal report*

Prepared for His Majesty's Government of Nepal
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Programme

Based on the work of Mr. J.G.Meredith,
Chief Technical Adviser/Chemist/Technologist
for the Production of Pharmaceuticals

United Nations Industrial Development Organization
Vienna

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V.84-80137

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## I. SUMMARY

The Project sets out to establish the par meters within which His Majesty's Government of Nepal can develop and exploit the wealth of indigenous herbs and the rich flora of medicinal plants as an intrinsic part of a broad health programme and as contributors to the foreign exchange earning capacity of the Kingdom.

Striving to make the country self-reliant in essential drugs by developing traditional medicines obtained from local herbs, the project aims at strengthening the analysis and processing techniques of medicinal plants as well as increasing the production level and equipment capacity for the treatment of essential oils and pyrethrum.

The importance attached to traditional medicine is based on the need to make available to the poorer and more remote parts of the country sufficient products and services to back up the health programme.

The project calls for the installation of up-to-date analytical and special laboratory equipment to develop the work being done in the fields of drug analysis and quality control, pharmacology, micro-biology and process development.

Semi-industrial equipment was recommended to assist in developing the pilot plant phase of the programme.

A fellowship programme, in conjunction with the WHO was initiated in 1982 and terminates in 1983. It is expected that further fellowships will be discussed directly between RDRL and UNIDO.

Regardless of the constraints and delays inherent in project implementation, the initial results obtained in the laboratories by means of the "in-situ" training programmes have been most encouraging.

Although a "go-slow" on the planned purchase of equipment was requested by the UNDP, most of the equipment has arrived and the balance will be dealt with on a priority and absolute necessity basis negotiated between HMG (through the RDRL), the UNDP Kathmandu and UNIDO, Vienna.

## II. INTRODUCTION

### A. Origins of the Project

Attaching great importance to the development of the Kingdom of Nepal's rich flora in medicinal herbs and plants, three United Nations missions were given the task of appraising the situation at first hand.

These missions, undertaken by the Joint UNIDO/Romania Centre, were given the following numbers and titles:

RP/RAS/76/009 : "Mobile Unit of Pharmaceutical and Essential Oils Industry to Least Developed Countries in Asia" (April 1977)

RP/RAS/78/012 : "Foundation for Economic Mapping" (1979)

SI/NEP/78/802 : "Economic Mapping of spontaneous flora of a geographical area of Nepal" (April 1980).

Prominent among the recommendations was the prime importance of developing the technical facilities of the Royal Drugs Research Laboratory for physical-chemical analysis and as a national institution for quality control of drugs, of raw materials, of intermediate and finished products. Also mentioned was the benefit that might come about by increasing the scale of the pilot plant equipment to meet anticipated domestic and export needs.

A recommendation was made for further training of national personnel by means of study tours and fellowships and UNIDO was advised accordingly.

The demanding nature and the importance of the recommendations was such that a specific project was called for. The UNDP, together with the Department of Medicinal Plants and UNIDO, set about drafting a Project Document which was duly submitted to the parties concerned for comment and amendment if required.

The Project Document, bearing the No. NEP/80/003 and entitled "Strengthening the Royal Drugs Research Laboratory" was given a scheduled duration of 3 years, and was duly signed on 14 May 1981 by UNIDO (Executing Agency), on 24 November 1981 by HMG, on 2 December 1981 by WHO (Associate Agency) and approved by the UNDP Resident

Representative on 17 December 1981.

The effective date of commencement was 15 March 1982.

3. Objectives of the Project

In view of the breadth of the concept, and following on the previous recommendations, it was necessary to envisage at least a two-tiered level of objectives, defined as:

1. Development objective
2. Immediate objective.

1. Development objective

The aim was "to make the country self-reliant in essential drugs, laying particular emphasis on traditional medicines manufactured mainly from locally available herbs. To develop the processing of medicinal herbs and the production of essential oils and pyrethrum as foreign exchange earning activities in Nepal".

The objective was and still is of far reaching importance for a landlocked country like the Kingdom of Nepal, relying as it must on the import of a great number of modern drugs to combat the major health problems.

The emphasis on traditional medicines is aimed at establishing products and services which can be made available to the inhabitants of the many and far flung villages outside the valley of Kathmandu.

The successful outcome of the programme depends to a large extent on the expansion and development of the agro-industrial sector and this is now the prime concern of DP/NEP/79/007 a Project run by the Food and Agriculture Organisation (FAO) of the United Nations, in conjunction with the Herbs Production and Processing Company Limited, an HMG Corporation.

Project DP/NEP/80/003 took on the task of developing the quality control and analytical aspects of raw material and product selection and became involved in the development of pharmacology and microbiology as being of foremost importance in the assay not only of

compound drugs but in the selection and screening of single plants and raw materials as well as complex mixtures.

The development objective, as laid down, should be considered as an overview of a broad programme, better served by a series of smaller projects, drawn up for single purposes but all tending towards the same end.

2. Immediate objective

The Royal Drugs Research Laboratory (RDRL) of the Department of Medicinal Plants, was given the task of determining the technical and commercial feasibility of large scale production by Royal Drugs Ltd., of pharmaceutical products based on locally available herbs.

The possible treatment of these herbs by distillation or extraction could lead to the establishment of essential oil production centres.

To pursue this objective it was decided that the project would:

i. Improve existing capabilities in the field of research into the potential of indigenous raw materials for the production of drugs and essential oils. Develop processing techniques and quality standards for these products.

ii. Develop the Drugs Control Laboratory to strengthen RDRL as the National Institution for drug quality control.

iii. Process local herbs with a proven medicinal or essential oils potential on a pilot scale basis.

iv. Test market drugs and essential oils manufactured from local herbs and determine their acceptability. Test market pyrethrum.

v. Look into feasibility of and give guidelines for large scale production of pharmaceuticals and essential oils based on indigenous raw materials. Look into the feasibility of large scale production of pyrethrum.

In June 1983, at the request of UNIDO, the Chief Technical Adviser submitted a Project Evaluation Report (PER), the purpose being to determine whether or not the objectives required amending.

This was followed by the Tripartite Review (TPR) on 8 August which enabled a complete review of Project Activities.

At the meeting an amendment to the Project document was submitted by Dr. S.S. Nalle and the CTA which in effect recommended not only a change in terminology but a redefining of the objectives.

i. The initial title "Development Objective" was to become: LONG-TERM AND OVERVIEW (10 years plus).

ii. The initial title "Immediate objective" was to become: MEDIUM TERM (5 years).

iii. A new title: SHORT TERM (Immediate objectives) was introduced to clarify those areas of activity where immediate results could be obtained.

The outputs were reviewed and amended to take into consideration a time-frame of 3-4 months remaining to the experts, before termination of their contracts.

Recommendations were made for modifications to the original Project Document to take into consideration any further developments.

The absence of an initial work plan gave rise to exchanges of views concerning the adaptability of such plans to research work.

The original critical path analysis for the construction work at Godavari could not be met, so an updated one was to be prepared based on actual commencement dates. The new programme and progress chart (ANNEX VIII) was presented to ENG, UNIDO and RDRL on 6 September 1983.

## C. Activities and Outputs

The national execution of the project is the responsibility of the Department of Medicinal Plants and the specific instrument chosen to carry out the project plan was the Royal Drugs Research Laboratory, established in 1961.

At the time the project document was drawn up, the RDRL was in the process of handing over most of its processing and production to a new corporation, the "Herbs Production and Processing Company Limited" (HPPC) so that in effect, the national objectives could be fulfilled by the RDRL working closely with Royal Drugs Limited and the new Herbs Production and Processing Company Limited.

