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PILOT PRODUCTION OF MEDICINES USING INDIGENOUS RAW MATERIALS

DP/VIE/80/032

THE SOCIALIST REPUBLIC OF VIET NAM

Technical report: Findings, work performed and recommendations*

Prepared for the Government of
the Socialist Republic of Viet Nam
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

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Vienna

* This document has not been edited

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BACKGROUND AND JUSTIFICATION

Vietnam has its own original traditional system of medicine which is deeply rooted in the society. The traditional plant drugs cater to the health needs of about 90 of the population and constitutes the major share of the expenditure on drugs . The Government of Vietnam is committed to a policy of intergrating the traditional and modern systems of medicine into a Vietnamese System of medicine. The modern doctors trained at the Medical Colleges in Vietnam are given a two year training in the use of traditional drugs and they prescribe the traditional drugs for the treatment of disease. These drugs are produced at the Central,Provincial and District level factories in modern dosage forms. Thus the use of traditional drugs is already more advanced in Vietnam than in some developing countries in the region where only powders and decoctions are used. However, a great deal of improvement is needed in formulation research,process monitoring and production technologies. The establishment of a pilot plant will thus be an essential facility as an interface between R & D work and the pharmaceutical industry.

The Institute of Materia Medica has been set up in 1961 as the main centre for research on medicinal plant drugs. It consists of eight divisions conducting research and development work on Pharmacognosy, Phytochemistry , Pharmacology,Toxicology,Analytical Chemistry,Cultivation and small scale pilot plant studies. Through sustained research, the Institute staff have selectively identified a number of medicinal plants which can be reliably used for the treatment of common ailments. Further credibility to this work has been provided through conduct of clinical trials. The Institute has also development laboratory scale processes for extraction and preparation of sophisticated standardized dosage forms of medicinal. The Institute of Materia Medica has carried out extensive

research on the utilisation of these plant material source to produce traditional medicines but the Institute did not have proper facilities to develop the technologies for producing drugs on modern lines. Although the Institute had developed laboratory scale processes for extraction, preparation of sophisticated standardised dosage form of drugs, the results of this R & D work lay unutilized for lack of proper pilot plant facilities which were essential for commercial adoption of these technologies. The Institute has links with the Industry, having in the past given some formulations for commercial production. However, several more sophisticated processes could not be transfered to Industry in the past due to lack of modern pilot plant facilities for process optimisation and scale up.

A. DEVELOPMENT OBJECTIVE

The development objective of this project corresponds to the national development orientation developing health work mentioned in para 9h of the approved 1982-1986 Country Programme for Vietnam. The project which is included in the Country Programme under para 63 will contribute to attaining this objective by enabling the country to develop pharmaceutical products from indegenous raw materials up to industrial scale production.

B. IMMEDIATE OBJECTIVES

To develop a national competence in the processing of drugs (in modern dosage forms) from medicinal plants used in the traditional Vietnamese phamacopoeias by :

(a) Establishing a pilot plant for the development of process technology, formulation and production of drugs in the Institute of Materia Medica in Hanoi.

(b) Carrying out pilot-scale formulation and production of the

drugs listed in Annex

(c) Arranging for the testing of such drugs according to the protocol in Figure 2.

(d) Training staff in the above activities and improving the facilities of the Insitute accordingly.

C. THE PROGRAMME OBJECTIVES

a. To upgrade the infrastructure and strengthen the R & D capabilities of the Institute of Materia Medica.

b. To establish scientific proof and credibility regarding the efficacy and safety of Vietnamese traditional herbal drugs.

c. To develop and demonstrate through modern pilot plant, the concept of good manufacturing practices.

d. To upscale and optimise the processes on pilot plant.

e. To transfer proven technologies to the Industry for the manufacture of medicines.

LOGICAL FRAMEWORK

A. PROGRAMME OBJECTIVES :

The logical framework of the Project and the relationship among its design elements have been described in the Project document. By provision of resources from both UNDP and Govt.for the purpose of undertaking specific activities shown in the workplan,the expected outputs were to be produced and these outputs were to achieve the immediate objectives. The overall Project results were to be considered as a step towards fulfilment of higher level development objectives.

The reasons and justification for undertaking of this project has already been explained in the introduction to this report.

The countrydevelopment objectives through successful implementation of this project are served through :

a/ Increased production of medicines to cater to health needs of the country.

b/ Providing protection to consumers of medicines by ensuring scientifically proven efficacy and freedom from toxicity with respect to indigenous medicines.

c/ Reducing import bill by indigenous production of medicines.

d/ Generation of know-how and self reliance.

e/ Export earning through export of phytochemicals derived from indigenous herbs.

For the programme goals to merge with National goals it was essential to provide to Institute of Materia Medica strengthened infrastructure,superior training,modern R & D equipment and a pilot plant to manufacture extracts phytochemicals and dosage form of medicines.

B.PROJECT OBJECTIVES

The primary function of the project as stated in the project document is Pilot Plant and secondary function is institution building. The Project is multidisciplinery and multifaced involving botanical raw materials generated through farm agrotechnology and multidisciplinary R & D involving research in pharmacology for efficacy testing and safety testing : chemistry for quality control and lab.scale process development : pharmacentical technology involved in manufacture of dosage forms (tablets etc.) and chemical technology and chemical engineering involved in extraction,purification and manufacture of

active phytochemicals from herbs.

Inconformity with such diverse activities the project document stipulates

a. Strengthening of infrastructure of the entire institute to enable it to cope up with complex tasks.

b. Strengthening R and D capabilities of the laboratories by input of equipment chemicals and solvents.

c. Providing a bench scale facility for scale up from laboratory process to an intermediate level or to optimise parameters of a process.

d. Provide Pilot Plant facility (in this case actually more than one type of Pilot plant) because of diversities of technology to be dealt with.

Finally the outputs have also been well defined in the project document in terms of equipment system, manpower (trained), technology and products.

Preparatory Assistance

In February-March 1982 UNIDO arranged for a mission to be carried out by Polytechna/Inpo who drafted a Project document which was not approved. A second mission (ATAL and DESILVA) prepared a draft Project Document in Dec.Jan.1984 While the basic approach,size,scope and many activities of the Project were agreed,it was decided to appoint a CTA under an extended preparatory assistance for 12 months. This was to enable the CTA to describe (i) fully and presicely the present status of the Institute and its links to raw material suppliers (ii) Institutes Commitment to the full process of drug approval under Govt legislation and (iii) Describe fundamental purpose of the Pilot Plant.

I joined as CTA on July,13,1985 and after briefing at VIENNA reached HANOI on July 25,1985. By November 1985 a full and final draft Project document was ready,incorporating (i) terms of reference for all experts (ii) Detailed training programme (iii) Full specifications of equipment and justification (iv) Detailed work plan for activities and (v) a report with recommendations for modifications of the existing buildings for which assistance of an International Civil engineering Consultant was also utilized for 4 weeks.

The Project Document was acceptable to all parties and was signed in December,1985. Thus effective date of commencement of Project activities is December,1985 because the bubget for equipment and trainigg purposes became available only after this date and requisitions for purchase could also be made only thereafter.

National Counterparts and National Project Staff

A generous and friendly atmosphere accompanied by keen and sincere cooperation was offered to the CTA by the National personnel since his first day of arrival in Vietnam and is continued upto the present time. The following senior staff members and even the Vice Minister of Health were often available for Project planning discussions and for removing bottlenecks that hindered progress on the implementation of the Project.

1.Prof.Dr.Nguyen Van Dan,Vice Minister of Health
2.Prof.Doan Thi Nha , National Project Director.

3.Prof. Nguyen Gia Chan,Director of Institute of Materia Medica.
4.Mr.Le Tung Chau,Deputy Director and Chief of Pilot Plant
5.Mr.Nguyen Thuong Dong,Deputy Chief of Pilot Plant
6.Mrs.Khuong Bach Tuyet,Project Officer
7.Mr.Nguyen Tuong Dung,Project Secretary.

Besides the above senior people involved in planning,the staff shown in the following list was always available for implementation of project activities. The number of staff and their requisite qualifications was exactly as per the promised Govt.inputs stated in the project document. This staff was identified at the very outset and available for project work whenever needed.

SCIENTIFIC AND TECHNICAL STAFF ACTUALLY ASSIGNED TO THE PROJECT

1. Extraction Unit		
A. Aqueous	Pharmacists	2
	Technician	1
Concentration and dry extract	Pharmacists	2
	Technician	1
B. Alcoholic extract and concentration	Pharmacists	2
	Technician	1
2. Tablet Unit		
A. Blending and mixing	Pharmacists	2
B. Granulation	Pharmacists	2
C. Drying	Pharmacist	1
D. Tabletting	Supervisor	1
	Operators	3
E. Coating and polishing	Pharmacists	2
3. Liquid preparations	Pharmacists	2
	Technicians	2
4. Phytochemical unit	Organic chemists	3
	Pharmacists	3
	Technicians	3
5. Quality control (chemical) Unit	Organic chemists	2
	Pharmacists	2
	Technicians	2
6. Pharmacology (bioassay, toxicology)	Pharmacologists	2
	Pharmacists	2
	Technicians	2
7. Formulation	Pharmacists	2
	Technician	1

8.	Workshop	Engineer	1
		Technicians	2
		Electrician	1
		Welder	1
		Fitter	1
9.	Boiler Room	Boilerman	1
		Assistant	1
		Labourers	2
10.	Animal house	Graduate (Veterinary)	1
		Technician	1
		Labourers	3
11.	Grinding room	Pharmacist	1
		Operator	1
		Labourers	2
12.	Washing room	Labourers	3
13.	Packaging and labelling	Pharmacists	3
		Technicians	3
		Labourers	2
14.	Finished Goods Store	Store keeper	1
		Assistant	1
		Labourers	2
15.	Raw material store	Store keeper	1
		Assistant	1
		Labourers	2
16.	Farm	Agronomists	3
		Pharmacist	1
		Seed store (in charge)	1
		Technicians	2

The UNDP input originally stated for preparatory assistance was subsequently extended in the ensuring budget revisions as follows :

Preparatory assistance Budget Code J			
dated 19/4/1985	: US $	155,423	
UNDP approved budget			
as per sighned PRODOC			
dated 2/12/1985	Budget Code K :	1,180,552	
Revised 17/4/1986	Code L :	1,178,612	- 1,940
Revised 5/12/86	Code M :	1,178,612	no change
Revised 15/4/87	Code N :	1,278,612	+ 100.000

The increase in the Project Budget is due to the 6 MM extension of the CTA on Budget Line 11.01. Lines 15,49 and 51 are increased to cover estimated expenditures,as proposed in telex MISC 862 and approved by Telex 30235.

Revised 22/12/87	Code O	1,289,720	+ 11,108

The increase in the Project Budget results from higher actual Expenditures on budget Line 49-99 equipment offset by savings on budget lines 19-99 Personnel. 39-99 Training and 59-99 Miscellaneous. US $ 5000 are transferred from budget line 31-10 Fellowships to budget line 33-00 In-service training as requested by the Government in letter dated 28 August,1987.

Revised 30/6/88	Code P	1,292,619	+ 2,819

Increase of Project budget is due to higher actual,costs in the ex ert components. Lines 39 and 49 are slightly decreased by 1987 refunds.

Revised 13/10/89	Code Q	1,309,319	+ 16,700

Confirmation copy of advanced authorization related to two months follow-up assignment by the pilot plant engineer for commissioning and start-up of operation of the pilot plant as recommended by the Tripartite review Meeting 14 May,1988.

Revised	Code R	1,371,057	+ 61,738

Authorisation to buy additional equipment and materials.

Revised 19/4/89	Code S	1,375,836	+ 4,779

The increase in the total bubget,due to higher actual cost in the expert component,higher estimated expenditure on budget line 49 ; and higher actual and estimated expenditure on line 51 is partially compensated by decrease on line 39,reflecting slightly lower actual expenditure.

FINANCIAL INPUTS ESTIMATED IN 1985 DECEMBER AS PER PROJECT DOCUMENT

		Total		Prior 1984		1984		1985		1986		1987	
		m/m	$	m/m	$	m/m	$	m/m	$	m/m	$	m/m	$
10	PERSONNEL												
11.01	Chief Technical Adviser	23	199,310	1	6,055		-	5.5	42,900	12	96,000	6.5	54,355
11.02	Civil Engineer	1	7,000		-		-	1	7,000		-		-
11.03	Pilot Plant Engineer	6	42,000		-		-		-	4	28,000	2	14,000
11.04	Indust. Pharmacist	6	42,000		-		-		-	3	21,000	3	21,000
11.05	Org/Anal. Chemist	6	42,000		-		-		-	4	28,000	2	14,000
11.06	Pharmacol/Toxicologist	4	28,000		-		-		-	4	28,000		-
11.50	Short term Consultant	5.6	29,798	3.8	12,487	1.8	17,311		-		-		-
11.99	Sub-total Experts	53.6	390,108	3.8	18,542	1.8	17,311	6.5	49,900	27	201,000	13.5	103,355
15	Project Travel		2,500		-		-		1,000		1,000		500
16	Mission Costs		15,465		3,465		-		-		12,000		-
19.99	Total Personnel costs	53.6	408,073	4.8	22,007	1.8	17,311	6.5	50,900	27	214,000	13.5	103,855
	TRAINING												
	Fellowships		80,000		-		-		-		80,000		-
	Study Tours		35,000		-		-				35,000		-
39.99	Total Training Costs		115,000		-		-		-		115,000		-
40	EQUIPMENT												
41	Expendable		50,000		-		-		1,000		40,000		9,000
42	Non-expendable		600,000		-		-		4,000		596,000		-
49.99	Total Equipment		650,000		-		-		5,000		636,000		9,000
50	MISCELLANEOUS												
52	Reports		1,000		-		-				1,000		-
53	Sundries		6,479		479		-		1,000		4,000		1,000
59.99	Total Miscellaneous		7,479		479		-		1,000		5,000		1,000
99.99	Project Total		1,180,552		22,486		17,311		56,900		970,000		113,855

FINANCIAL STATEMENT AT THE CLOSE OF PROJECT (APRIL 1989)