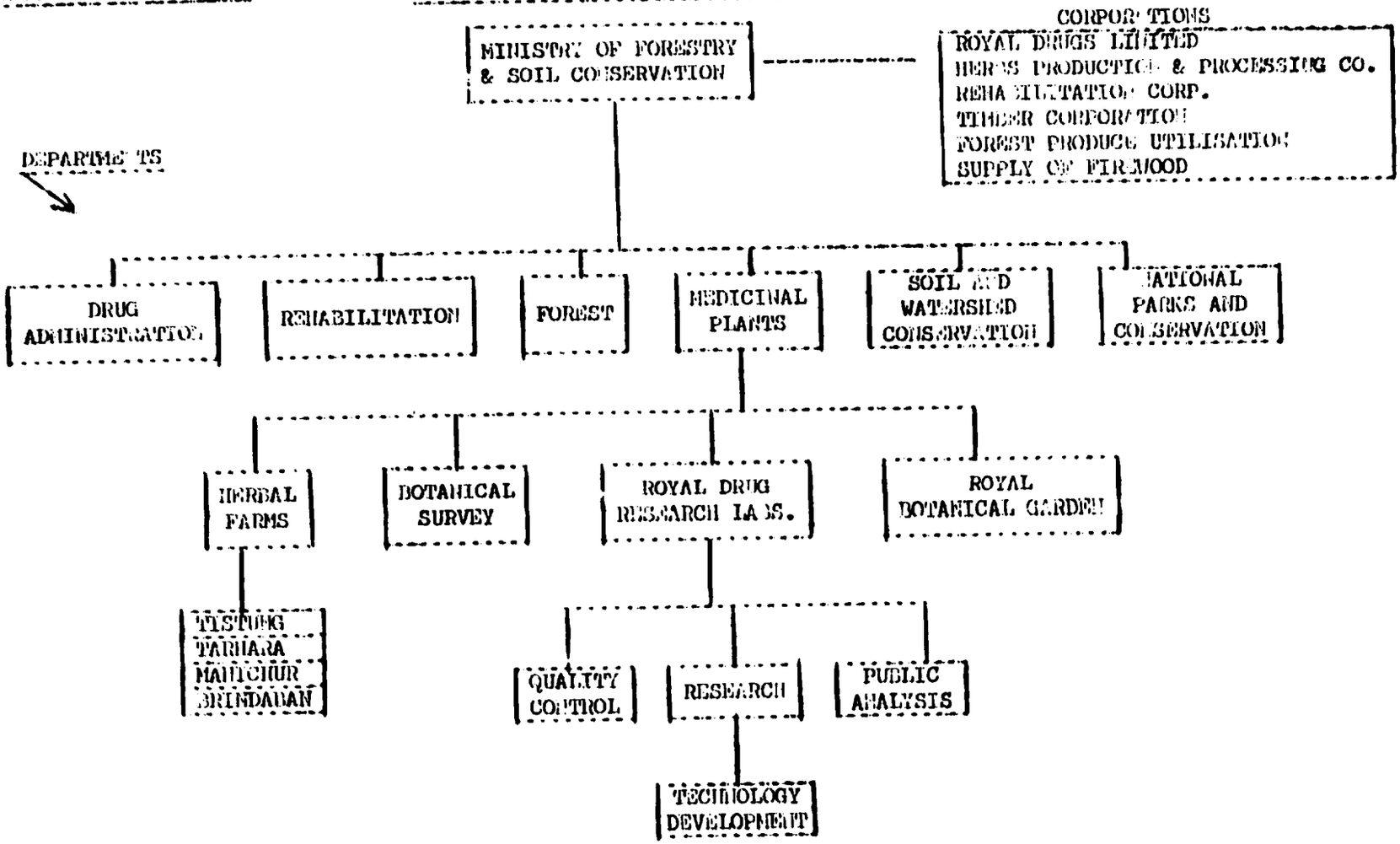
Organisation chart (No. 1) shows the relationship between the Royal Drugs Research Laboratory and the Department of Medicinal Plants, both coming under the Ministry of Forest and Soil Conservation.

Also shown is what appears to be an indirect relationship with the two Corporations, Royal Drugs Limited (1971) and Herbs Production and Processing Company (1982).

What is important is the fact that the Director General of the Department of Medicinal Plants (Dr. S.B. Malik) is a member of the Governing Board of Royal Drugs Ltd. and is also Head of the Royal Drugs Research Laboratory. There is thus a formal link between the two organisations.

ORGANISATION CHART (No. 1)

CENTRAL ORGANISATION OF NEPAL



To meet its specific national objectives the RDRL functions through its four main divisions.

1. Quality Control
2. Research and Development
3. Public Analysis
4. Pilot Plant.

Organisation Chart (No. 2) shows the relationship between the divisions and the main activities in which they are engaged.

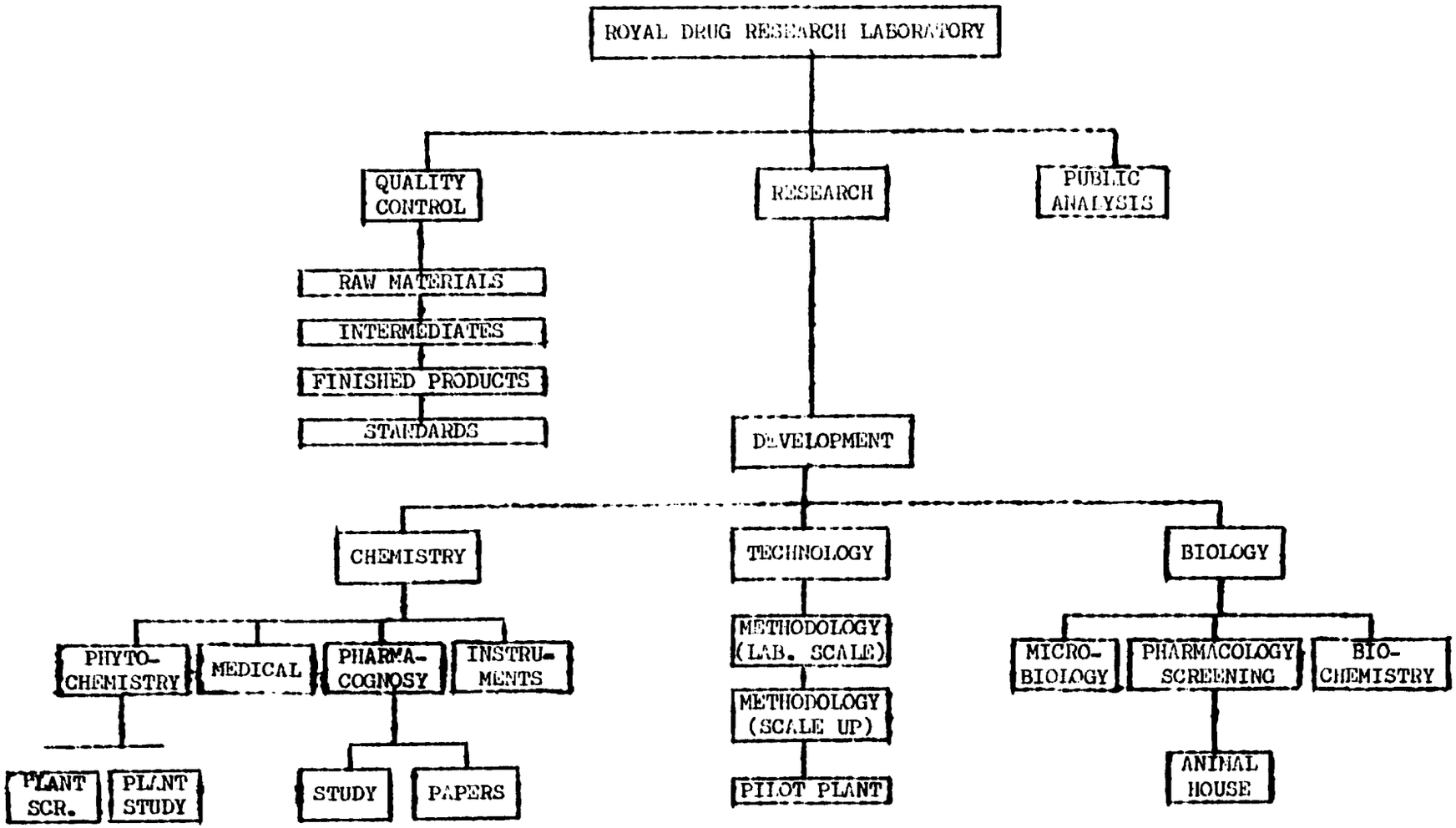
This in itself amply justifies the recruiting of specialised experts in the fields of Quality Control, Analysis, Pharmacology and Micro-biology, as well as in Methodology for scale-up.

The integrated activity of their functions called for a modification of the original purchasing order of equipment so as to meet the international standards of assay and quality control. (ANNEX VII)

The original list was augmented by the purchase of special analytical and quality control equipment, brought in by air to enable the experts to proceed with the "in-situ" training programme.

ORGANISATION CHART (No. 2)

INTERNAL ORGANISATION CHART



1. Quality Control

The most important of the four divisions is that of Quality Control because it influences all the other activities by determining whether or not certain raw materials are satisfactory and can be safely used. Equally important is the quality control of any intermediary products prepared or manufactured because these lead to finished products and the establishing of Nepalese norms or standards, the latter having to comply with certain stringent international requirements.

Although quality control is an integral part of all the functions, it plays a special role when allied to detailed analysis and research and development.

It links together the activities of the Analytical Expert (ANNEX IV(D) the Pharmacology Expert (ANNEX IV(B) and the Microbiology Expert (ANNEX IV(C) in that all these activities are tending not only to the development of their own programmes but to make sure that all products developed comply with international standards (limits of contents).

By including in the equipment purchased and installed such items as computers, instrumentation for chemical analysis as well as special microscopes (equipped with camera) and new sensitive balances, the project has contributed effectively to the immediate objective of strengthening the RDRL as the national institution for drug quality control.

2. Research and Development

In the case of RDRL, research and development involves three distinct sub-divisions; Chemistry, Technology and Biology.

The activities carried on by the Chemistry and Biology sub-divisions are fully reported on by the UNIDO Experts concerned and for these divisions, special equipment has been purchased and installed, enabling not only advances in instrumentation but advances in pharmacology screening for anthelmintic activity and anti-dysentery activity as well as in tests for hypoglycaemic activity.

In the chemistry sub-division, the pharmacognosy and phytochemical activities enable the preparation of samples for screening.

The advances achieved in the installation of the microbiology laboratory and in the animal house strengthen the whole development programme.

3. Public Analysis

The pressures on this division are growing and the application of the Drug Laws of Nepal will add further importance to a division so closely linked to Quality Control.

4. Pilot Plant

As the pilot plant division of RDRL was becoming too small for the development programme envisaged and in order to investigate improved methods of production, larger equipment was included in the immediate requirements of the project which called for the processing on a pilot scale basis of local herbs, with a proven medical potential, or essential oils having specific export interest.

Unfortunately, the proposed time-frame for the project could not take into consideration the delays which eventually occurred, so the installation of the new and larger distillation and extraction units could not take place. This is now scheduled for June/July 1984.

The commissioning of the pilot plant at the new site at Godavari should take place during the latter half of 1984. This delay, and the problems of gathering sufficient material for processing through the existing pilot plant, has hampered the developing of new or improved processing techniques.

However, work has continued on the improvement and rationalisation of the methodology applied to laboratory scale production prior to the development of the required scale-up methodology applicable to increased pilot plant output.

This work involves not only the study of processes used at present but the application of those processes to specially selected raw materials and their extracts, such as Dioscorea deltoidea (diosgenine), Berberis aristata (Berberine hydrochloride), Atropa belladonna (Atropine), Solanum khasianum (solasodine), as well as essential oils of the Cymbopogon species, Timur oil, Mentha oils, Amomum oils.

D. Institutional Framework

The project comes under the Ministry of Forest and Soil Conservation, more specifically through the Department of Medicinal Plants, whose Director General is Dr. Samar Bahadur MALLA.

1. Contributions

In terms of contributions, the only figures readily available are those for Project NEP/80/003:

| HM Government of Nepal | UN Development Programme |
|---|---|
| N.Rs. 8,2000,000<br>(US$ 625,954 @ 13.10) | US$ 1,498,850 |

The HMG/N contribution is deemed to be "in kind" whereas the UNDP contribution covers the acquisition of equipment and vehicles, the services of expert and support staff and all costs falling within the limits of the budget.

2. Official Dispositions

In order to achieve the aims of the project, and at the request of the Government of Nepal, it was decided that UNIDO would be requested to field certain experts. Requirement began in April 1982.

The Government accepted the candidature of Mr. John G. Meredith, Ingenieur en Chimie Technique for the post of CTA and Project Co-ordinator. He took up his duties on 1 August 1982.

There followed the acceptance of Dr. J.P.G. Williams, Pharmacologist, whose duties began on 1 December 1982; Dr. Jan Karlsen, Analyst and Quality Control whose duties began on 21 January 1983 and Ms. M.H. Cordes, Microbiologist, whose duties began 24 January 1983.

An Associate Expert, Mr. W.J. deBoeck had been transferred from his post of JPO at the UNDP on 15 March 1982.

The Department of Medicinal Plants allocated the counterpart positions to the Senior Officers of the Royal Drugs Research Laboratory.

Dr. B.B. Malla, Director General as National Director of the Project; Dr. S.B. Rajbhandary, Deputy Director General. Dr. P.L. Adhikari, Senior Scientific Officer (Chemistry); Dr. S.R. Adhikari, Senior Scientific Officer (Chemistry); Mr. A.D. Shrestha, Senior Scientific Officer (Pilot Plant Production) and Mr. S.K. Joshi, Scientific Officer (Pharmacologist); all backed up by the staff of the RDRL.

3. List of Personalities Involved

I. Ministry of Forest and Soil Conservation

Mr. Emerald Jung B. RANA, Secretary
Mr. Purushottam Bhakta Singh PRADHAN, Planning Officer
Mr. Kapil B. CHITRAKAR, Chief Training Officer
Mr. Bill HART, Counterpart.

II. Ministry of Finance/Foreign Aid Division

Mr. Heet Singh SHRESTHA, Additional Secretary
Mr. Punya Prasad DAHAL, Under Secretary

III. National Planning Commission

Mr. A.R. JOSHI, Section Officer

IV. Corporations

Dr. Asfaq SHEAK, General Manager, HPPC
Dr. A.B. SHRESTHA, General Manager, RDL

V. HMG Department of Ayurveda

Mr. K.K. ADHIKARI, Director General
Mr. K.R. ADHIKARI, Assistant to the Director General

VI. United Nations Development Programme

Mr. John B. MELFORD, Resident Representative until May 1983
Mr. Toshiyuki NIWA, Resident Representative from June 1983

VII. Food and Agriculture Organisation

Mr. G. AXINN, Representative since January 1983

Mr. T. TYLER, Rome

VIII. World Health Organisation

Dr. B.A.V. PERERA, Project Manager, Primary Health Support Service Programme.

Dr. P.N.V. KURUP, Consultant

IX. Netherlands Development and Volunteer Service

Dr. Rob VISSER, Representative

X. Community Forestry Development Project

Mr. E. PELINCK, Chief Technical Adviser

Mr. B.B. PRASAD, Counterpart

XI. Forest Produce Utilization Board

Mr. I.M. MAKARMI, Chief

## III. FINDINGS

The development objective of the project, mentioned on page 3, is vaster in scope than the words might seem to convey.

The topography of the Kingdom of Nepal, the varied nature of the terrain, comprising a flat area in the South, a central zone of hills and a mountainous belt the whole length of the country to the North makes rapid communication entirely dependent on air-transport. What good roads exist run on an East-West axis along the flat area known as the "Terai", with limited roads leading up to the hills.

The terms "locally available herbs" and "traditional medicine" illustrate quite rightly the problem of creating a central source of essential "natural drugs" capable of being used as replacements for imported complex medicines.

In itself, the processing of medicinal herbs comes up against the immensity of the geographical dispersion of the growing areas. The farms and collecting areas are situated in East and West Nepal where access roads are inexistant and where transport is dependent on porters carrying heavy loads of fresh or dried herbs over long distances. Hazardous journeys contribute to making collection and field processing irregular.

The Development Objective was thus broken down into five Immediate Objectives requiring a series of recommended outputs for which certain activities were prescribed.

Immediate Objective No. 1, requiring the improvement of existing facilities in the field of research into the potential of indigenous raw materials for the production of drugs, was approached by the experts with regard to their own specialisation.

In conjunction with the RDRL Senior Scientific Officers, plants and herbs of prime interest were defined, collection and recording undertaken and physio-chemical examination and assay instituted.

Specially selected laboratory equipment was ordered and although activity was a little slow to begin with, by July 1983 the programme was gathering momentum.

Immediate Objectives 2 and 3 were also being met by the development of the analytical laboratory and the Quality Control division.

The whole pilot-plant programme had to come under review because the new equipment on order was to be housed outside Kathmandu, at Godavari, and the installation and operation of the larger extraction units was subject to adequate buildings being provided. Preparation of the site, the building of a dam to obtain the required supply of water to the decantation and sedimentation tanks was delayed and it is unlikely that installation of the equipment will take place before June/July 1984.

This meant that any considerations concerning pilot plant operations had to be geared to the present equipment used at the RDRL and could not at this stage be related to the larger capacity envisaged.

A close look at the present operation was undertaken following agreement between Dr. S.B. Malla (RDRL), Dr. R.O.B. Wijesekera (UNIDO) and Mr. J.G. Meredith (CTA-HEP/SC/003) to see to what extent the information available could be extrapolated to the larger scale envisaged.

With the redistribution of an important part of the pilot plant processing to the Herbs Production and Processing Company, the pilot plant (in its true sense) is at present involved in the processing of Dioscorea deltoidea, for Diosgenine; Solanum khasianum and S.laciniatum, for Solasodine, and Berberis aristata for Berberine hydrochloride. A status report, finalised in July 1983, setting out the different problems affecting regular operations of the pilot plant (interruption in the supply of electricity, water, etc.) should enable a review and examination in detail of all operations likely to affect the new installation.

The status report is part of the project outputs prepared by the Experts and covers the period March through July 1983.

Immediate Objective No. 4 recommending the test marketing of drugs and essential oils from local herbs, as well as pyrethrum was and still is an impossibility on an organised basis.