PERSONNEL DU PROJET EXPERTS/DESIGNATION DU POSTE	TOTAL H/M	TOTAL $	1989 H/M	1989 $	82-86 H/M	82-86 $	1987 H/M	1987 $	1988 H/M	1988 $
11-01 CHIEF TECHNICAL ADVISE	31.1	221,676			18.6	128,358	9.6	69,114	2.9	24,204
11-03 PILOT PLANT ENGINEER	8.0	63,074	2.0	19,871			6.0	43,203		
11-04 IND. PHARMACIST	3.0	20,658					.9	6,422	2.1	14,236
11-05 ORG/ANAL. CHEMIST	3.0	19,331					2.0	14,404	1.0	4,927
11-50 CONSULTANTS COURT TERM	4.8	37,977			4.8	34,368				
11-XX	49.9	362,716	2.0	19,871	23.4	162,726	18.5	133,143	6.0	43,367
15-00 VOYAGES EXPERTS PROJEC		8,151		461		2,310		4,217		1,163
16-00 AUTRES DEPENSES D.PERS		33,453		24,850		3,465		2,729		2,409
18-00 SURRENDER PY OBLIGS		4,227-				1,136-				3,091-
1X-XX	49.9	400,093	2.0	45,182	23.4	167,365	18.5	140,089	6.0	43,848
31-00 BOURSES INDIVIDUELLES		39,848						32,516		7,332
32-00 VOYAGES COLLECTIVE PNU		38,469				38,334		135		
33-00 FORMATION DURANT EMPLO		2,000		2,000						
38-00 SURRENDER PY OBLIGS		857-						74-		783-
3X-XX		79,460		2,000		38,334		32,577		6,549
41-00 MATERIEL CONSOMPTIBLE		94,484		27,294		56,784		8,065		2,341
42-00 MATERIEL NON CONSOMPTI		812,547		60,111		616,016		103,867		32,553
48-00 SURRENDER PY OBLIGS		24,726-						20,621-		4,105-
4X-XX		882,305		87,405		672,800		91,311		30,789
51-00 DEPENSES DIVERSES		13,995		783		8,659		3,110		1,443
58-00 SURRENDER PY OBLIGS		17-				17-				
5X-XX		13,978		783		8,642		3,110		1,443
TOTAL	49.9	1,375,836	2.0	135,370	23.4	887,141	18.5	267,087	6.0	82,629

Position regarding Govt.obligation for inputs to the Project

Promised inputs	
1.Making available national staff for the Project as proposed in the Pro.doc.	1.Obligation fully met staff in adequate numbers with requisite qualifications provided at promised timeframe.Please see annexure * for details.
2.Building to house pilot plant facilities with also proposed modifications and renovations.	2a.Complete ground floor space provided for modifications,Pl.see Annex 2b.Complete Bench Scale Lab provided for modification,Pl.see Annex 2c.Major renovation and modifications carried out as required by international Consultants for tablet and liquid section as per Annex 2d.Major renovation/alteration carried out to house extraction pilot plant as per Annex. 2e.A new building (not promised in Pro.doc) built to house the multi-purpose solvent extraction pilot plant 2f.Demolition of old boiler house and building a new boiler house to accomodate the new boiler 2g.A new building at the farm ready.

FINANCIAL INPUTS BY VIET NAM GOVERNMENT

I. Infrastructure :

I.1. Building :

Year	Description	Area (in m^2)	Costs (in
1985	Civil modification of mechanical workshop and Storehouse.	240	68,000
1986 - 1987	Civil modification of Pilot Plant (1st Floor)	388	550,000
1988	Construction of Versatile Extraction Plant Building.	54	6,100,000
1987	Construction of Power Sub-Station Building.(220/380V) 400 KVA.	27	1,100,000
	Sub - Total :	719 m^2	7,818,000
Present - 1989	-Construction of Power Sub-Station (220/380V, 100 KVA) at Van Dien Farm.	20	15,000,000
	-Construction of Drying Room and Seed Storage House in Van Dien Farm.	375	78,000,000
	Total :	1114 m^2	100,818,000 D

I.2. Service :

a. Power :

1985 - Power consumption 110/220V 55 KW/h 82,000 Dong/

1989 - Power consumption 220/380V 125 KW/h 3 million dc month

- Installation of power distribution system (Cost: VN Dong 2,487,000).

b. Water :

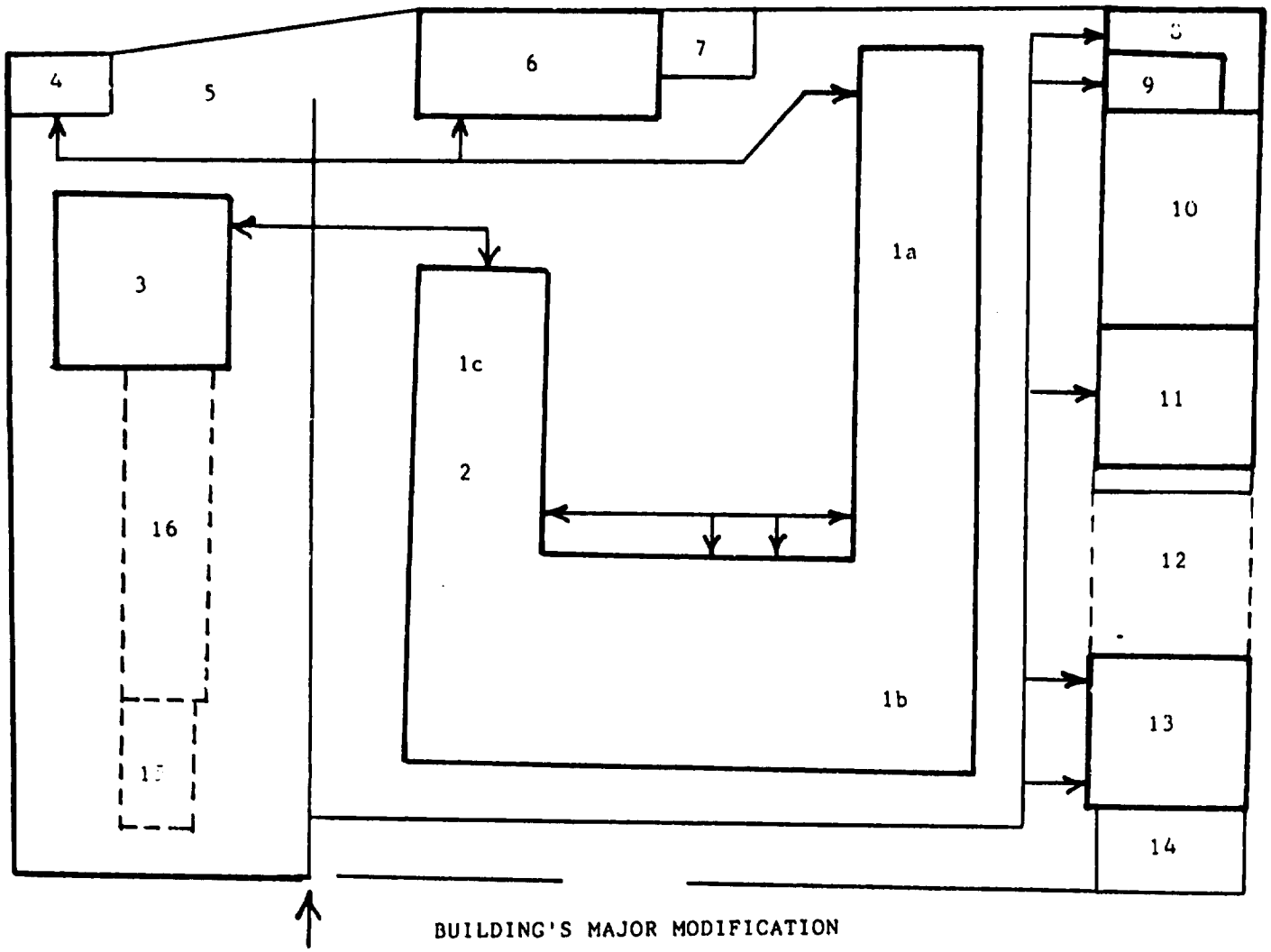
- Two Top water tanks, cap. 50 m^3 , distribution efficacy 10
- Installation of water service line (Cost VN Dong 2,000,791

c. Installation of Pilot Plant equipments 10,907,474 d

- Civil modification of Boiler house
- Building of Boiler Furnace
- Installation of Boiler and Pilping Steam distribution system
- Installation of equipments and insulation

GOVERNMENT INPUTS
OF MAJOR MODIFICATIONS TO BUILDING & NEW BUILDINGS

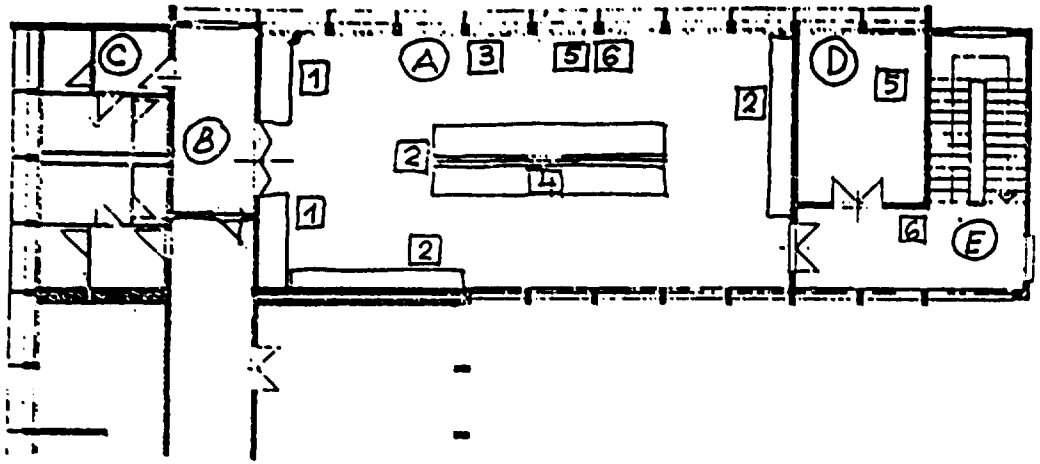
The following 5 pages show the drawings of buildings and space requirement of the project. Civil engineering details of major modifications carried out to the existing building as well as blueprints of new building are given. The Government has provided the total floor area of 1,114 sq. m. costing about 100 million VN Dong.



1 - main building ground floor
1a tabletting unit
1b liquid unit
1c batch-extraction
2 - main building third floor bench-scale laboratory
3 - continuous solvent extract and hydrolysis unit
4 - existing chemical store
5 - solvent storage in barrel
6 - boiler house and coal storage
7 - water supply
8 - laundry
9 - glass blowing room
10 - maintenance and repairs
11 - animal house
12 - 15 - 16 - temporary building unit
13 - store for desintegrated material in sacks
14 - garage

BUILDING'S MAJOR MODIFICATION

Lay out of the pilot plant and related building requirement



Existing Building Third floor

Bench-Scale Laboratory

(A) Bench-scale laboratory

1 - benches;

2 - frame for glass-apparatus and instruments;

3 - walls to be covered with glazed tiles up to 1800 height; remaining portion of walls and the ceiling to be surfaced with washable paint; all doors and windows to be repainted;

4 - r. oncrete platform 450 high;

5 - electrical wires, switches and fittings are to conform to material standards and safety regulations;

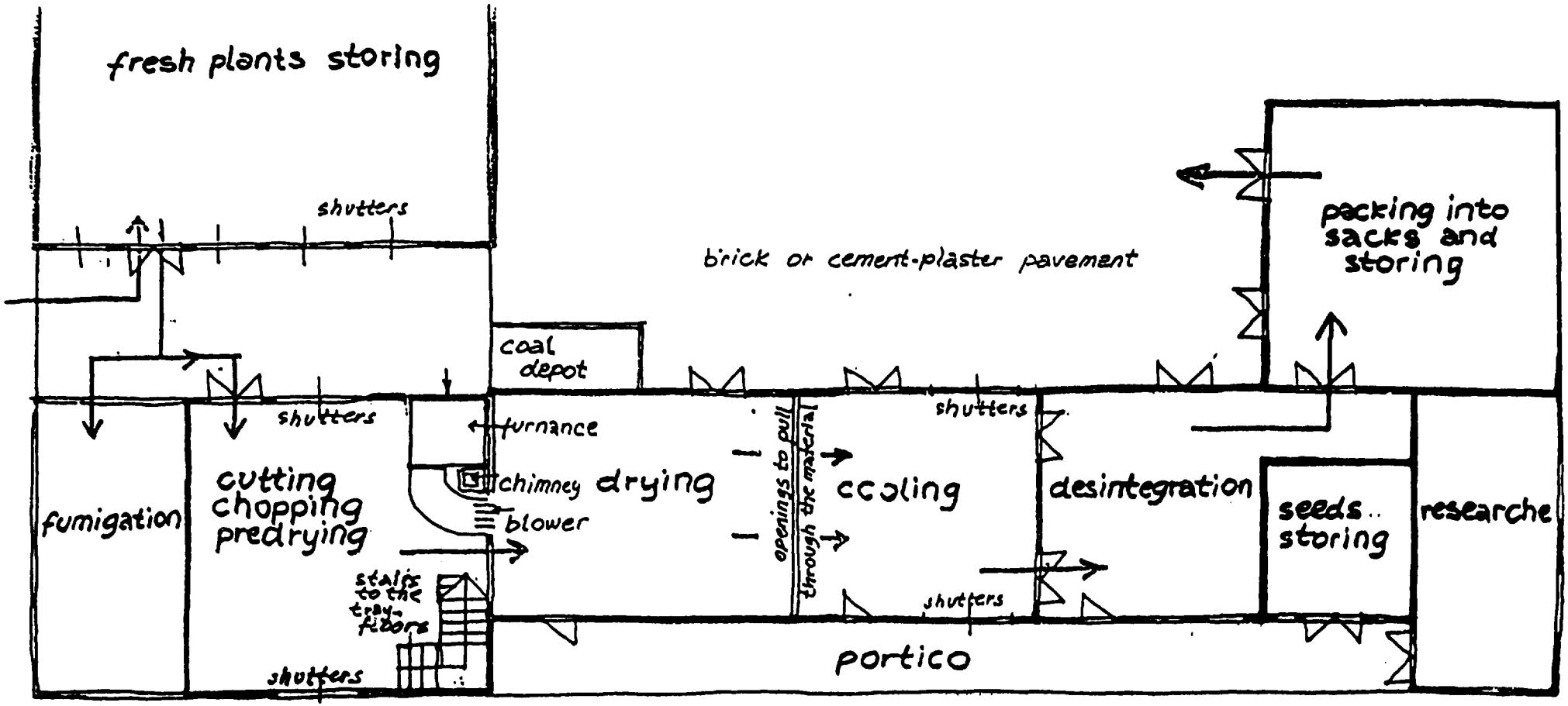
6 - prescribed fire fighting equipment, such as sand buckets, foam extinguishers are to be placed;