The whole mechanism represents a new concept and is to be approached jointly by the RDRL and the HPPC. Close liaison, through a specialised and well informed link-man will enable both parties to get the necessary "feel" of world-wide market conditions and to programme a systematic approach.

By extension, Immediate Objective No. 5 had to be abandoned through lack of sufficient background information and the impossibility of building up the required international contacts in the short time available.

In the final analysis, the immediate practical objective of the project had to be that of strengthening the Royal Drugs Research Laboratory. The new equipment installed, the in-situ training and the fellowship programme all point to the necessity of developing all laboratory activities and raising the level of investigation possibilities.

The reports submitted by the Experts provide the necessary detailed recommendations concerning operations, training and where necessary further equipment.

## IV. RECOMMENDATIONS

The practical recommendations that follow deal more with the Institution Building aspect of the project, as the more particular aspects of each experts activity is dealth with in their own reports which have been circulated separately.

However, and this is a fundamental aspect of the whole project, it is important to stress the need for having an overall project concept which can be split into smaller projects more capable of satisfying each particular aspect of the overall concept, in its own way and in its own time.

This leads, by gradual development of each activity, to a strengthening of the whole.

1. Strengthening the Royal Drugs Research Laboratory must be considered, by HMG, UNDP and UNIDO as an on-going process requiring sustained attention.

2. The technical output of the RDRL must be monitored and selected experts fielded when required, on short or medium term appointments.

3. The technical capability of the RDRL must be advanced by means of appropriate and specific fellowships agreed with UNIDO.

4. The overall training programme must take precedence over new equipment requirements.

5. Selected members of Senior staff should be trained in modern management techniques.

6. The concept of horizontal communication in conjunction with vertical communication should be introduced at junior level, subject to proper control.

7. The yearly HMG Work Plans should be broken down into periods, either on a quarterly or a monthly basis.

8. Once the period is established, operational plans should be given to each division, with target dates for execution.

9. The PROGRAMME and PROGRESS CHART for the building site at Godavari be followed and amended if necessary.

10. UNDP, UNIDO, BYS (SATA) and Ets. TOURNAIRE must be kept informed of building progress and estimated installation date.

11. A close relationship to be maintained between RDRL and the different engineering sections of BYS.

12. BYS engineers should be invited to join in the installation of the Pilot Plant.

13. Primary manufacturing, such as platforms, steps and hoist tracks to be undertaken by BYS on the basis of the Tournaire drawings.

14. BYS (SATA) to have a hand in training the pilot plant maintenance engineers.

15. Maintenance procedures, as mentioned in the CTA Programme dated 25 August 1983 should be introduced and improved upon at regular intervals.

16. The introduction of Health and Safety measures should be followed up by the appointment of a Safety Officer.

17. The appointment of a LINK-MAN to work with the Herbs Production and Processing Co. Ltd. on joint problems of marketing should be made without delay. The results of his work could lead to a technico/commercial project.

18. Standards of essential oils should be established and strictly observed.

19. The development of pyrethrum extracts as insecticides for use on the home market should be re-examined to determine the export potential of the pyrethrum extract as well as the finished product.

ANNEX I

JOB DESCRIPTION

DP/NEP/80/003/11-01/A/32.1.D

| | |
|---|---|
| Post title | Chemist/Technologist for the Production of Pharmaceuticals |
| Duration | Twelve months, with possibility of extension |
| Date required | As soon as possible |
| Duty station | Kathmandu |
| Purpose of project | To further develop the existing facility for the production of plant-derived pharmaceuticals at the Royal Drugs Research Laboratory. |
| Duties | The expert will assist the Director of the Royal Drugs Research Laboratory to organise the Laboratory and Pilot Plant facilities for the production of pharmaceuticals from medicinal and aromatic plants. More specifically, the expert will be expected to:<br>1. Assist in the installation of the laboratory and pilot plant facilities for the production of pharmaceuticals in the country;<br>2. Supervise the installation of analytical instrumentation for the quality assessment of drugs, essential oils and other pharmaceutical products, and for biological screening procedures;<br>3. Organise optimum utilisation of all equipment and regular maintenance procedures;<br>4. Conduct market studies with a view to matching production to the actual requirements;<br>5. Exercise general supervision of project activities.<br>The expert will also be expected to prepare a final report setting out the findings of the mission and recommendations to the Government on further action which might be taken. |
| Qualifications | University degree in Chemistry, with wide experience in chemical technology, particularly in the production of pharmaceuticals, or degree in Mechanical or Chemical Engineering with long experience in the production of pharmaceuticles from plants, or any similar and equivalent qualifications and background experience; experience in chemical technology, natural product research, marketing studies, and similar work in developing countries an asset. |
| Language | English |

ANNEX II

List of Counterparts

| S.No. | Name | Post Description |
|---|---|---|
| 1. | Dr. S.B. Malla | Director General |
| 2. | Dr. S.B. Rajbhandary | Deputy Director General |
| 3. | Dr. P.M. Adhikari | Senior Scientific Officer |
| 4. | Mr. A.D. Shrestha | Senior Scientific Officer |
| 5. | Dr. S.R. Adhikari | Senior Scientific Officer |
| 6. | Dr. K.R. Amatya | Scientific Officer (Chemistry) |
| 7. | Mr. S.K. Joshi | Scientific Officer (Pharmacology) |
| 8. | Mr. A.B. Upadhyay | Scientific Officer |
| 9. | Dr. P.R. Shakya | Scientific Officer |
| 10. | Dr. M.S. Bista | Scientific Officer (Botany) |
| 11. | Mr. N.C. Shrestha | Assistant Scientific Officer (Pharmacy) |
| 12. | Mr. P.M. Shakya | Assistant Scientific Officer (Microbiology) |
| 13. | Mr. Mahesh Adhikari | Assistant Scientific Officer (Botany) |
| 14. | Mr. B.R. Tuladhar | Assistant Scientific Officer (Pharmacy) |
| 15. | Dr. B.P. Acharya | Assistant Scientific Officer |
| 16. | Mrs. Sumitra Vaidya | Scientific Officer (Phytochemistry) |

ANNEX III

List of Fellowships

| No. | Fellowship | Duration (months) | Name of fellow, Country of study | Started Sched. | Started Actual | Completed Sched. | Completed Actual |
|---|---|---|---|---|---|---|---|
| 1. | Drug analysis | 6 | Mr. D.D. Bhattarai (INDIA) | 1982 | 28/2/83 | | |
| 2. | Drug analysis | 12 | Ms. Nuna Rajbansi (INDIA) | 1982 | 1/3/83 | | |
| 3. | Microbiological assays | 6 | Mr. P.M. Shakya | 1982 | 1/3/83 | | 31/8/83 |
| 4. | Bio-assay | 6 | Mr. M.P. Amatya | 1982 | 28/2/83 | | |
| 5. | Drug analysis | 6 | Mr. D.P. Neupane | | | | |
| 6. | Drug analysis | 6 | Mr. L.K. Vaidya | | | | |
| 7. | Microbiological assays | 12 | Miss K. Manandhar | | | | |
| 8. | Bio-assay | 12 | Mr. S.K. Joshi | | | | |
| 9. | Breeding and maintenance of laboratory animals | 6 | Mr. Khan | | | | |

Note: Rest of the fellowships programme as scheduled in the technical report by Prof. F. Sandberg is being discussed directly between RDRL, UNDP, UNIDO.

ANNEX IV(A)

Summary of CTA Progress Reports

6 September 1982.

Short report on conditions of project after arrival of CTA. First plan for development at Godavari.

14 October 1982.

Recapitulation of project activity for the period 15 March to 30 September. Further information on Godavari site development. Discussion with WHO on Fellowships. Reference made to Economic Field reports and a Marketing mission to Bombay in July.

3 December 1982.

The report refers to the second visit of Prof. F. Sandberg and indicates preparations made for the arrival of the Pharmacologist Dr. J.P.G. Williams. The clearance for Ms. M.M. Cordes is still awaited from HMG, whereas the acceptance of Dr. Jan Karlsen by HMG, is notified to UNIDO.

The associate experts' field trip to West Nepal is planned. Mention of the Joint Report - "Strategy Proposal" - by W.J. deBoeck and Bart Dominicus.

Further comment on development of Godavari site, study tours, the Madurai Symposium and the Beijing workshop.

A first attempt at "in-house" training by the preparation of an "Introduction to Corporate Planning".

Report on safe arrival of project vehicles and recruitment of driver.

Initiation of advance quotations for project NEP/80/044.

10 January 1983.

In December HMG signified acceptance of Ms. M.M. Cordes as microbiologist. She and Dr. Karlsen will take up their duties in January.

Negotiation for the prolongation of the Associate Expert/Economists stay in Nepal.

Pressure maintained on WHO to finalise the fellowship programme already running late.