(B) corridor strictly to serve movement only of personnel working in the bench-scale laboratory;

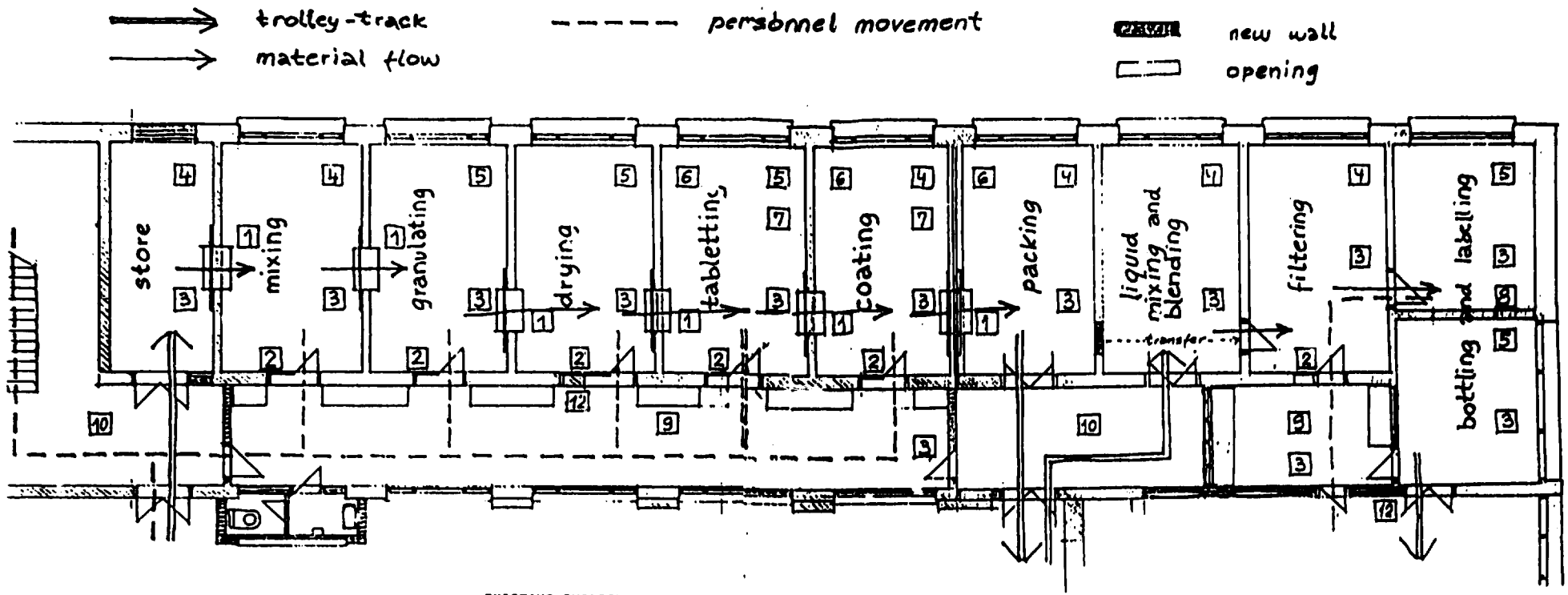
(C) toilet and washroom are to conform to good hygiene standards;

(D) substore for small quantities of chemicals; definitely not to be used for bulk storage of solvents;

(E) staircase to be kept free from all kinds of obstruction



POST HARVEST MANIPULATIONS BUILDING



EXISTING BUILDING GROUND FLOOR
PART 1

1 material handover openings 700/1000 parapet: 900; closed by sliding glass sash windows; window counter projecting both sides 200

2 permanent fixing one door-panel in closed position; blocking wall openings above the door

3 PVC sheet flooring heat fused to seal the gaps and up turned at the floor - wall angles - or terrazo flooring

4 room walls to be covered with glazed tiles up to 1200 height; remaining portion of wall and the ceiling to be resurfaced with washable paint; all door and windows to be repainted

5 same as 4 but tiles up to 1800

6 window panels to be permanently fixed in the closed position. Replace broken and missing glass

7 dehumidifier/filtered air ventillation and maintain positive air pressure

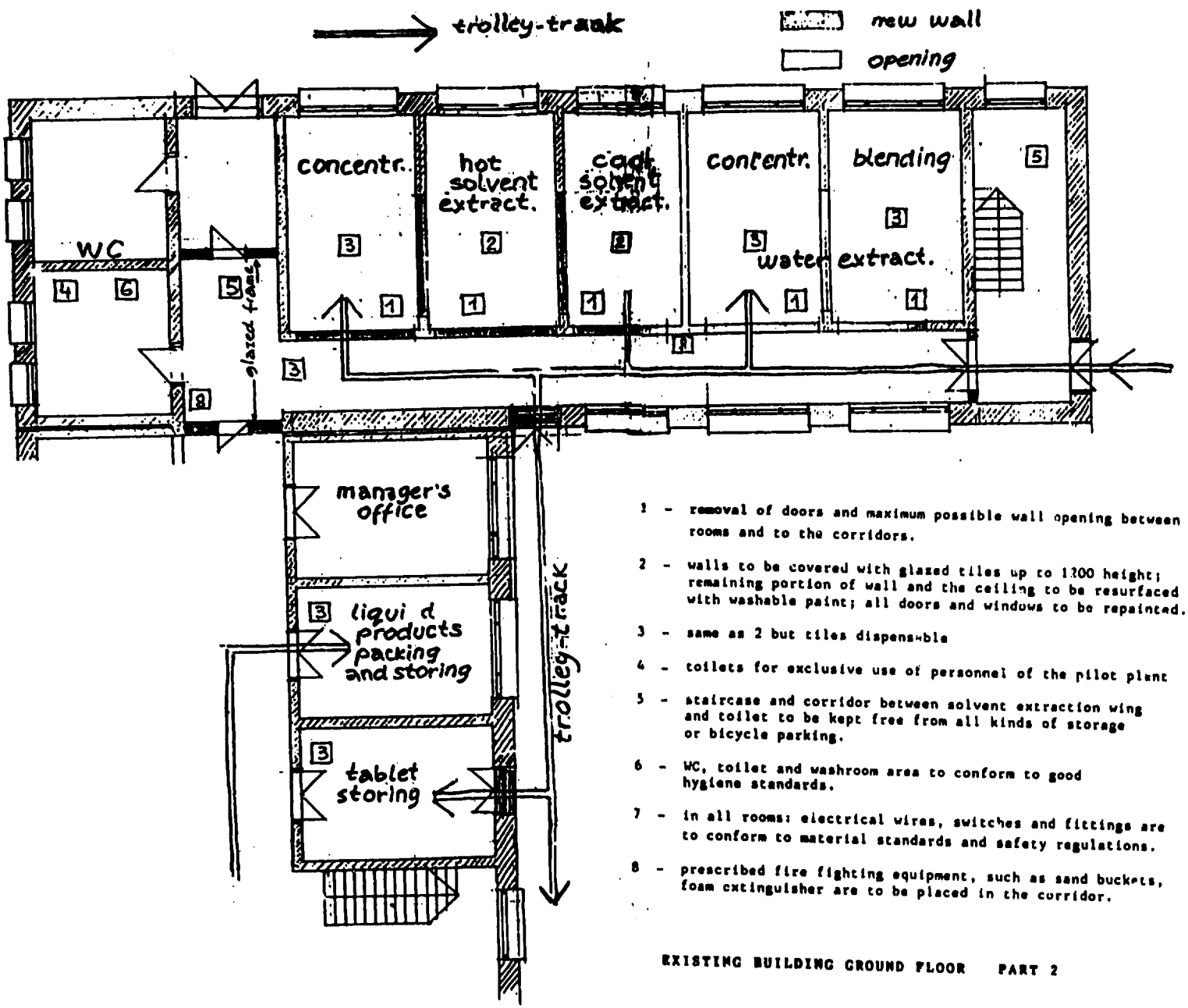
8 wall opening between two rooms to prevent change of accidental mislabelling

9 corridor strictly serve movement only of personnel working in tablet, respectively in liquid sortition; restriction on unauthorized entry - all workers to wear clean laundered white aprons and shoes provide clean painted cloth- racks and shoeshelves in the corridor

10 trolley must move only along trolley tracks

11 in all rooms: electrical wires, switches and fittings are to conform to material standards and safety regulations

12 prescribed fire fighting equipment, such as sand buckets, foam extinguishers are to be placed in the corridor



1 - removal of doors and maximum possible wall opening between the rooms and to the corridors.

2 - walls to be covered with glazed tiles up to 1300 height; remaining portion of wall and the ceiling to be resurfaced with washable paint; all doors and windows to be repainted.

3 - same as 2 but tiles dispensable

4 - toilets for exclusive use of personnel of the pilot plant

5 - staircase and corridor between solvent extraction wing and toilet to be kept free from all kinds of storage or bicycle parking.

6 - WC, toilet and washroom area to conform to good hygiene standards.

7 - in all rooms: electrical wires, switches and fittings are to conform to material standards and safety regulations.

8 - prescribed fire fighting equipment, such as sand buckets, foam extinguisher are to be placed in the corridor.

EXISTING BUILDING GROUND FLOOR PART 2

ENORMITY AND NATURE OF THE TASKS

This project is an industrial project with an exceptionally large equipment component (20 major items of manufacturing machinery). It should also be realised that the project is complex, multidisciplinary and ambitious. The project also involves substantial inputs, not only by UNIDO/UNDP but also by the Government, the latter in the form of buildings (new and major modifications). The Government inputs also include services and power such as electricity (150Kw), water, pumping and storage (10 cubic meter) and deployment of specialised contracting agencies for installation of electrical sub station and a heavy boiler (500 kg/hr) complete with professionally laid pipeline and distribution system. The outputs expected from the project are of 3 categories: (i) training component; (ii) research and development component including process development and scale up; (iii) Pilot production. I must say that the first component, i.e. training, has been fully completed both with respect to study tour and training fellowships. Qualitatively. the study tour delegation members and various trainee fellows have reported great satisfaction and derived excellent experience. The training also included in-house training, i.e. both theoretical and practical. All the international experts on this project delivered a series of lectures on professional topics and technologies and conducted a group discussions. The technical and engineering staff of the institute derived special experience, for the first time, by learning through direct involvement in the installation, assembly and testing of equipment. We must record here the great sense of dedication and devotion displayed by a large number of staff members of the institute, who often worked for prolonged hours, beyond working hours and on holidays. They even unloaded heavy equipment and assembled heavy steel structurals and fittings, a task which is normally done by contractors.

The same sense of devotion has been displayed by majority of the staff in the laboratories. These are the people who develop the initial process and they have not done their job well but also completed their part of process development, which is now only awaits adoption at large pilot plant scale. The work of the laboratory scientists has produced valuable scientific documents on 5 medicines. This documentation is an essential requirement by law for approval of new medicines before they are manufactured and marketed.

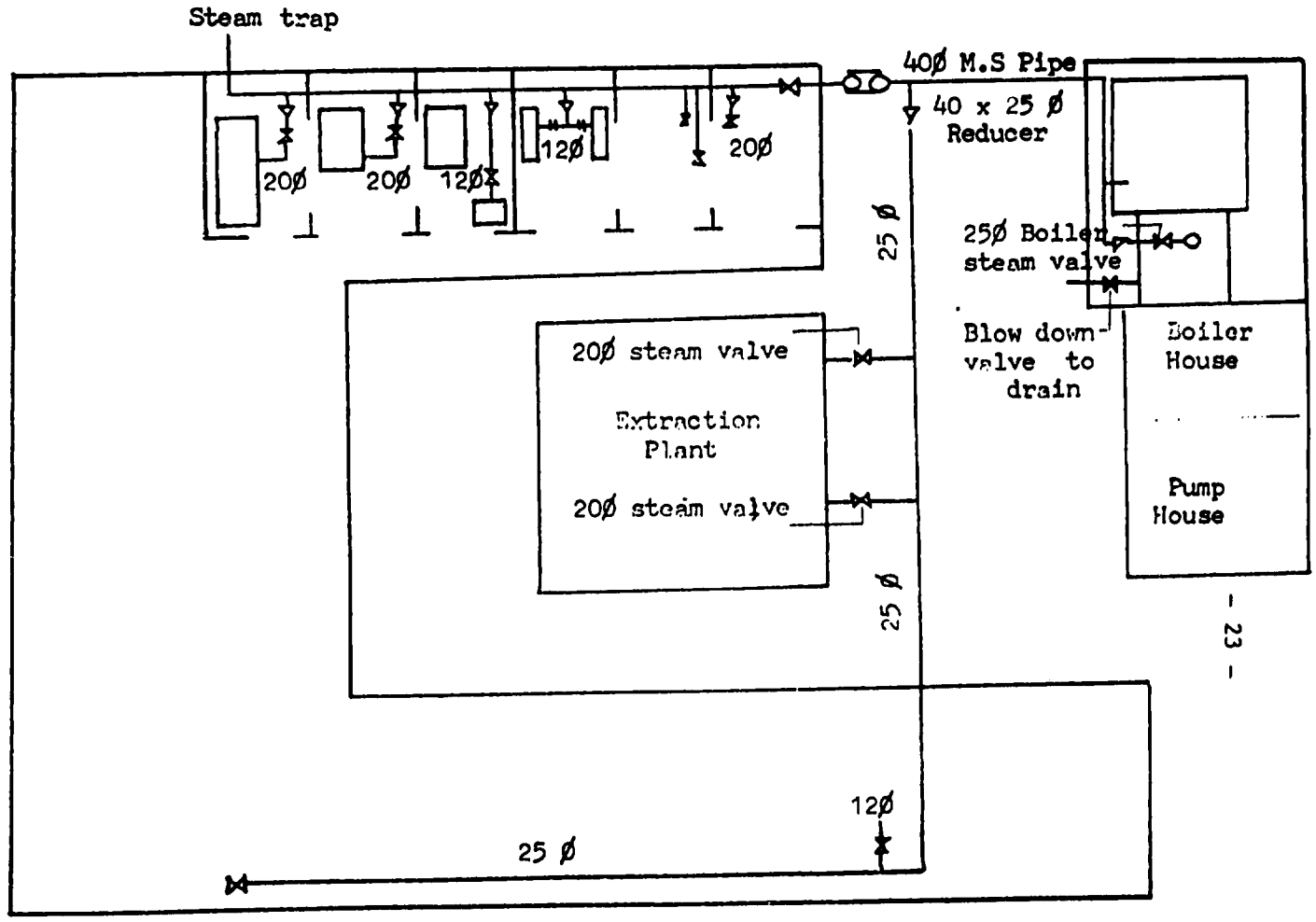
PRE REQUISITE TO COMMISSIONING OF PILOT PLANT

Preparing blueprint of service lines and implementation of laying of water, power and steam distribution systems

Another example of the complexities of implementing a project of this nature is afforded by the extensive expertise that because necessary pre-requisite to commissioning of all major equipment. The Institute had inadequate power supply, insufficient water storage capacity and water pumping system and there was no steam source available for process steam. Therefore the pilot plant engineer consultant had to prepare complete specifications for power substation, water storage, water pumping and water distribution pipelines. Power lines of 220 V & 380 V had also to be laid afresh. Similarly while the boiler of 500 kg steam per hour capacity was purchased, the entire installation and process steam distribution system was designed and executed by national staff under guidance of international experts and with materials input by UNDP.