The dam on the Godavari site has been constructed, work on the sedimentation and decantation tanks has started.

Final Project Document NEP/80/C44 submitted to UNDP and UNIDO.

Records of Field Visits circulated.

4 March 1983.

Consolidated report for the period 15 March 1982 to 31 December 1982.

7 April 1983.

General Account covering meetings between all the Experts and Dr. Malle and the Senior Scientific Officers of RDRL.

Report on progress at Godavari, the site having been visited by Dr. Wijesekera during his stay in Kathmandu.

The Thermex/Steamax boiler delivered to Godavari on 27 March.

Report on new constraints imposed by UNDP, resulting in 'moratorium" on equipment purchases. Re-appraisal of laboratory requirements by all experts.

After long delays, four candidates benefitting from the WHO fellowships began their training.

A new work programme prepared for the Associate Expert, to cover the present activity of the Pilot Plant.

8 July 1983.

Covering the period 1 April to 30 June 1983 the report leads in to the TPR planned for August, by updating the Pharmacology activity as well as the microbiology and essential oil work.

Report on discussions with Mr. T.E. Tyler of the FAO re NEP/79/C07. Contact established with Mr. G. Axinn, FAO Representative.

29 July 1983.

Following presentation in June of the Project Evaluation Report, a Consolidated Progress Report was drawn up at the end of July in time for the Tripartite Review (TPR) on 3 August 1983.

The report collated all the information previously produced and provided up-to-date information about the Godavari pilot plant site and the state of project activities. A list of equipment supplied was included as well as a schedule of installation activities and "in situ" training.

Period 8 August/27 October 1983.

Reports to UNIDO were in letter form dealing with specific problems as they arose.

27 October 1983.

A General Account was presented prior to the CTA Final Report. The account covers Institution Building and Problem solving, Comments on equipment and transfer of technology, as well as "in situ" training and Future prospects.

The account also mentions the mistakes made and the contingency measures adopted to deal with special situations.

ANNEX IV(B)

Summary - Pharmacology

The object of the project "Strengthening the Royal Drugs Research Laboratory" is to help the RDRL to fulfill the objective of HMG Nepal that Nepal should be self-sufficient in essential drugs. The project document was signed in December 1981. Purchase of pharmacology equipment commenced in September 1982 and a technical expert in Pharmacology was fielded in December 1982 for a period of 12 months.

After arrival the pharmacology expert made an appraisal of the situation in RDRL and a number of areas of potential development were identified. During the expert's continued presence in the laboratory further areas became apparent. Of particular importance in any scientific drug development programme is the existence of a well organised and efficient animal house. The expert has devoted much of his energy to emphasizing this point which has been well received. Recommendations were made to the Director of the Laboratory and to the UNIDO CTA and many of these suggestions have been or are being incorporated into the animal house. The Director General of the Department of Medicinal Plants identified at meetings with the expert a number of particular areas in which it was felt the RDRL should work, accordingly the expert turned his attention to these areas advising on protocols and techniques etc. Consideration of training aspect of his job led the expert to make a number of recommendations especially in relationship to the library and a substantial number of books on pharmacology have been or will be added to the department's library. Recommendations for training in specific areas eg. Ph.D. in toxicology have also been made.

The Director General has requested that the UNIDO experts provide a work plan for the laboratory to pursue after their departure. In response to this the pharmacology expert has presented a generalised flow chart for the investigation of biologically active materials from biological sources at the research level.

The necessity to purchase a generator and other equipment for the animal house together with certain other factors led to reappraisal of the original equipment list and the substitution of certain other items.

ANNEX IV(C)

Summary - Microbiology

a. The microbiological aspects of pharmaceutical products, of their production and/or of their development are equally important as the chemical and physical aspects. The microbiological facility within RDRL can render a valuable contribution to the product development activities of RDRL and quality control of the production of pharmaceuticals, and through these activities will become more utilized and better integrated into the institutional framework.

b. Concerning the product development activities of RDRL contributions from microbiology could be rendered to the following subjects:

- in standardization: microbiological contamination.
- in stability studies: testing for sterility or resistance to microbial growth in the determination of optimum formulation, the most suitable container, the optimum storage conditions and the shelf-life.
- control procedures for the final production.

The participation of the microbiological laboratory in standardization could already start this fiscal year.

A guideline is given for the development of microbiological control procedures.

c. Concerning the quality control of the manufacture of pharmaceuticals, the following contributions are identified:

- microbiological control of raw materials, end products, water supply, environment and package materials;
- control of sanitation practices;
- propagation of hygienical attitudes.

d. It is expected that the section will have to handle much more samples in the future. Some measures have to be taken in anticipation, of which immediately needed:

- a constant and adequate electrical supply.
- a more spacious housing.
- a good supply of smaller items at the bench.
- the installation of an autoclave with higher capacity.

e. The methodology currently in use has been revised as far as possible. It is strongly advised to follow pharmacopoeial or standard methods for tests/analysis of pharmaceutical products.

The quality of the analysis results has to be given much attention. In broad lines this concept is explained and specified.

f. Preparatory work has been done for the establishment of the cultivation of axenic Entamoeba histolytica, the cause organism of amoebic dysentery, to extend the screening of plant extracts for antidysentric activity. Due to the late arrival of the indispensable materials and non-availability of amoeba the actual cultivation could not be initiated. Methodologies and media formulations were provided to the section.

g. The screening programme could be strengthened by the following measures:

- a centralised record keeping;
- the establishment of a data bank;
- the forming of a formal research group for this activity;
- the screening of a higher number of plants followed by
- a further testing of the active plant parts.

The centralised record keeping has been discussed and was agreed upon as well as its computerisation.

A guideline for the follow-up testing of active plant parts is presented.

h. Record keeping was found inadequate. The microbiological section should have records for methodology, samples, results of analysis, equipment, media, reagents, etc.. A guideline for the establishment of a laboratory manual and models for forms are presented.

i. The outfit of the section is modernized and extended; an air-conditioner was installed; the library is enriched with literature on microbiology and its applications.

ANNEX IV(D)

Summary - Analysis/Quality Control

The basis of this report is concerned with the aspects of the instrumental equipment at the RDRL, bringing it up to a position where the instrumentation meets modern requirements for a research laboratory. Furthermore, the setting up of a working programme for the screening of plant material selected for investigation was of importance and is to be continued in the coming years.

The conditions in Nepal are favourable for the starting up of small-scale production of plant products. However, rigorous standard methods for the control of the products must be developed and applied if these products are to achieve market success. A UNIDO expert in economic mapping has started a survey of Nepal and his investigation will naturally be the basis for the plants selected for cultivation or collection. However it is my opinion that RDRL should carry on with the collection of the essential plants from all over Nepal to establish a Nepalese standards (i.e. Cortex Granati) now that the necessary instrumentation for phytochemical work is present. However rich the flora of Nepal may be, the amount of work necessary to establish proper local standerds must not be underestimated.

The biological departments of the RDRL are the weakest and most in need of future strengthening. Therefore some of the instruments have been chosen deliberately to enable the chemical departments either to provide the section of pharmacology with purified extracts or "pure" compounds - or to analyse more thoroughly any extract showing positive pharmacological effects.

To replace imported pharmaceutical products with indigenous drugs requires extensive pharmaceutical/pharmacological testing without which no success can or will be achieved. It is therefore stressed that the development and production of medicine based on indigenous material is a long and tedious process. RDRL being the key laboratory in this, the development in Nepal certainly will need long term support to achieve the goals set by HMG.

Specially mentioned is the necessity of close cooperation with other universities concerned with research in phytochemistry. Such a contact could lead to a joint Ph.D. programme and facilitate the exchange of Ph.D. students.

To enable Nepal to enter the market of perfumery chemicals a number of essential oils are investigated. Total oils or "cuts" thereof may be successful products for Nepal in the future. The programmed harvesting - distillation and analysis being done at present will be carried on into 1985 and should provide RDRL with necessary data for product evaluation. This programme will be extended to other plants containing essential oils. Instrumentation and methods for essential oil control have been established, essential oil standards have been set and a good start in the field of essential oil evaluation achieved.

In the field of pharmaceutical drug control the instrumentation provided should be sufficient for efficient control, however, post-graduate experience from other drug control laboratories is urgently needed for the officers. Further-more support from UN-experts is also strongly recommended because the concept of state drug control depends upon international cooperation if it is to be of any use to the country in which it is applied. It is therefore necessary and recommended that regional cooperation between Nepal and Sri Lanka, Bhutan, Bangladesh, India, Burma, Thailand, Malaysia is established on a continuous basis. This cooperation does not only concern the aspect of drug quality control, but should also include the establishment of small manufacturing units based on indigenous plant material.