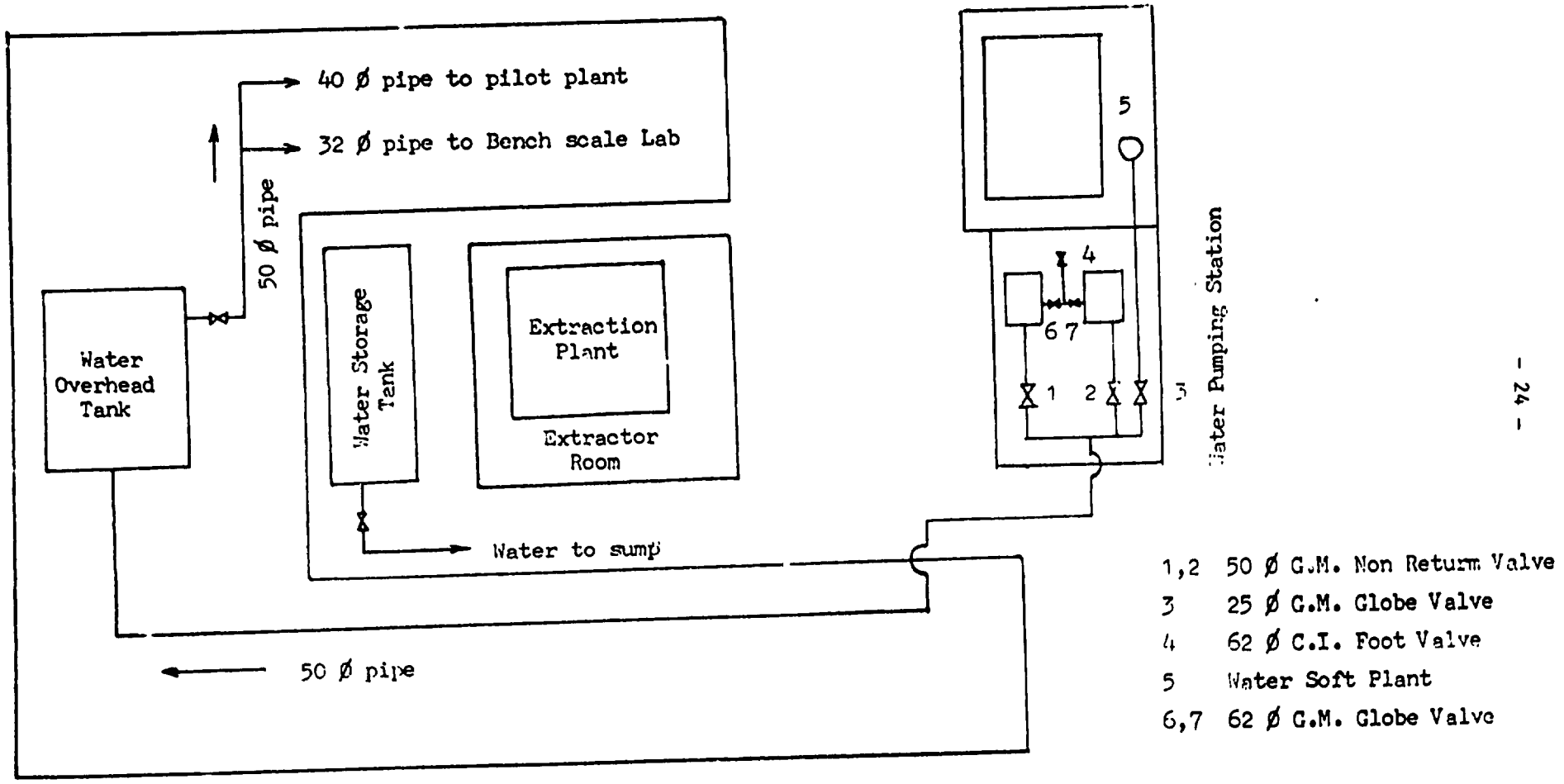
Details of water, power and steam distribution system and chilled water supply system are given in the form of blue-prints on following 5 pages.

ANNEXTURE - STEAM PIPING LAYOUT FOR PILOT PLANT AND TABLET SECTION



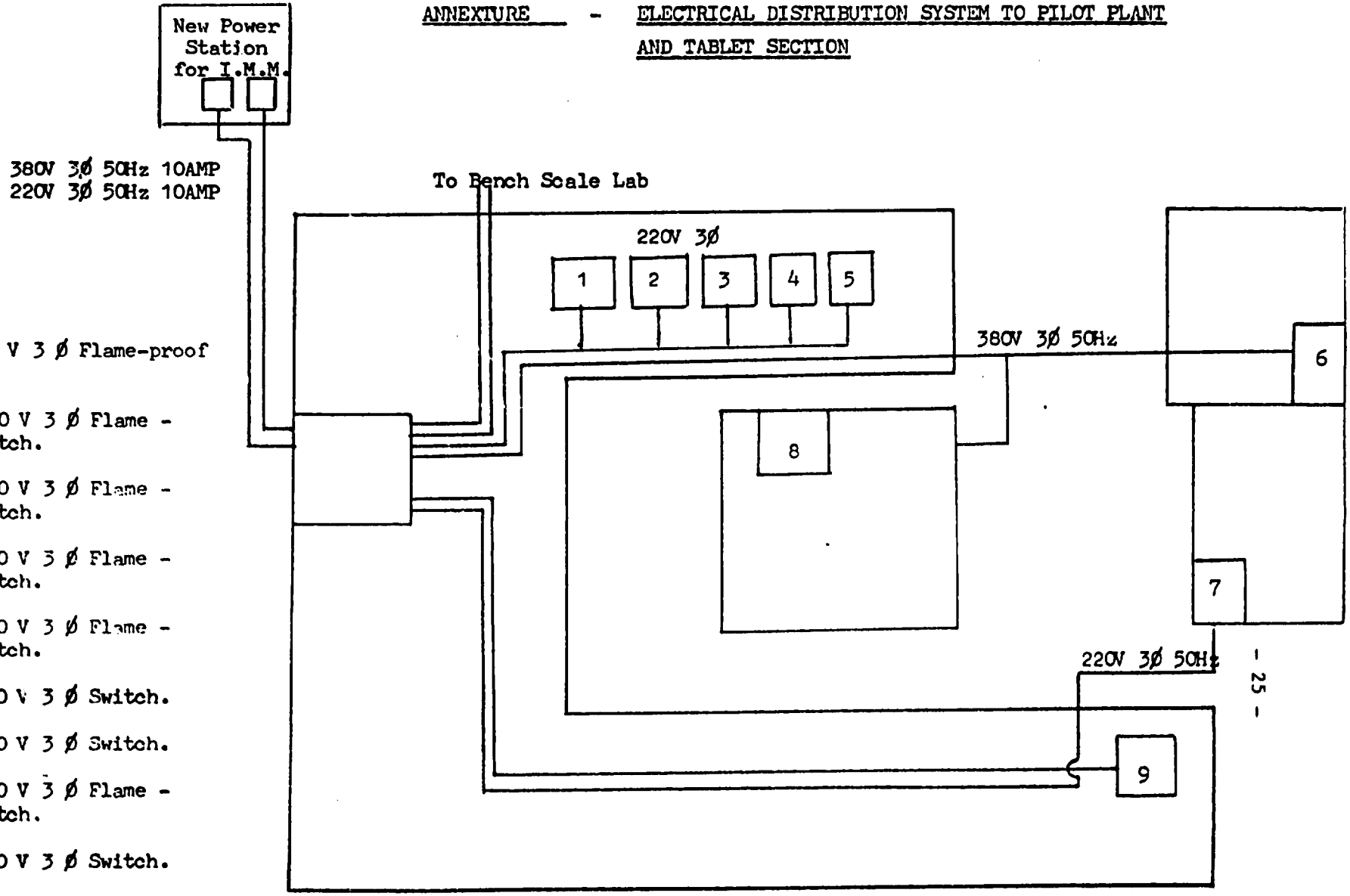
1. M.S. steam pipe to be welded and provided with flanged joints.
2. High temperature resistant permenite steam gasket to be provided with flanges.
3. Steam pipeline to be insulated with50 thick glass wool.
4. Glass wool insulation to be covered with aluminium sheet.
5. Expansion joints and steam traps to be provided where ever shown.

ANNEXTURE - WATER PIPING LAYOUT FROM PUMP HOUSE TO OVER HEAD TANK



1,2 50 Ø G.M. Non Return Valve
3 25 Ø G.M. Globe Valve
4 62 Ø C.I. Foot Valve
5 Water Soft Plant
6,7 62 Ø G.M. Globe Valve

ANNEXTURE - ELECTRICAL DISTRIBUTION SYSTEM TO PILOT PLANT AND TABLET SECTION

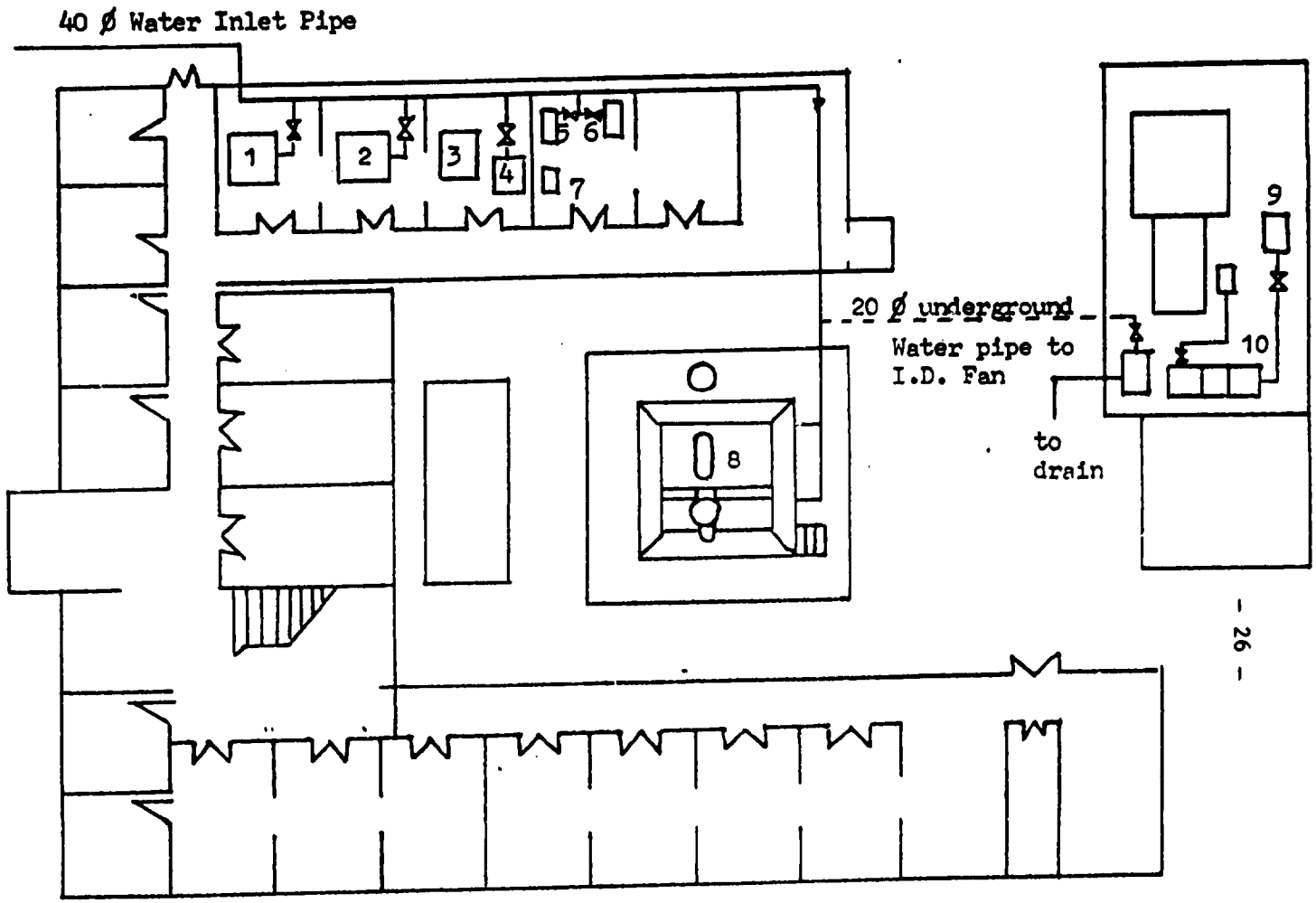


1. 5 AMP 220 V 3 Ø Flame-proof switch.
2. 30 AMP 220 V 3 Ø Flame - proof switch.
3. 30 AMP 220 V 3 Ø Flame - proof switch.
4. 30 AMP 220 V 3 Ø Flame - proof switch.
5. 15 AMP 220 V 3 Ø Flame - proof switch.
6. 30 AMP 380 V 3 Ø Switch.
7. 30 AMP 220 V 3 Ø Switch.
8. 60 AMP 380 V 3 Ø Flame - proof switch.
9. 15 AMP 380 V 3 Ø Switch.