Concern is given to the necessity of having a regular supply of chemicals, vector gases and a constant supply of electricity without which the work being done will turn out to be extremely inefficient.

The regular meetings of staff (every week) which are initiated to discuss problems occurred will further strengthen the cooperation.

It is the opinion of the expert that RDRL has been considerably strengthened due to the input of instrumentation and to the discussions with RDRL's officers on the planning of research activity. As pointed

out research in the field of drugs and drug production is a long-term undertaking and needs therefore long term support. Observing the need for Nepal to develop production facilities for cheaper drugs this must be considered a laudable project.

Practical results

1. Complete analysis of the valepotriates of Valeriana wallichii has been carried out. Stability testing of these compounds by means of HPLC started in September. Preliminary results will be ready in December.

2. Regular batch control of lemongrass oil, Palmarosa oil and Citronella oil (produced by the experimental farms) have started in July and will be continued until next year.

3. A number of "new" essential oils of indigenous plants have been analysed and discussed. These analysis are standardized for comparison with oils obtained from European companies.

4. Regular and standardized terpene analysis of any essential oil distilled in RDRL have started and will be continued.

5. Weekly scientific meetings initiated with local staff started in July and have been continued on a regular basis.

6. Computer filing of all analyses carried out by the section "quality control" the last five years started. The filing of new analyses is being done.

7. Training of local staff in the use of HPLC instrumentation for drug control is being done.

ANNEX IV(2)

Summary - Economics

a. The associate expert's work programme was aimed at providing useful information on the socio-economic side of the programme for the development of Nepal's resources in the field of medicinal and aromatic plants.

b. Early on in the work programme, a "strategy proposal" was prepared for the overall programme, based on information gathered on cultivation and collection aspects, national and international market characteristics and the situation with regard to health care and drug supply in the country.

c. As far as the agronomic aspects are concerned, the decision of HMG/N to set up a company for commercial exploitation of the country's resources in this field, will require some important changes with regard to:

- cost-benefit conscious management for commercial farms
- setting up a comprehensive and professional extension programme for cultivation by private farmers.
- re-defining the roles of the departmental herbal farms as supporting agents to the commercialization programme.

d. Cost-benefit studies were undertaken for following products:

- Atropa belladonna
- Pyrethrum
- Rauwolfia serpentina
- Citronella
- Lemongrass
- Palmarosa
- Mentha arvensis

Although a variety of methods had to be used and the estimate of cultivation costs and yields could not be based on long-term in-situ observations (for some plants the growth cycle is four years), the studies can provide information regarding the most important cost components and could be helpful in the selection of an appropriate production-package and in setting farm gate prices for private growers.

e. A detailed proposal for small-scale production of herbal medicine was worked out for the Far Western "Seti Zone". This programme should be combined with clinical testing of the proposed drugs through the health post and ayurvedic dispensary system.

f. A status report on RDRL's pilot plant was prepared. At the pilot plant, many problems of an organisational and technical nature are encountered, and there is no clarify at present as to how the pilot plant's work fits into the overall programme.

g. Although it was intended to prepare a feasibility study for large scale production of pharmaceuticals and essential oils by the Herbs Production and Processing Company, this could not be done due to insufficient market information. It is envisaged that such a study can be made after approximately one year, when more information is available. This activity would then fall under the scope of the NEP/80/C44 project.

## ANNEX V

### List of Documentary Outputs

| S.No. | Date | Title | Author(s) |
|---|---|---|---|
| 1. | 30 March 1982 | Belladonna Cultivation in Panauti Area - Preliminary Report | Mr. M.S. Bista, Dept. of Medicinal Plants and Mr. W.J. deBoeck, UNIDO Associate Expert. |
| 2. | 1 August 1982 | Project Status Report | Mr. W.J. deBoeck, UNIDO. |
| 3. | 3 August 1982 | Mission Report (Marketing Visit to Bombay 25-28 July 1982) | Mr. W.J. deBoeck, UNIDO. |
| 4. | 5 August 1982 | Cultivation, Processing and Marketing of Belladonna by the Herbs Production and Processing Co. Ltd. | Mr. W.J. deBoeck, UNIDO. |
| 5. | 1 November 1982 | A Strategy Proposal Concerning the Programme for Development of Nepal's Resources in the field of Medicinal and Aromatic Plants. | Mr. Bart Dominicus, Netherlands Development Volunteer Service; and Mr. W.J. deBoeck, UNIDO. |
| 6. | 10 December 1982 | Minutes of the meeting on development of Nepal's Resources in the field of Medicinal and Aromatic Plants. | |
| 7. | 15 December 1982 | Field Visit Report - Pyrethrum Cultivation in Helambu. | Mr. Bart Dominicus, NDVS and Mr. W.J.deBoeck, UNIDO. |
| 8. | 20 December 1982 | Proposal for Restructuring the Doti Branch of the Herbs Production and Processing Company. | Mr. Bart Dominicus, NDVS and Mr. W.J.deBoeck, UNIDO. |
| 9. | 17 January 1983 | Status Report on Pharmacological Activity at the Royal Drugs Research Laboratory. | Dr. J.P.G. Williams, UNIDO Expert/Pharmacologist. |
| 10. | 15 February 1983 | Proposal for the development of Tamagurdi herbal farm. | Mr. W.J. deBoeck, UNIDO and Mr. G. Amatya, HPPC. |
| 11. | 17 February 1983 | The cost-benefit of the cultivation of Rauvolfia serpentina in Nepal. | Mr. W.J. deBoeck, UNIDO. |
| 12. | 25 February 1983 | The cost-benefit of the production in Nepal of some essential oils. | Mr. W.J. deBoeck, UNIDO. |
| 13. | February 1983 | Status Report on Analytical Chemical and Phytochemical Activity at the Royal Drugs Research Laboratory. | Dr. Jan Karlsen, UNIDO Expert/Analytical Chemist. |
| 14. | March 1983 | Recommendations for Primary Record Keeping in the Examination of Plant Materials for Biological Activity. | Dr. J.P.G. Williams, UNIDO Expert/Pharmacologist. |
| 15. | 4 April 1983 | Report on a visit to investigate the possibility of setting up an extension programme for herb cultivation in Eastern Nepal. | Mr. W.J. deBoeck, UNIDO and Mr. G. Amatya, HPPC. |

| S.No. | Date | Title | Author(s) |
|---|---|---|---|
| 16. | April 1983 | Report on Visit to Central Drug Research Institute, Lucknow (20/3-25/3/1983). | Dr. J.P.G. Williams, UNIDO Expert/Pharmacologist. |
| 17. | May 1983 | First Interim Report on Pharmacological Activity at the Royal Drugs Research Laboratory - January-April 1983 (1st Poush 2039-16 Baisakh 2040). | Dr. J.P. Williams, UNIDO Expert/Pharmacologist. |
| 18. | June 1983 | Report of field visit to Kanter, Seti Zone (27 May-6 June 1982). | Mr. W.J. deBoeck, UNIDO. |
| 19. | 22 June 1983 | Report of field visit to Doti (13-20 June 1983). | Mr. W.J. deBoeck, UNIDO. |
| 20. | 24 July 1983 | Economic Report. | Mr. W.J. deBoeck, UNIDO. |
| 21. | August 1983 | Amendment to Project Document (for Tri-partite Review on 8 August 1983). | Mr. J.G. Meredith, Project Co-ordinator/CTA. |
| 22. | 25 August 1983 | Programme of Maintenance Procedures. | Mr. J.G. Meredith, Project Co-ordinator/CTA. |
| 23. | 1 September 1983 | Basic approach to health and safety in laboratories. | Mr. J.G. Meredith, Project Co-ordinator/CTA. |
| 24. | 16 September 1983 | Report on Microbiology. | Ms. M.M. Cordes, Consultant in Microbiology. |
| 25. | 10 October 1983 | Technical Report: Pharmacology Laboratory. | Dr. J.P.G. Williams, UNIDO Expert/Pharmacologist. |
| 26. | | Report on Analytical Chemistry/ Quality Control. | Dr. Jan Karlsen, UNIDO Expert/Analytical Chemist. |

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Note: Report No. 26 will be ready for circulation in November/December 1983.

ANNEX VI

## List of Books

| Item No. | Description |
|---|---|
| 1. | Industrial Fermentations<br>vols. 1 and 2<br>New York, Chemical Publishing Co. |
| 2. | Kieslich, Klaus:<br>Microbial transformation of non-steroid cyclic components.<br>New York, Wiley Interscience.<br>ISBNO-471-0182-0 |
| 3. | Antibiotics: isolation, separation and purification.<br>Ed. by Mavin J. Weinstein and Gerald HlWagman<br>Schering - Plough Co., N.J. |
| 4. | Board and Lovelock:<br>Some methods for microbiological Assay. Tochn.<br>series No. 8, Soc. for Applied Bateriology. |
| 5. | U.S. Pharmacopoeia<br>latest ed. |
| 6. | Mitraka, B.M.:<br>Gas chromatographic applications in microbiology and medicine.<br>Krieger 1975<br>IBBN 0-471-61183-2 |
| 7. | Pirt, S.J.<br>Principles of microbe and cell cultivation.<br>London, Blackwell Scientific Pubs. |
| 8. | Yawada, S. Kinoshita, T. Sanido et all:<br>The Microbial production of amino acids.<br>New York, Wiley. |
| 9. | Progress in industrial microbiology<br>(complete, except vol.I)<br>London, Heywood and Co. |
| 10. | Berdler, L.M. (editor):<br>Handbook of sensory physiology.<br>vol.4 (2 parts - Olfaction and Taste) |
| 11. | Manzu-ul-Hacq Hasuri:<br>Assay of vitamins in pharmaceutical preparations.<br>New York, Wiley. |

| Item No. | Description |
|---|---|
| 12. | Shapton, D.A. and Board, R.G.:<br>Safety in microbiology<br>(Society of Applied Bacteriology, Technical series, No.6)<br>ISBN 0-12-638860-1<br>London, Academic Press. |
| 13. | Finney, D.J.:<br>Statistical method in biological assay.<br>London, Hafner Publications. |
| 14. | Antibiotics and chemotherapy.<br>5th ed.<br>London, Churchill-Livingstone, 1973. |
| 15. | Olfaction and odours (William McCartney)<br>New York, Springer, 1981. |
| 16. | Iizuka, H. and Natto, A.:<br>Microbial conversion of steroids and alkaloids.<br>New York, Springer, 1981. |
| 17. | Fermentation Technology Today.<br>Proceedings of the 4th International Fermentation Symposium<br>(or latest)<br>Washington, American Society for Microbiology. |
| 18. | Cooper, M.S. (ed.):<br>Quality control in the pharmaceutical industry 3 vols.<br>New York, Academic Press, 1972. |
| 19. | Microorganisms in foods II:<br>Sampling for microbiological analyses; principles and<br>specific applications.<br>Int. Commission on Microbiological specs. for Foods (ICMSF),<br>University of Toronto Press. |
| 20. | Board. R.G. and Horelock, D.W.:<br>Sampling - Microbiological Monitoring of Environments.<br>London, Academic Press, 1973. |
| 21. | Hartman:<br>Miniaturized microbiological methods.<br>(Suppl.I of Advances in Appl Microbiology) |
| 22. | Collings, C.H.:<br>The prevention of laboratory acquired infection.<br>London, Her Majesty's Stationary Office, 1977. |

| Item No. | Description |
|---|---|
| 23. | Hewitt, William:<br>Microbiological Assay: an introduction to quantitative principles and evaluation.<br>New York, Academic Press. |
| 24. | Kavanagh, Frederick:<br>Analytical microbiology. vol.II.<br>New York, Academic Press. |
| 25. | Norris, J.R. and D.W. Ribbons:<br>Methods in microbiology, Vols. I and II.<br>London, Academic Press, 1969/70. |
| 26. | Charus, W. and Hezos, H.K.:<br>Microbial transformation of steroids. (handbook)<br>New York, Academic Press. |
| 27. | Annual Reports on Fermentation processes.<br>vols. I and II.<br>edited by D. Perlman.<br>New York, Academic Press, 1977/78. |
| 28. | Solomans, Gl.:<br>Material and methods in fermentation.<br>New York, Academic Press, 1969. |
| 29. | Malek, I.K. and Berin:<br>Continuous cultivation of microorganisms.<br>New York, Academic Press. |
| 30. | Pryde, A. and M.T. Gilbert:<br>Application of High Performance Liquid Chromatography. |
| 31. | Shyder, L.R. and J.J. Kirkland:<br>Introduction to modern liquid chromatography.<br>New York, Wiley Interscience. |
| 32. | Connors, K.:<br>Chemical stability of pharmaceuticals.<br>New York, Wiley. |
| 33. | Brochmann-Hansen, E. and Higuchi, T.:<br>Pharmaceutical analysis.<br>New York, Wiley. |
| 34. | Jellinek, J.S.:<br>The use of fragrance in consumer products.<br>New York, Wiley. |

| Item No. | Description |
|---|---|
| 35. | The British Pharmacopoeia.<br>Latest ed. (1980) |
| 36. | Perry et al.:<br>Practical liquid chromatography.<br>New York, Plenum Press, 1972. |
| 37. | Silver-Lindbergh:<br>Computers in life science research.<br>New York, Plenum Press. |
| 38. | Blau, K.A. and Kind, G.S.:<br>Handbook of derivatives for chromatography.<br>American Society for Testing and Materials. |
| 39. | Barheim Svendson and R. Verpoorte:<br>Chromatography of alkaloids.<br>Amerdam, Elsevier, 1983.<br>Part A: Thin Layer chromatography<br>Part B: Gas Liquid and high perfromance liquid chromatography. |
| 40. | Ariens:<br>Introduction to general toxicology.<br>New York, Academic Press, 1976. |
| 41. | Bruce, Clark and D.A. Smith:<br>An introduction to pharmacokinetics.<br>Mosbye Pubs., 1981.<br>ISBN 0-632-00743-5 |
| 42. | Filov:<br>Quantitative toxicology.<br>New York, Wiley. |
| 43. | Gorrod, J.W. ed.):<br>Testing for toxicity.<br>Publ.: Burgess, 1981. |
| 44. | Loomis, TEd:<br>Essentials of toxicology.<br>Philadelphia, Lea and Febiger, 1975. |
| 45. | Goodman, L.S. and Gilmen A.:<br>The pharmacological basis of therapeutics:<br>a textbook of pharmacology, toxicology, and<br>therapeutics for physicians and medical students.<br>London, Collier-Macmillan, 1970. |

| Item No. | Description |
|---|---|
| 46. | Mosby + Ryan:<br>Handbook of practical pharmacology.<br>St. Louis, Mosby, 1980. |
| 47. | Animal and clinical pharmacologic techniques in drug evaluation.<br>Chicago, Year Book Medical Publishers, 1967. vol.2 |
| 48. | Osborn, J.F.:<br>Statistical exercises in medical research.<br>Halstead Press, 1979. |
| 49. | Philips, D.S.<br>Basic statistics for health science students<br>San Francisco, Freeman, 1978.<br>ISBN 0-7167-0050-6 |
| 50. | Strike, P.W.:<br>Medical Laboratory Statistics.<br>(= Monograph in Medical Laboratory Science)<br>Wright, 1981.<br>ISBN 0-7236-0582-3 |
| 51. | Swinscow, T.D.V.:<br>Statistics at square one.<br>Ed. by British Medical Journal editors, 1980<br>State Mutual Bk. |
| 52. | Spector, S., Beck, N. and A.R. Liss:<br>Modern methods in pharmacology.<br>vol. 1, 1982<br>New York, A.R. Liss Pubs.<br>ISBN 0-8451-2500-1 |
| 53. | Bowman, William:<br>Textbook of pharmacology<br>Oxford, Blackwell Scientific, 1980. |
| 54. | Lewis's pharmacology.<br>Edinburgh, Livingstone, 1970<br>ISBN 0-443-00656-3 |
| 55. | Goldstein, A. et al.:<br>Principles of Drug Action.<br>Wiley-Medical, New York. |
| 56. | Inman, W.H.<br>Monitoring for drug safety.<br>Lippi cott 1980. |

| Item No. | Description |
|---|---|
| 57. | Sbindon and Gross<br>Pharmacological methods in toxicology.<br>Pergamon, Oxford, 1979. |
| 58. | Smith, R.V. and Steward J.T.:<br>Textbook of biopharmaceutic analysis;<br>a description of methods for the determination of drugs in biologic fluids.<br>Philadelphia, Lea and Febiger, 1981. |
| 59. | Armitage, P.:<br>Statistical methods in medical research 1982.<br>New York, Wiley, 1971. |
| 60. | IRC Handbooks of Pathology |
| 61. | IRC Handbooks of Screening |
| 62. | Wooton, and Freeman:<br>Microanalysis in medical biochemistry.<br>Churchill-Livingstone. |
| 63. | Hodgson and Guthrie:<br>Introduction to biochemical toxicology 1980.<br>Amsterdam, Elsevier, 1980. |
| 64. | Martin:<br>Quantitative drug design. A critical introduction.<br>New York, Marcel Dekker, 1978.<br>ISBN 0-8247-6574-5 |
| 65. | Eccles:<br>Physiology of synopses.<br>New York, Academic Press, 1964. |
| 66. | Foster and Cox:<br>Basic Pharmacology.<br>London, Butterworths. |
| 67. | Graeme S. Avery:<br>Drug treatment principles and practices in clinical pharmacology. |
| 68. | Discovery development and delivery of new drugs.<br>(= S.P. Medical Publication) |

| Item No. | Description |
|---|---|
| 69. | Flabour and Fragrance materials.<br>Wheathon, Ill, Allured Publishing Co.,<br>1981. |
| 70. | Van Beer, W. and Lal, H.:<br>Modern pharmacology and toxicology, vol. 7<br>(Synthetic antidiarrheal drugs)<br>New York, Marcel Dekker, 1976. |
| 71. | Hugo, W.B. and Russel A.D.<br>Pharmaceutical microbiology and toxicology. |
| 72. | Reeves, D.S. et al.:<br>Laboratory methods in antimicrobial chemotherapy.<br>Publ.: Churchill Livingstone. |
| 73. | Ham, A.W.:<br>Histoloty. 8th ed.<br>Lippincott, 1979.<br>ISBN 0-397-52089-1 |
| 74. | Clark, G.:<br>Staining procedures. 4th ed.<br>Williams and Wilkins, 1981.<br>ISBN 0-683-01707-1 |
| 75. | Annual Review of Biochemistry<br>1976-1982. |
| 76 | Subscription to:<br>Annual Review of Biochemistry<br>effective 1 Jan. 1983 (if possible)<br>to be supplied for 3 years. |