ANNEXTURE

WATER PIPING LAYOUT FOR PILOT PLANT & BOILER HOUSE

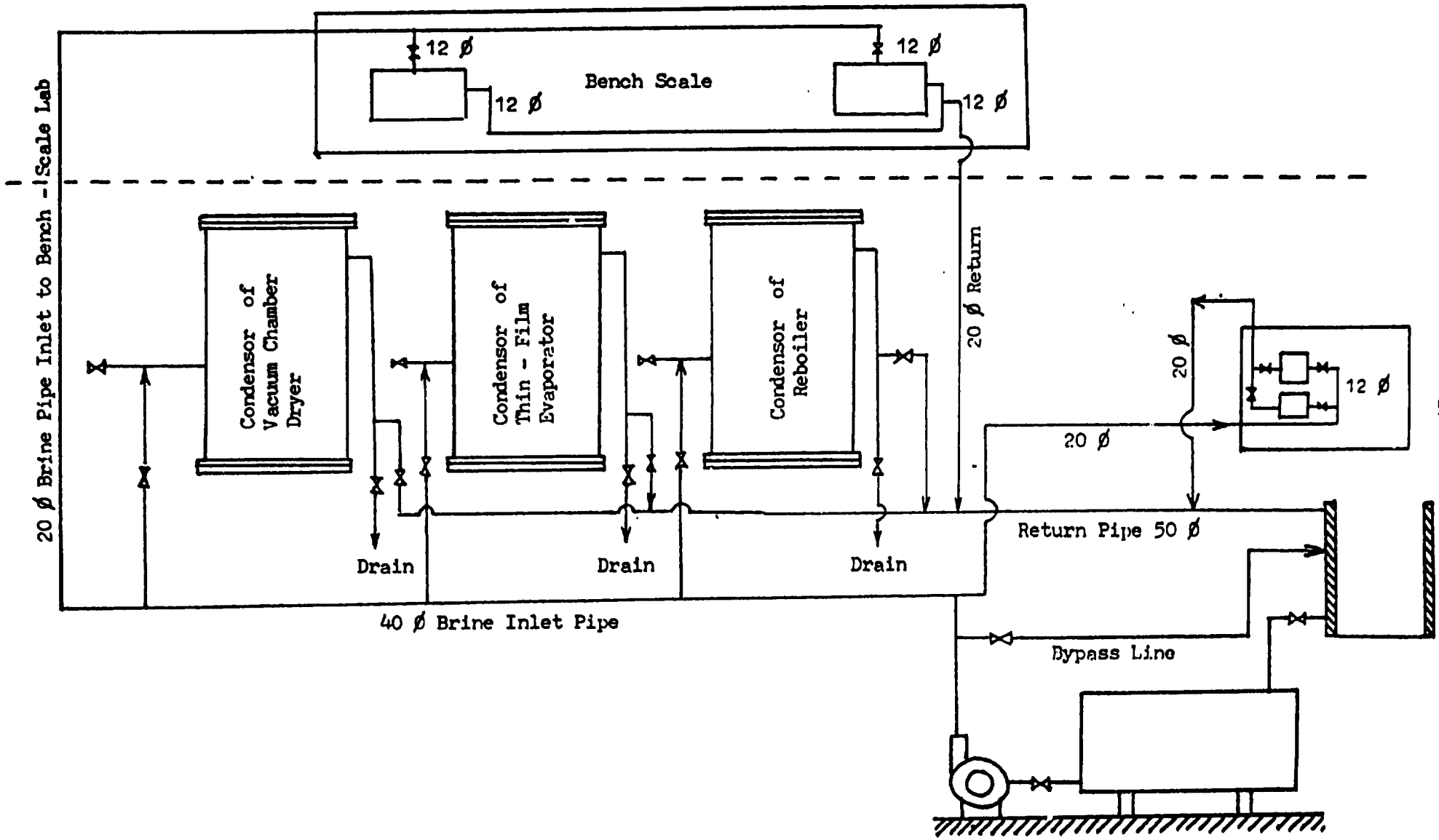
1. Drying Unit to be connected with 20 Ø pipe connection
2. Evaporation Unit to be connected with 20 Ø pipe con - nection
3. Liquid-liquid Extraction Unit
4. Reaction Vessel to be connected with 12 Ø pipe connection
5. Circulating Evaporation Unit to be connected with 12 Ø pipe connection
6. Water Evaporation Unit to be connected with 12 Ø pipe
7.
8. 25 Ø water pipe connection to Extraction Plant.
   20 Ø branch connection to Reboiler Condensor and
   20 Ø to extractor condensor



9. 25 Ø water pipe from water softening plant to Over Head Tank

10. 25 Ø water pipe from Over Head Tank to Boiler Feed Pump

ANNEXTURE - PIPING FLOW SHEET FROM CHILLING PLANT TO DIFFERENT UTILITIES



PRESENT STATUS OF THE PROJECT

The project was envisaged to upgrade the infra structure and strengthen the research and development capabilities of the staff of the Institute of Materia Medica by

1. Setting up of a modern Pilot Plant for producing bulk drugs.
2. A pharmaceutical unit for making finished drugs in the form of tablets, capsules, injectables and syrups.
3. Monitoring, standardization and optimization of process technologies.
4. Better presentation of finished drugs in modern dosages.
5. To set up a small repair and maintenance workshop.
6. To develop competence in the staff of materia medica in way of giving in-house training , both at theoretical level and in practice.

To achieve the above objectives, series of activities were to be accomplished which were started from zero base. These were :

1. Civil construction and civil modification in the Institute of Materia Medica to house Pilot Plant equipment, Boiler House, Tableting Section and Workshop.
2. To provide process water, steam and power distribution systems to the pilot plant and boiler house.
3. Finalization of equipment specification and initiating tender procedures, requisition of equipment, chemicals, solvents and other consumables.
4. To make field purchases, like pipe fittings, valves, power cable, switche sockets etc. for utility services.
5. Delivery and installation of Pilot Plant equipment, boiler and workshop machinery.
6. Verification and checking of the equipment and machinery.
7. Final commissioning of the pilot plant equipment and other machinery.
8. Trial runs on pilot plant.
9. Training to Vietnamese on operation of pilot plants and their repair & maintenence through theory and practice.

All these objectives have been achieved by way of successful commissionin, of the pilot plant equipment and other auxilary machines. Numerous trial runs have been conducted and the Vietnamese staff have been fully trained about the operation of the pilot plant.

At present, the pilot plant is fully functional. It incorporates all unit operation and unit processes which are required for the isolation of drugs from different plant materials and can produce both bulk phytochemical drugs and finished drugs in the form of capsules, tablets, injectables and syrups in considerable quantities.

The pilot plant being quite versatile in its function can take up any bench scale process for optimization and process scale up. It can act as a demonstration plant for the proven technologies to be trasferred to the industry. It can generate process and engineering data for the industries to design bigger commercial plants and also can provide feed-back.

The staff of the Institute of Materia Medica have been fully trained both in theory as well as in practice by way of holding intensive in-house training workshop course where stress was given on the efficient operation repair and maintenance of pilot plant equipment and machines. They were further given concept of process optimization and scale up of bench scale processes. This was achieved through series of lectures delivered by the consultant which included theoretical background, working principle, operational steps of plant equipment, their maintenance and repair. This was followed by actual practice on pilot plant equipment running so that the Vietnamese staff could gain competence, confidence and ability to undertake not only the present jobs but some bigger jobs in future. The pilot plant staff of the Institute of Materia Medica were subjected to written test to know the competence they have gained during the commissioning of the plants which was really commendable.

The project has been completed by way of successful commissioning of the pilot plant and training to the staff of Institute of Materia Medica, which has given competence, confidence and skill to the Vietnamese for absorbing any process technology in the field of modern drug manufacture.

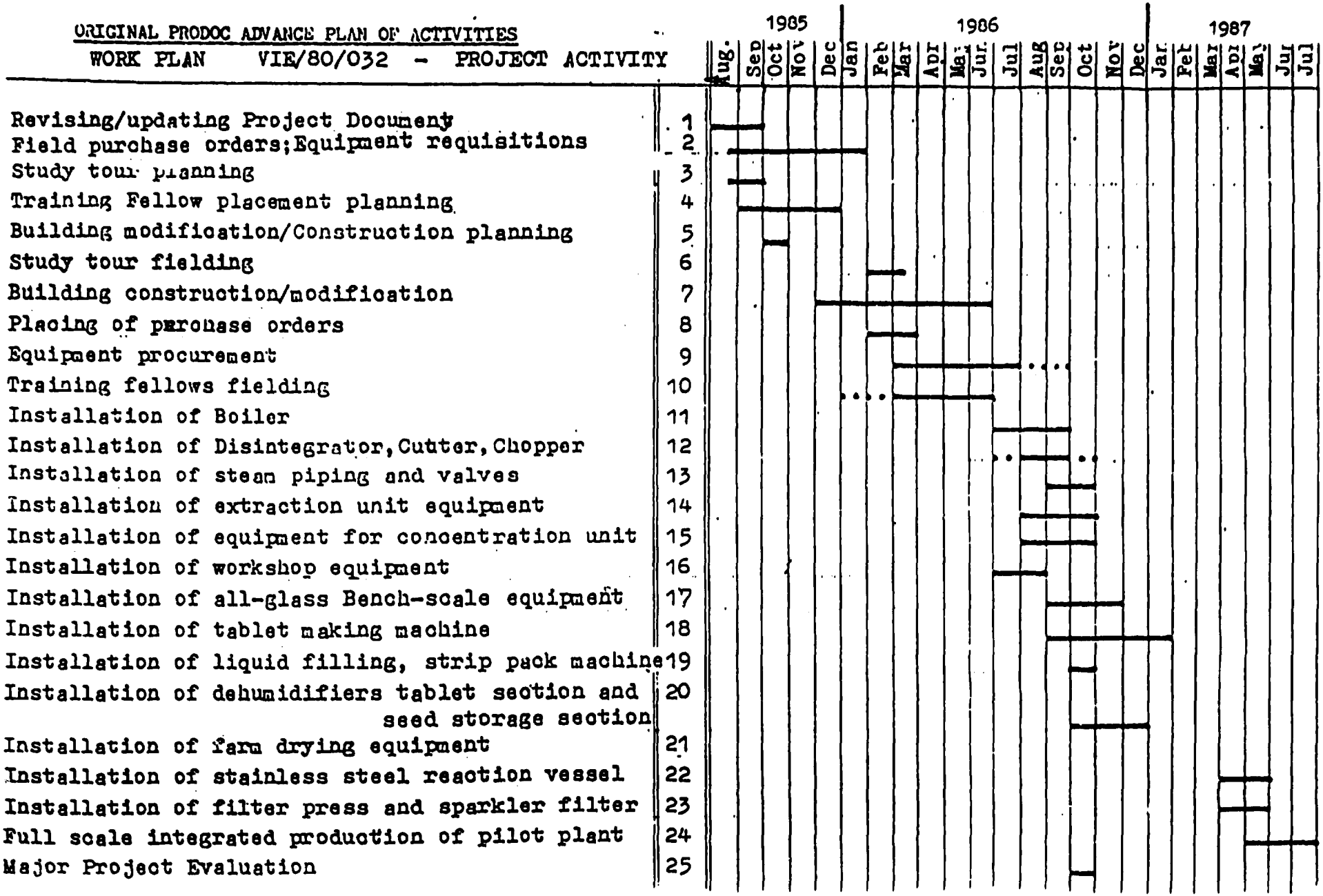
All objectives envisaged in the project document have been achieved. The project design had some unique features which have provided to the Institute of Materia Medica much more than the mere UNDP inputs and expertise of the experts. In the project design the emphasis was laid to impart to the staff of Institute of Materia Medica a high degree of self-reliance, self-confidence and ability to do things by themselves. To achieve

results of this nature and to fulfil this objective the equipment and machinery component purchased were not in the form of a total system which is necessary for the production of pharmaceuticals of various kinds , but in the form of various unit processes. As such the various components of the unit process and unit operation equipment had to be assembled, installed and commissioned. This was done jointly by the international experts and the engineers and technicians of the Institute of Materia Medica. The experts were asked to jointly work and design the total system. This needed complete revamping of the utility service of the institute i.e. rendering of water, steam and power which involved detailed designing and layout of process water piping, steam distribution piping network and power distribution of multiple voltages for the entire pilot plant and tableting section. During the designing of the system the Vietnamese were constantly involved and trained in a manner that even after the project is complete they should be in a position to do similar or even bigger tasks independently.

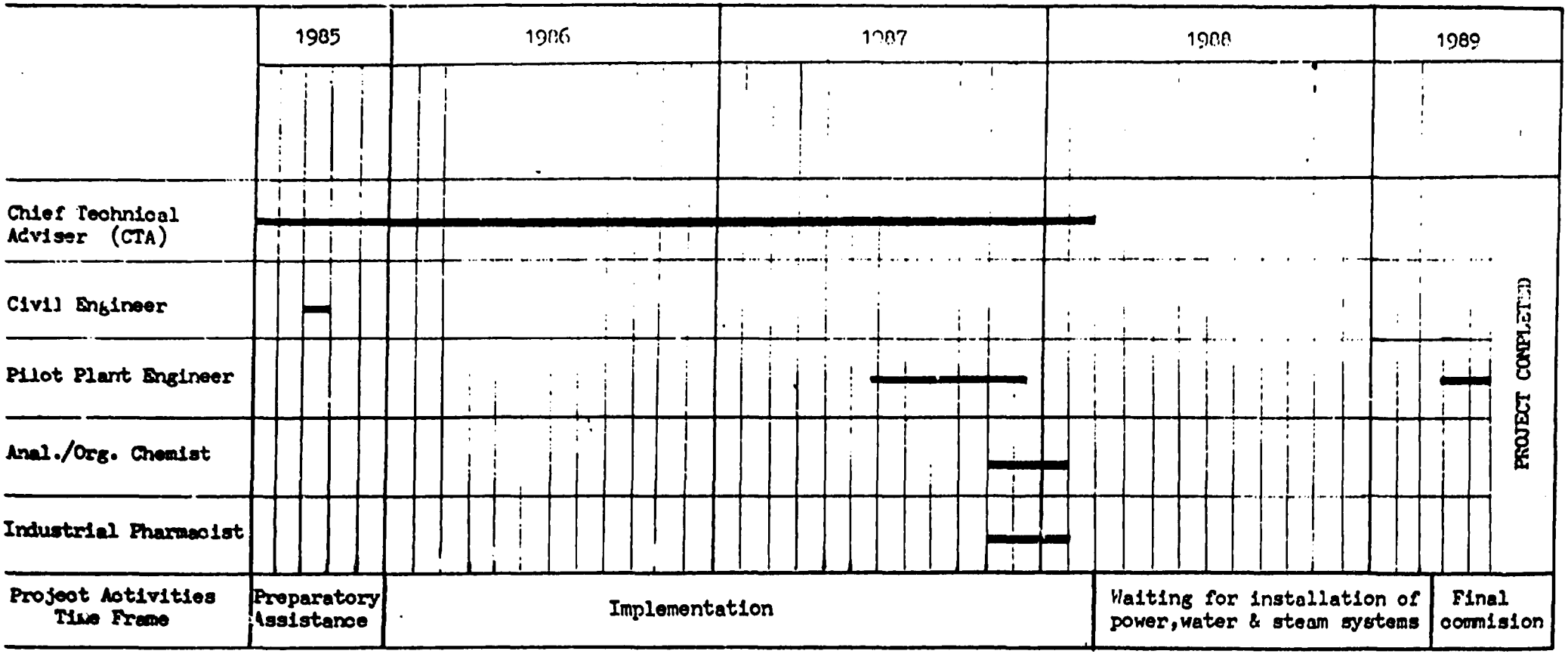
The Vietnamese were further involved closely in the installation of the equipment and machinery right from foundations to the erection, installation and commissioning. They have undergone minutes' details with regard to laying of service pipe lines and process piping network system which has not only given them the feel of the total system but competence and confidence to do many more such jobs. The same emphasis on creating self-confidence among the Vietnamese scientists was adopted with respect to process scale up in which Vietnamese scientists were given an opportunity to shed their conservative approach, inhibition to undertake new and different processes which they had never handled before. They were further provided opportunity and training not only to scale up their processes based on laboratory scale work but to try out new technological processes which they had never handled even on the lab scale. For example, extraction of Rutin by water under steam pressure or 2 Bars were demonstrated to the Vietnamese on pilot plant, which is much cheaper and more efficient process than the conventional process of extracting Rutin with ethanol.

ORIGINAL PRODOC ADVANCE PLAN OF ACTIVITIES

WORK PLAN VIE/80/032 - PROJECT ACTIVITY



DP/VIE/80/032 Indigenous Medicines - DEPLOYMENT OF INTERNATIONAL EXPERTS



PROJECT OUTPUTS

The major outputs envisaged within the project are the following:

1. The commissioning of a pilot plant facility for the development of process technology, formulation and production of drugs for clinical trials. The nature and number of drugs and the minimum quantities in which the same will be produced are given in annexure 1.

2. The strengthening of research capabilities of the Pharmacology, Analytical, Standardization, Formulation and Phytochemistry units of the Institute of Materia Medica for conducting toxicology, process monitoring, standardization, dosage formulation, synthesis and product evaluation work for the development of drugs. In terms of trained manpower, personnel of the Institute would have received training in science, technology, techniques and instrumental methods. A 5 member delegation of senior scientists and R and D administrators would acquire knowledge on the state of art as practiced in other developing countries and advanced countries. Three experts for medium term would visit the institute to train a large number of project staff in commissioning and running of pilot plant and handling process control instruments. The number of Vietnamese scientists and technicians who will benefit from this in-house training is about 75.

3. The transfer of production technology and quality standards to Central and Provincial factories.

All three outputs have been fully achieved. Further details of the technologies generated and implemented on pilot plant production scale have been described elsewhere in this report giving in a tabulated form names of 15 medicines and quantities produced as well as names of some factories with which linkage has been for large scale production. Besides this development, Vietnam Government has authorised I.M.M. to engage in large scale commercial production on some of the items, specifically Vitamin P Rutin and anti-malarial artemisinin.

PRODUCTS TO BE MANUFACTURED AT PILOT PLANT AS PROMISED IN PROJECT DOCUMENT

Recommended list of Drugs to be initially produced utilizing the pilot plant facilities

Phase I - Category I

	Name of Plant	Formulation	Estimated quantity to be used per year	Usage in Therapy
1.	Desmodium triangulare	Tablets	1.2 m *	Infant diarrhea
2.	Eleuterina subaphylla	Tablets	0.7 m	Cough
3.	Angelica dahurica) Kaempferia galanga) Puerveria thomsoin)	Tablets	2.0 m	Fever
4.	Achyranthes bidentata	Tablets	1.2 m	Rheumatism
5.	Achyranthes bidentata) Solanum hainanense) Eleuterina subaphylla)	Liquid	10,000 bottles of 100 ml	Rheumatism
6.	Achyranthes bidentata) Solanum hainanense) Smilax glabra)	Tablets	1.2 m	Rheumatism
7.	Rauwolfia species	Tablets	0.7 m	Hypertension
8.	Nelumbo nucifera	Tablets	0.4 m	Tranquiliser
9.	Strobilanthes flaccidifolius	Tablets	0.8 m	Menstrual disorder

Phase I - Category II

1.	Berberine (Coscinium nsitatum)	Tablets	0.4 m	Diarrhoea
2.	Tetrahydropalmitin (Stephania sp.)	Tablets	0.2 m	Tranquiliser
3.	Tetrahydroberberine (Coscinium nsitatum)	Tablets	0.2 m	Tranquiliser
4.	Stropanthin (Stropanthus divaricatus)	Ampoules	4.0 m of 1 ml	Cardiovascular disease
5.	Reserpine (Rauwolfia sp.)	Tablets	5,000	Hypertension
6.	Raubasine (Cathavanthes roseus)	Tablets	2,000	Cerebral circulation

* m - million

ACTUALLY MADE USING PILOT PLANT

Products	Form of products	Produced quantity	Raw material quantity	Lab scale	Bench scale	Pilot plant	Collaborating factories	Referal factories	On-going clinical	Production clearance
2	3	4	5	6	7	8	9	10	11	12
D - Strophantin	glycoside powder	1000 g	100 kg of seeds		+			Factory No. I		+
Divarin	Injection ampoules 0.25mg	2,000,000 ampoules					Factory No. I			+
Rutin	Powder	200 kg	1000 kg of flower-buds		+	+		+		+
Putin - C	Tablets of 0.02 Rutin	4,390,000 tablets						Chemopharma & Thai Binh factories		+
Arteimisinin	Powder	15,000 g	5,000 kg of leaves		+	+				+
	Tablets	60,000 tablets								+
Rauwolfia	Extract		200 kg		+					
Raucaxin	Tablets								+	
Rauvamin	Tablets 0.002g	200,000 tab.							+	
Adenosma	Extract	13.5 kg	200 kg			+				+
	Essential oil	1000 ml								
Abilin	Tablets	43,700 tab.								+

1	2	3	4	5	6	7	8	9	10
6	Achyranthese	Extract	50 kg	500 kg		+			
		Saponin	30 kg	900 kg		+			
	Aranthin	Tablets from extract	30,000 tablets						Factory No.II
		Syrup from extract	1000 bottle (80 ml)						Factory No.25
		Tablets from saponin	200,000 tablets						
7	Cindarin	Alkaloidal powder	3 kg	100 kg	+				
		Tablets	10,000 tablet						
8	T.H.B.	Alkaloidal powder	1000 g	100 kg	+				
		Tablets	20,000 tab.		+				
9	A.P.D.	Liquid	500 bottles				+		Hanoi Factory
10	Bach Dia Can - Angelica dahurica - Kaemferia galanga - Pueraria thomsonii	Tablets	300,000 tablets				+		Factory No.II
11	Progesteron	Powder	50 g 1000 ampoul		+				

2	3	4	5	6	7	8	9	10	11	12
uyen Tam Lien (Andrographis aniculata)	Tablets 0.2 lacton	200,000 tablets				+				+
t	Oleoresin	25 kg	150 kg		+	+				
urification of										
- Solvent										
- Alcohol		300 lts.			+	+				
- Petrol (technical grade)		4000 lts.			+	+				
am Qhi Elixir	Tonic elixir	20,000 lts.			+	+				+

MAJOR PLANT EQUIPMENT AND MACHINERY RECEIVED & ITS UTILIZATION

Sr. No.	Name of equipment	Present status
1	Solvent extraction plant	Installed
2	Wiped film evaporator	Installed
3	Vacuum chamber dryer	Installed
4	Liquid-liquid extractor	Installed
5	Reaction vessel	Installed
6	All glass solvent extraction unit	Installed
7	Fractionating column	Installed
8	Air compressor	Installed
9	Circulation evaporation plant	Installed
10	Verifuge	Installed
11	Basket centrifuge	Installed
12	Ribbon blender	Installed
13	Kneader mixer	Installed
14	Cryostat	Installed
15	Sharples centrifuge	Installed
16	Mixer settler	Installed
17	TURAX stirrer	Installed
18	Circulation evaporation plant	Installed
19	Three-roller mill	installed
20	Label-printing machine	installed
21	Bottle washing machine	installed
22	Oil / coal fired boiler	installed
23	Metal working lathe	Installed
24	Milling machine	Installed
25	Drilling machine	Installed
26	Bench grinder	Installed
27	Combination pipe and machine vice	Installed
28	Power mixer	Installed
29	Air mixer	Installed
30	All glass solvent recovery unit	installed
31	Chilling plant	installed
32	Planetary mixer	installed
33	Multimill	installed
34	Single punch tablet machine	installed
35	Plate & frame filter press	installed

AN EXPLANATION OF NATURE OF EQUIPMENT AND TASKS INVOLVED IN COMMISSIONING

Installation of Pilot Plant Equipment :

1. Multi-purpose solvent extraction plant :

This is/multipurpose, multicomponent system, which is a complete pilot plant in itself. Because of the diversity of functions which it can perform, the plant has been provided with complex network of piping and valves system. Therefore it needs proper amssembly of components, interfitting piping and overall alignment so that the system works without any problems. Since such system handlesinflammable solvent in close circuit, meticulous care is ensured to make it leak proof unit. The plant consists of the following subunits

a. Extractor
b. Multitubular condenser
c. Reboiler with reflux column
d. Multitubular reflux condenser
e. Solvent service tank
f. Coil type condenser cooler
g. Florentine flask
h. Glass decanter

i. Solvent circulation pump
k. Water ring vacuum pump
l. Interconnecting pipeline, valves and fittings
m. Steel structurals

The unit was received in complete dissembled form and following sub-tasks were done by the consultant for installation :

a. Preparation of cement concrete foundation to bear the load of the plant.

b. To assemble the steel structurals.

c. To align the structure and place it on the foundation.

d. To assemble the plant components and install these on the structure.

e. To interconnect various vessels through interconnecting pipelines, valves and fittings.

f. To install vacuum pump and solvent circulating pump.

The above tasks were completed by the consultant and the plant was completely installed.

2. Vacuum Chamber Drying Unit :

The unit is a complete system in itself for drying of wet cakes, thick slurries and concentrates under reduced pressure. It can work both on steam and hot water circulation system. The unit consists of :

a. Drying chamber

b. Heating plates

c. Multitubular condenser

d. Condensate receivers

e. Hot water circulation device

f. Water ring vacuum pump

g. Vent tank and draining vat

h. Interconnecting pipeline, valves and fittings

The unit was received in complete dissembled form. The following tasks were carried out for installation :

a. Assembly of steel structure, steel rails and gaurd rails

b. Assembly of plant components and fixing these on the structure
c. Installation of drying chamber on the rails
d. Connecting components of the unit through interconnecting pipelines
e. Alignment of drying chamber and its rails with steel structure
f. Overall alignment of the plant
g. Grouting of the plant and complete installation
h. Testing of the plant for vacuum leakage

3. Wiped film evaporation plant :

The plant is a complete system for concentration of water/solvent extracts under reduced pressure and shortest possible residence time to prevent thermal degradation of heat sensitive materials. The plant consists of the following sub-components :

a. Main evaporator body with revolving rotor
b. Multitubular condenser
c. Condensate receiving tank
d. Concentrate receiving tank
e. Water ring vacuum pump
f. Interconnecting pipelines, valves and fittings
g. Steel structure

The componentsof this plant were received in dissembled form including the pipelines and steel structure. The steel structure of this plant was assembled and aligned with extreme care to withstand viberation of revolving parts of the evaporator. The components of the plant were assembled and placed on steel structure with proper alignment. The condensate receiving tank was connected to the evaporator through a multitubular condenser and goose neck and then grouted on cement concrete foundation. The other components of the unit were connected through interconnecting pipelines, valves and fittings and the plant has been completely installed.

4. Liquid - Liquid Extraction Plant :

This plant is a complete system to perform verious types of liquid - liquid extraction operations. It is a four stage continuous type counter current system and consists of the following sub-components :

a. Centrifugal extractor
b. Solvent extract tank
c. Aqueous extract service tank
d. Solvent service tank
e. Interconnecting pipelines, valves and fittings
f. Steel structure

The plant was received in dissembled condition and needed following tasks to be carried out for its installation :

a. Assembly of steel structure
b. Alignment of the structure and its grouting on cement concrete foundation.
c. Installation of centrifugal extractor on the structure and its alignment
d. Installation of aqueous extract tank, solvent tank and solvent extract tank on the structure
e. Connection of various components through interconnecting pipelines, valves and fittings

The plant is completely installed

5. Reaction vessel unit :

This unit is quite versatile for performing various unit processes. The unit consists of :

a. Reaction vessel with stirrer

b. Multitubular condenser
c. Reflux system
d. Interconnecting pipelines, valves and fittings
e. Steel structure

The various components of this unit were assembled and installed on steel structure. The unit was properly aligned and grouted on cement concrete foundation. The components of this unit were connected with pipelines, valves and fittings.

6. Installation of boiler :

In most of UNDP assisted project in which boiler forms one of the input, the installation of boiler is contracted to boiler supply company. In the present project the difficult task of planning the installation of boiler was assigned to the consultant. The boiler assembly and installation is a complex task involving a number of sub-tasks and sub-installations, such

a. Preparation of strong cement concrete foundation for main boiler, furn induced draught fan, forced draught fan and chimney
b. Refractory lining of the furnace with refractory bricks
c. Installation of chimney, I.D. fan and F.D. fan
d. Installation of water softening plant
e. Assembly of boiler mountings, design of boiler feed water systen and commissioning of boiler

The existing boiler house of the Institute could not house the boiler because one of the pillars of the building was obstructing the installtio Necessary modifications to overcome this difficulty were reccommended by the consultant, which is completed. The chimney required for the boiler was not supplied by supplier and therefore it had to be designed in consultation with Smoke Nuisance Control Department.