ANNEX VII

List of Equipments

| UNIDO Purchase Order No. | Supplier | Description |
|---|---|---|
| 15-2-K0777 | Toyota Motors Co., Japan | 2 Land Cruisers; 1 Sedan Corona |
| 15-2-K0618 | Thermax India Pte.Ltd., India | Steam Generator |
| 15-2-K0649 | Tournaire, S.A., France | Pilot Plant Equipments |
| 15-2-K0895 | Grass Instruments Co., USA | Polygraph with transducers |
| 15-2-K0836 | Osaka Kizai Kogyo Ltd., Japan | Diesel Engine Generator |
| 15-2-K1293 | Personal Computers Ltd., UK | Apple II Computer and Accessories |
| 15-2-K1504 | Harris Systems (P) Ltd., UK | Pallet trucks |
| 15-3-K0413 | Olympus Optical Co. Ltd., Japan | Trinocular Microscope (complete); Stereoscope zoom 3. |
| 15-3-K0367 | Waters Associates (P) Ltd., Singapore | HPLC equipment (complete) |
| 15-3-K0362 | Mercantile Agency, Hong Kong | Airconditioners |
| 15-3-K0422 | Aerni-Leuca Ltd. Liege fold, Switzerland. | Graph papers |
| 15-3-K0490 | Karl Kolb GmbH, West Germany | Distillation Apparatus |
| 15-3-R4042)<br>15-3-R4052) | Munksgaard, Denmark | Books and Periodicals |
| 15-3-K0385 | Nissei Trading Co., Japan | Olympus Inverted Microscope |
| 15-3-K0386 | A. Gallenkamp, UK | Balance and stirrers |
| 15-3-K0478 | Mettler A.G., Switzerland | Micro balance M-3 |
| 15-3-K0494 | Bode A.G., West Germany | Water Distillation Equipment |
| 15-3-K0569 | C.ITOH & Co.Ltd., Japan | Diesel Generator 75 KVA |
| 15-3-DC699 | A. Gallenkamp, UK | Fermenter |
| 15-3-D0726 | D. Bonapace Milono | Capsule filling |
| 15-3-D0734 | Niro Atomizer | Spray drying unit |
| 15-3-D0736 | Kennedy Intl. Sheffield | Hammer Mill, Medium Jaw Crusher. |

| Field Purchase Order No. | Supplier | Description |
|---|---|---|
| 001875 | Life Science Associates, USA | Computer software |
| 002074 | Chrompack Nederland BV, The Netherlands | Chromatographic columns |
| 001239 | Karl Kolb GmbH, West Germany. | Knives and strop for microtome |
| 002035 | A. Gallenkamp, UK | Miscellaneous Microbiology equipments |
| 002036 | Sigma Chemical, USA | Reagents (chemicals) |
| 002037 | Waters Associate (P) Ltd., Singapore | Miscellaneous items for HPLC |
| 003651 | LKB Produkter AB, Sweden | Multirac fraction collector |
| 003652 | LKB Produkter AB, Sweden | Tube racks for above |
| 003653 | Interactive Microware, USA | Computer software |
| 003654 | Votrax Pte. Ltd., Singapore | Computer software |
| 003656 | Personal Computer, UK | Computer software |
| 003657 | Amalgamated Suppliers, India | Senior Rotary Microtome |
| 003658 | Sybex-Verlag GmbH, USA | Books |
| 003659 | Microcomputing Periodicals | Books |
| 003660 | J. Dibby Science Products, UK | Chromatography columns |
| 003661 | Mercantile Agency, Hong Kong | Emergency PC Power Supply units |
| 003662 | Chemie und Filter AG | Duramat dosing pump |
| 003663 | Bector Dickinson BV, The Netherlands. | Biosate, Trypticase yist extract |
| 003664 | Merck Darmstadt, West Germany | "FLORIR" equipment for chromatography |
| 003665 | Miles (India) Ltd., India | AMES Blood Analyser |
| 003666 | A. Gallenkamp, UK | Miscellaneous laboratory equipments |
| 003667 | Bio Science, UK | Gut vessels |
| 003668 | Omega Microware, USA | Computer software |
| 003669 | Videx, Inc., USA | Computer software |
| 004871 | Chrompack Nederland BV, The Netherlands. | Sampling vials and caps |
| 004872 | Milton Roy | Diode Assembly (electronic spareparts) |
| 004873 | Waters Associates (P) Ltd., Singapore | Hamilton syringes |

| Field Purchase Order No. | Supplier | Description |
|---|---|---|
| 004874 | Rudolf Brand GmbH, West Germany | Transferpette and pipette |
| 004875 | J. Bibby Science, UK | Extractor II EX/H2 |
| 004876<br>004877<br>004878<br>004879 | Mercantile Agency, Hong Kong | Corvus Removable Hard Disk Drive<br>Appl. II Computer<br>EPSON LX80<br>Refrigerator and deep freezer |
| 004880 | Millipore/Waters Associates (P) Ltd., Singapore | Miscellaneous Laboratory equipments for microbiology |
| 004882 | Fisher Scientific, Singapore | Cork punches |
| 004883 | Waters Associates (P) Ltd., Singapore | Bondapack columns (chromatography) |
| 004884 | Karl Kolb GmbH, West Germany | Adaptors for distillation equipment |
| 004886 | The Discount Software Group, USA | Computer softwares. |

Local Purchase

| | Supplier | Description |
|---|---|---|
| 1. | Balaju Yantra Shala, Balaju, Kathmandu. | Aluminium sheets - 10 sheets<br>Incinerator - 1<br>Drawing Board/Table - 1<br>Trolley (wheeled rack) - 1<br>Rabbit cages; Pans; spare bottoms for cages. |
| 2. | Mercantile Traders, New Road, Kathmandu. | Typewriter - 1<br>Voltage Stabilizers - 3<br>Airconditioner - 1 |
| 3. | Kathmandu Furniture Works Bagbazaar, Kathmandu. | Wooden supports for gas cylinders - 4<br>White boards - 6<br>Soft board - 1 |
| 4. | Tripura Traders, Bag Bazaar, Kathmandu. | Filing cabinet - 1 |
| 5. | Life Science Associates, New York, USA. | Diskette - 1 |
| 6. | Hindustan Dehydrated, India. | Dehydrated culture media. |

ANNEX VIII

PROGRAMME AND PROGRESS CHART — Pilot Plant: Godavari - rescheduled starting 15 August 1983

| Item of Work | | 1983 Aug | Sep | Oct | Nov | Dec | 1984 Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | 1985 Jan | Feb | Mar | Apr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mark-out site | Plan | == | | | | | | | | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Dig trenches | Plan | | === | | | | | | | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Lay Foundations | Plan | | | ========= | | | | | | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Erect Walls (Ext) | Plan | | | | | | ===== | | | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Lay paths | Plan | | | | | | | ==== | | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Erect roof | Plan | | | | | | | | = | | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Erect Walls (Int.) | Plan | | | | | | | | = | ==== | | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Complete building | Plan | | | | | | | | | | ======== | | | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Install equipment | Plan | | | | | | | | | | | | ========== | | | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Final (Tournaire) check-up | Plan | | | | | | | | | | | | | | ==== | | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Commission Pilot Plant | Plan | | | | | | | | | | | | | | | ==== | | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |
| Start up | Plan | | | | | | | | | | | | | | | | = | | | | | |
| | Act. | | | | | | | | | | | | | | | | | | | | | |

Note: Actuals to be filled in by RDRL upon completion of work.