The following was done by Vietnamese contractors and I.M.M. engineers

a. Civil foundation for boiler, furnace, I.D. fan and chimney
b. Assembly of mountings of boiler and interconnecting pipelines
c. Fabrication of chimney
d. Installation of boiler and furnace on its foundation
e. Installation of chimney
f. Installation of I.D. fan and F.D. fan
g. Refractory brick lining of the furnace
h. Installation of water softening plant and feed water piping system for the final commissioning the boiler company engineer.
Consultant was invited for one week.

7. Installation of workshop machines

The following machines in the workshop have been installed:

a. Metal working lathe
b. Milling machine
c. Drilling machine
d. Husky grinder
e. Combination pipe and machine vice

In addition to above major installations the following equipment and machines have also been installed:

a. Circulation evaporation plant

b. Water evaporation plant

c. All glass high efficiency fractionating column

d. All glass multi purpose solvent extraction unit

e. Air compressor

f. Sharples centrifuge

g. Rotavapour

h. Verifuge

i. Basket centrifuge

j. Cryostat

k. Mixer-settler

l. Power mixer

m. Air driven mixer

n. SEN multisheet filter press

o. Ribbon olender

p. Kneader mixer

q. Turax stirrer

Commissioning of the equipment and machines

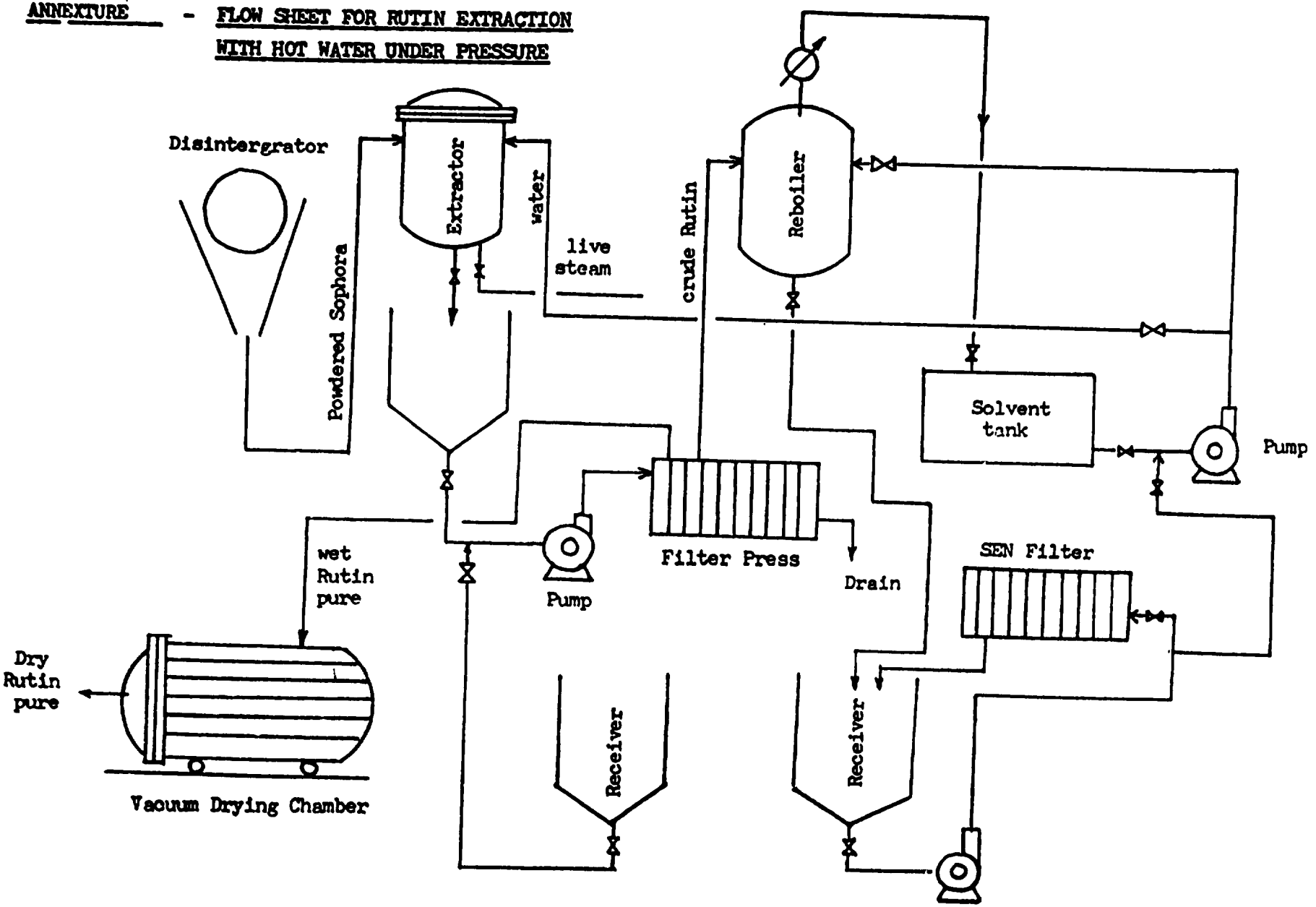
1. Multi-purpose Solvent Extraction Unit :

The plant was commissioned by taking trial runs on Sophora drug for solation of Rutin. The steps involved are :

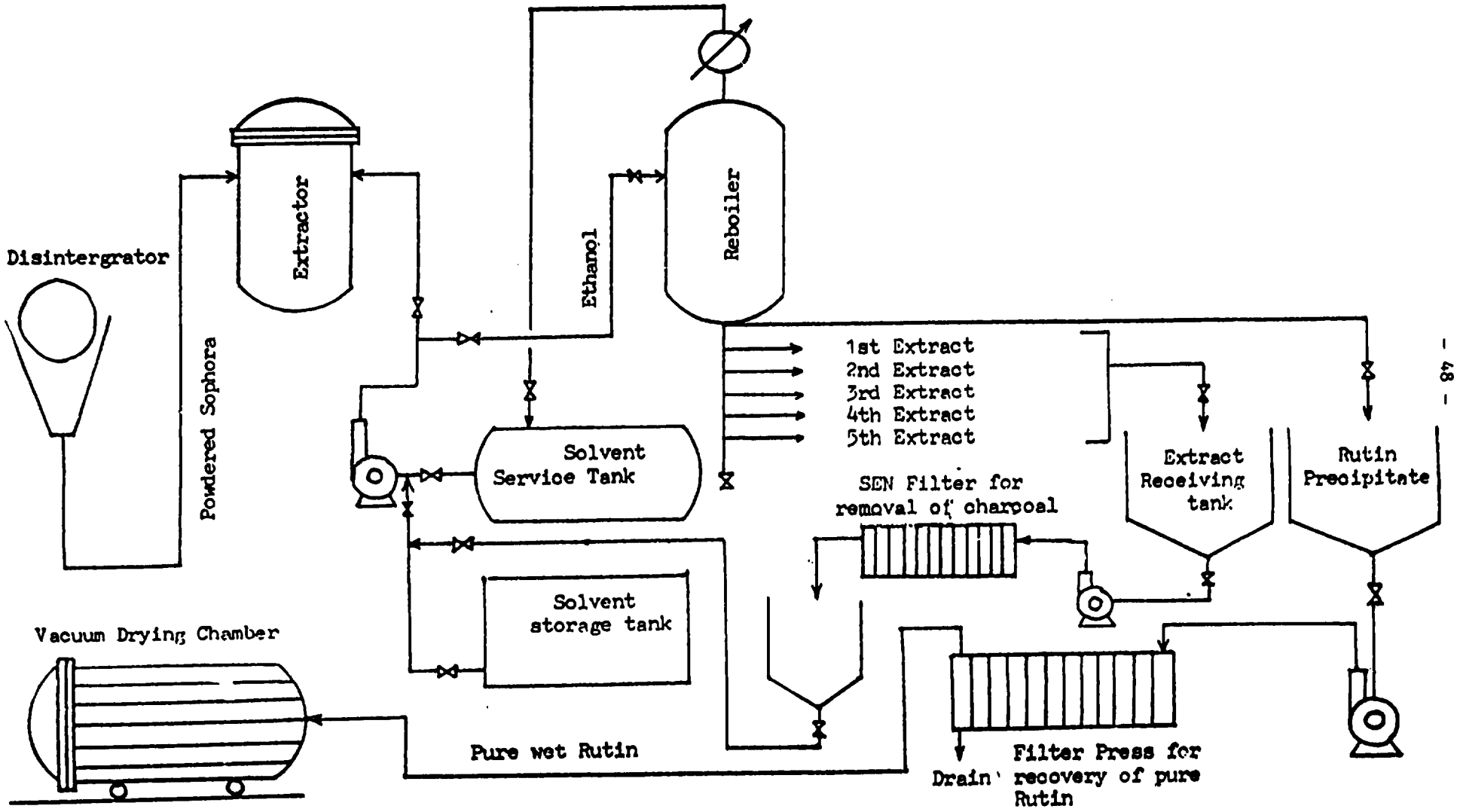
1. Extraction of Sophora under reflux condition with ethanol as the solvent.
2. Contact period 1 hour.
3. Number of extraction : 4
4. Cooling of extract to precipitate out impurities.
5. Filtration of impurities in the form of precipitate.
6. Activated charcoal treatment to the filtered extract for removal of chlorophyl and other colouring agents.
7. Concentration of extract.
8. Dilution of extract with hot water to precipitate out Rutin.
9. Filteration of Rutin.
10. Drying of Rutin.

About 50 kgs of drug were charged into the extractor. With the help of solvent recirculating pump, 200 litres of ethanol were charged into the extractor through measuring service tank. The heating was carried by supplying steam through the limpet coil of the extractor. Necessary pressure was maintained to control the refluxing. After one hour of contact the extract was taken to the reboiler and the reboiler was heated up with steam for the recovery of solvent. Meanwhile another 150lits of ethanol were subjected to the extractor and the extraction was carried out. About 75lits of solvent were recovered from reboiler and received in the service tank. The remaining 75 litres in the reboiler were taken out. The service tank was replenished with another 75 litres of solvent to keep it ready for the third extraction. This way five extractions were carried out. The total extract received from the reboiler amounting to 375 litres was allowed to cool to precipitate out the impurities. The ethanol present in the mare as hold up was subjected to live steam to get ethanol water mixture in the decanter. This was taken to a storage tank for recovery of solvent through fractional distillation. The

ANNEXTURE - FLOW SHEET FOR RUTIN EXTRACTION WITH HOT WATER UNDER PRESSURE



ANNEXTURE - FLOW SHEET FOR RUTIN EXTRACTION BY ETHANOL SOLVENT



extract containing impurities in the form of precipitate was filtered through SEN Filteration Unit to get clear liquid which was then subjected to charcoal treatment in the reboiler to remove chlorophyl and other colouring materials. Again the extract was then subjected to SEN Filteration Unit to remove charcoal and the colour-free extract was concentrated in reboiler to its one fifth volume which was further diluted with 600 litres of boiling water to precipitate out Rutin. Rutin was filtered and subjected to drying in vacuum chamber dryer. The sequence of the operation is given in the Flow Sheet/Annexture I A series of batches were carried out for fully commissioning of the versatile extraction unit.

The consultant advised the Vietnamese counterparts to extract Rutin with water under pressure. This would involve less steps and the cost of production would be considerably low. Few batches were carried out with water extraction under 2 Bar pressure. The results so obtained with this process were considerably better than the ethanol extraction system and the Vietnamese counterparts were convinced about its merits over ethanol extraction. The sequence of the operations involved are given in the Flow Sheet Annexture II.

During commissioning of the plant about 60 kgs of Rutin were produced. Besides this, the consultant demonstrated how the extraction unit can be used under different conditions which is as under.

1. Extraction with cold solvent under circulation.
2. Extraction with hot solvent under circulation.
3. Extraction under pressure.
4. Steam distillation under atmospheric pressure and under super atmospheric pressure.
5. Hydro-distillation under cohobition.
6. Recovery of solvent under atmospheric pressure and under vacuum.

<u>Liquid Liquid Extraction Plant</u>

This is a 4-stage centrifugal extractor with built-in stages. The bowl of the extractor is connected to a motor and is provided with one extract receiving tank, one feed tank and one solvent tank.

Trial runs on this extractor were conducted by taking colouring matter dissolved in little quantity of ethanol and mixed with water to make it feed. The solvent for extraction selected was cyclohexane. The two streams of feed and solvent at a ratio of 5 : 1 were subjected to the extractor to see the performance of the machine. A clear raffinate free from colouring matter was received on one hand and extract containing all the colouring matter extracted from the feed was received on the other side. There were no traces of water in extract or solvent in water. This determined the efficiency of the extractor to extract out solute from the feed with the help of selective solvent. Numerous runs were taken and the Vietnamese operators were thoroughly made to understand the principle and the efficient operation of the machine. They were further explained how weir diameter should be changed with variation in densities of feed and solvent and how solvent to feed ratios should be adjusted to get best results.

The extractor is now fully operational and can be used as a commercial unit for separating active principles from aqueous or any non polar solvent with help of polar solvents which are immicible with each other. It can also be used as good utility for process optimization of liquid - liquid extraction process. The capacity of the plant is to handle about 300 to 1000 litres/hour at different speeds of the bowl.

Vacuum Chamber Dryer

The unit consists of main chamber with a flange which is movable on a rail. The fixed end which acts as the second flange is provided with pipe manifold system and a vapour pipe line. The pipe manifold system is connected to the heating plates over which there are trays for drying the material. The vapour line is connected to the tubular condenser for condensing of vapour. The condensate is received in two receivers which are used alternatively to keep the system under operation without disturbing vacuum at the time of removing of the condensate. The whole unit is connected to a vacuum system through a liquid ring vacuum pump.

The equipment was tested under vacuum and the leakages detected were plugged. Drying of Rutin cake was conducted both under steam heating and under water circulation by varying the vacuum in the system This was done to demonstrate how both systems can be operated separately when the need arises.

Numerous trial runs were conducted and thorough demonstration of its operation was shown to the Vietnamese trainees. They were further trained to use this dryer under different conditions of temperature and vacuum to establish temperature vacuum relationship on a particular system. The unit is completely functional and can cater large quantities of material for drying.

Chilling Plant

This is a trolley mounted portable chilling plant with a refrigeration capacity of about 15 tons/hr. It consists of a two stage compressor, a condenser, an evaporator, a receiver, an expansion valve and interconnecting pipe to form a refrigeration cycle. It is also provided with an internal cooling pump, a service tank and a discharge pump to be connected to the utilities. The unit is quite compact and provided with automation and safety devices.

The plant was filled with brine solution, a mixture of propylene glycol water mixture and put to operation. The temperature of brine was brought down from +25°C to -10°C. The operational steps for running the plant were explained to the Vietnamese trainees and the function of each component of the machine was also explained. The designing of piping system for connecting the plant with different utilities has been done and is given in Annex III.

Rapid Heating Circulation Evaporation Plant

The unit consists of a main body which is fitted with a turbular calandria. The inside body is provided with baffle plates for defrothing and entrainment. The system is connected to an air-moist pump which sucks the vapor directly into the water separator thereby condensing the vapour and creating vacuum in the system. The calandria is heated with the help of steam. This plant was subjected to vacuum testing to find out any leakage.

Commissioning of This Film Evaporator

The unit consists of main body which is jacketted. Inside this there is a rotor with blades which rotates. On top of the rotor there is a distributor which distributes feed uniformingly. The rotor shaft is coupled to a motor through a ball bearing and a mechanical seal. The bottom of the body is connected to product receiving tank. The side of the body is connected to turbular condenser through a vapour line and the bottom of the condenser is connected to the distillate receiving tank. The unit is connected to a water ring vacuum pump. For the measurement of feed rate a rotameter has been provided.

This plant was subjected to vacuum testing and the leaks where ever found were detected and plugged.

For trial runs a dilute solution of sugar in water was taken up as the feed. It was subjected to concentration in the Thin Film Evaporator. The necessary vacuum setting and corresponding steam pressure were adjusted to get the optimum conditions. The machine worked very well and gave satisfactory results.

The steps of operation were demonstrated to the Vietnamese operators. Numerous trial runs were taken to establish its operative capacity and efficiency. The capacity of the plant is to evaporate about 250 litres of water per hour. This way the plant was commissioned and put to operation.

Numerous trial runs were conducted on aqueous solutions to be concentrated under vacuum. The operational steps for running of this equipment were demonstrated and explained to the Vietnamese operators. The setting up of feed control against specific vacuum and steam pressure were optimized and shown to the operators. The plant is fully functional and can evaporate 25 to 30 litres of water per hour.

SEN Filteration Unit

This unit is a recessed plate type filter unit which is mostly used for clarification of liquids. This press was assembled and put to operation by filtering out activated charcoal in the extract. The press gave excellent results and large quantities of extract were filtered in very short time. The operational steps including assembly and disembly of filter plates and use of proper filter medium were explained to the Vietnamese operators.

Numerous trial runs were conducted on this equipment with excellent results and the press is now fully operational.

All-Glass Solvent Recovery Unit

The unit consists of a 100 litre reaction vessel provided with a variable speed agitator and connected to packed column followed by a reflux condenser and cooler. The unit is provided with solvent measuring flask and two solvent receiving flasks. The unit is provided with hot bath for heating under controlled conditions and can work under vacuum also.

The plant has been successfully commissioned and put to operation for carrying out different reactions and also for recovery of solvent. The operational steps to operate this unit have been demonstrated to Vietnamese staff and the unit is fully operational.

All-Glass Multipurpose Solvent Extraction Plant

The unit consists of 50 litre flask which is connected to a reflux condenser and a cooler. The condenser outlet is connected to a soxlet. This plant can work as solid - liquid or liquid - liquid extraction unit with a facility to recover solvents. The plant was put to operation by carrying out several trial runs on different raw materials. The operational steps for operating this unit were demonstrated to the Vietnamese operators.

Hydrogenation Unit

The Parr hydrogenation unit was assembled and made operational. The commissioning of the unit was carried by way of demonstrating hydrogenation of pregnenolone acetate to convert it into pregnenolone. The reaction was carried out by using palladium as the catalyst. Complete conversion of pregnenolone acetate to pregnenollone was achieved. The operational steps and the safety of the unit were explained to the Vietnamese staff.

Besides this, other small Bench-Scale units like cryostat, mixer settler, Traux emulsifier, Sharples super centrifuge were commissioned and made fully operational. Their working and operational steps were explained to the Vietnamese staff.

UNITED NATIONS DEVELOPMENT PROGRAMME

TRAINING

Fellowship, Training Course Study Tour, or In-service Training	Duration (months)	Name and gender of Fellow(s). If training undertaken abroad, indicate country and institution of study	Started (date)		Completed (date)	
			Scheduled	Actual (Est.)	Scheduled	Actual (Est.)
Study tour	2 months	Mr. Nguyen Van Dan Ms. Doan Thi Nhu Mr. Le Tung Chau Ms. Khoung Bang Tuyet Mr. Nguyen Tuong Dung in India, FRG, Holland and Italy		25/4/86		16/6/86
Fellowship						
Pharmacology	2 months	Mr. Pham Duy Mai Universite Rene Descartes Paris, France		2/4/87		30/5/87
Phytochemistry	2 months	Mr. Pham Van Thanh CNRS Institut Chimie Paris, France		15/9/87		15/11/87
Organic Chemistry	3 months	Mr. Ngo Ngoc Khuyen RRL, Jammu, India		19/7/87		18/10/87
Pilot-production	3 months	Mr. Nguyen Que RRL, Jammu, India		19/7/87		18/10/87
Drug formulation	3 months	Mr. Nguyen Thuong Thue RRL, Jammu, India		19/7/87		18/10/87
Machine maintenance	3 months	Mr. Nguyen Ba Bot RRL, Jammu, India		19/7/87		18/10/87
Technical workshop	3 months	Mr. Dang Dinh Tien RRL, Jammu, India		19/7/87		18/10/87
Analytical Chemistry	3 months	Mr. Do Viet Trang RRL, Jammu, India	12/1/88		11/4/88	
Extraction Techniques	3 months	Ms. La Thi Kim Oanh RRL, Jammu, India	12/1/88		11/4/88	

In-House Training Workshop

A training workshop was organized in the institute to impart intensive training to the staff for the:

1 Safety use of pilot plant equipment and machinery.
2. Theoretical background and the working principle of the equipment and machinery.
3. Operational steps of plant equipment and machinery including their repair and maintenance.
4. Safety regulations.

About thirty people from the staff of Institute of Materia Medica participated in the training workshop. The consultant delivered series f lectures in which theoretical background, working principle of the equipment and machines were explained to the trainees. They were further made to understand how to operate each individual equipment by way of giving sequence-wise operational steps. They were given complete understanding as to how repair and maintenance on the plant equipment should be carried out. They were further made to understand what type of operational difficulties they could face, what troubles there could be during the operation and how to overcome these difficulties. Stress was also given on the safety rules and regulations i.e. what safety measure should be taken during the running of pilot plant equipment especially those equipment which are working under pressure, how to prevent fire hazzards and in case of such evnetuality how to overcome accidents due to fire. The trainees were given thorough practice on the operation of pilot plant and thereafter they were asked to run the pilot plant equipment and machines in presence of the consultant to know their skill and competence. This was followed by a written test and issuance of certificates to the successful trainees. The training lasted for about ten days which provided skill, competence and confidence among the trainees for the efficient running of pilot plant including its repair and maintenance.

LIST OF LECTURES DELIVERED BY INTERNATIONAL EXPERTS AIMED AT IMPROVING THE PROFESSIONAL KNOWLEDGE OF THE PERSONNEL OF I.M.M.

Lectures delivered by Dr. C.K. Atal, CTA

1. Manufacture of tablets - Pilot plant scale up considerations
2. Manufacture of liquid and semi-liquid preparations.
3. Scale up & machinery considerations
4. Stability of pharmaceuticals
5. Preservatives and anti-oxidants to increase shelf-life.
6. Bioavailability series - Absorption of drugs
7. Bioavailability series - Liver function and liver bared metabolism of drugs
8. Methods for determination of bioavailability and bioequivalence
9. Toxicology and clinical trial protocols for new drugs
10. Teratology and mutagenesis testing of new drugs
11. Drug receptor theory
12. Drug design
13. Immune system & Immuno-modulator drugs
14. Solubility and solubilization of drugs
15. Filteration and clarification
16. Biotechnology - Recombinant DNA techniques. Genetic engineering
17. Biotechnology - Monoclonal antibodies & hybridoma technology
18. Interferon
19. Anti-inflammatory drugs research
20. Antiasthmatic drugs research
21. Anti-arthritis drugs research
22. Pharmacognostic standards on raw materials

Lectures delivered by Prof. K.T.D. DeSilva, Industrial Pharmacist Consultant

1. Formulation, production, quality assessment and stability of syrups
2. Tablet technology - Excipients, size reduction, mixing, granulation, granule characteristics, compression and handling of defects.
3. Tablet formulations & in-process control
4. Coating of tablets including sustained release forms.
5. Good manufacturing practices, sampling, stability testing and packaging.

TECHNICAL HELP, TRAINING AND DEMONSTRATIONS GIVEN BY DR. K.T.D. DESILVA, CONSULTANT INDUSTRIAL PHARMACIST

1. Compilation of a monograph on Tetrahydropalmatine THP
2. Assay method for determining purity of THP
3. Assay method for THP using tablets by HPCL method
4. Providing accelerated stability testing model and stability protocol
5. Formulation development for THP HPCL tablets
6. Monograph compilation for berberine hydrocloride
7. HPCL assay method for berberine hydrocloride tablets
8. Formulation and manufacturing of Berberine Tablets
9. Introducing I.M.M. staff to film coating technology
10. Monograph compilation on tetrahydroberberine
11. Tetrahydroberberine tablet formulation
12. Monograph on Achyranthes bidentata Benth roots
13. Standardization of Saponin contents of A. Bidentata based on haemolytic index
14. Development of a good formulation for A. bidentata syrup and its standard specifications
15. Improvement in A. bidentata extraction technology
16. A proposed improve method for making total extract of Adenosma
17. Formulations of tablets of Adenosma

PROBLEM SOLVING AND PROCESS IMPROVEMENT AND DEMONSTRATION ON ISOLATION OF PHYTOCHEMICALS

Technical help rendered by Dr. S.K. BAMERJI Consultant organic chemistry/ analytical chemistry.

1. Demonstration of an approach for removal of colour from isolated samples of Tetrahydropalmatine: this method based on reduction of coloured impurities (formed by oxidation of THP) using sodium borohydride was demonstrated and adopted as process technology.

2. A UV spectrophotometric method for assay of THP based on its absorbance at 282 nm was demonstrated.

3. A process for isolation of THP on lab scale was demonstrated and process for 25 kg batch of Stephania based on actual work done by the expert elsewhere was passed on to I.M.M.

4. A process for converting Berberine to Tetrahydroberberine was demonstrated on 100 batch using sodium borohydride reduction method.

5. A method to isolate pure oleanolic acid (suspected to be the active substance in Achyranthes bidentata roots) was demonstrated.

6. Demonstration of process for standardization of Adenosma extracts based on estimation of total phenolics.

7. Demonstration of process for isolation of diosgenin from Dioscorea roots.

8. Demonstration of a process for conversion of diosgenin to 16 DPA.

9. Providing a process for conversion of serpentine to Ajmalicine (Raubasine).

LIST OF PUBLICATIONS, MONOGRAPHS AND GOVT. CLEARANCE FOR MANUFACTURE OF DRUGS TO BE MANUFACTURED AT THE UNIDO ASSISTED PILOT PLANT

MONOGRAPHS ON :

1. Achyranthes bidentata as hypocholesteremic agent
2. Tetrahydroberberine as a hypnotic tranquiliser
3. A formulation containing Angelicadahurica, Kaempferia galanga and Pueraria thomSonii as an antipyretic and analgesic agent in fevers.
4. Tetrahydropalmatin (Gindarin) as a potent tranquilosedative in mental disordes.
5. D-strophanthin ex strophanthus divaricatus as a cardiotonic drug.

RECOMMENDATIONS

1. There should be adequate supply of raw materials, solvents, chemicals and other consumables to run the pilot plant effectively with an object to produce bulk phytochemicals and finished drugs in large quantities.

2. There should be adequate stock of spare parts of the plant equipment and machinery to avoid break down.

3. The project needs post operative assistance for some time till the Institute of Materia Medica is on its firm footing. This shall include assistance in procuring spare parts, some quantities of solvents, chemicals and other consumables. This also includes periodic monitoring of the progress of the project and its evaluation. This also involves providing assistance of an expert for training the Vietnamese for process optimization and scale up techniques for future process technologies.

4. The consultant suggests and recommends to press in two pressure extractors of 1500 litres capacity each into the system for the extraction of Rutin on commercial scale. Since basic infrastructure is now available with the institute therefore by enhancing the extraction capacity the institute can produce Rutin to the tune of 15 to 20 tons/year. The Rutin can be sold in the international market thereby considerable foreign exchange can be earned which shall meet the operative cost to conduct research and development, optimization and process scale up of new technologies.

5. The management should have strict control and monitoring on the operation and maintenance of pilot plant equipment and machinery. The management should give more emphasis on safety rules and regulations to be observed by the operators and declare pilot plant area as a non-smoking zone to avoid hazards due to fire.

6. Artermizinin, which is a new and interesting output of the project and which has now been the focus of attention as an anti-malarial drug need to be produced in bulk. Additional investment is needed for large scale equipment and working capital. This should be given high priority.

FUTURE UNDP ASSISTANCE

A phase II project had already been proposed amounting to a financial UNDP commitment of US$ 0.6 million, according to 1985 estimates. The project document for phase II will involve setting up a pilot plant for manufacture of steroid hormones and other more sophisticated semisynthetics like progesterone, methyl testosterone and ethynyl estradiol. The project document (draft) for phase II is ready for submission. The implementation time for phase II will be two years. It will be desirable that the independent in-depth evaluation mission which will evaluate Phase I terminal report also examine formally the phase II draft document draft document and make its recommendations.

It may be noted that I.M.M. has already taken advance action on starting commercial cultivation of Dioscorea composita which will form the starting raw material for all steroid work proposed in phase II. It is also praiseworthy that I.M.M. has also developed technology on lab scale for production of diosgenin, 16 DDA and progesterone in advance preparation for scaling up the same with inputs expected under phase II.

It is requested that mission may make recommendations on post investment inputs necessary to consolidate the gains accomplished under Phase I.