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HIGH-LEVEL ADVISORY SERVICE TO THE KOREAN TECHNICAL CENTRE FOR TRADITIONAL MEDICINE FOR THE IMPROVEMENT OF THE PRODUCTION AND QUALITY OF PLANT-BASED PHARMACEUTICAL FORMULATIONS

SI/DRK/93/802/11-01

DEMOCRATIC PEOPLE'S REPUBLIC OF KOREA

Technical report: For the improvement of the production and quality of plant-based pharmaceutical formulations*

Prepared for the Government of the Democratic People's Republic of Korea
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Y. J. Chen, chemical technologist

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* This document has not been edited.

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Explanatory notes

The value of the Korean currency in US dollars during the period of the mission was 1 US dollars = 2.11 Wons.

Abbreviations used in this report are as follows:

DPRK :	Democratic People's Republic of Korea
KTCTM:	Korean Technical Centre for Traditional Medicine
MHK:	Ministry of Health, Korea
GBAKTM:	General Bureau for Administration of Korea Traditional Medicine, Ministry of Health, Korea
PMH:	Pyongyang Maternity Hospital
SSFMP:	Sangwon State Farm for Medicinal Plants
SPF:	Sangwon Pharmaceutical Factory
JPF:	Junggu Pharmaceutical Factory
PJF:	Pyongyang Jangsudongyak Factory
PMU:	Pyongyang Medical University
KMAS:	Korea Medical Academy of Sciences
TKM:	Traditional Korean Medicine
SCPF:	Sunchan Pharmaceutical Factory
SIQCD:	State Institute for Quality Control of Drugs
KMYH:	Kim Man You Hospital

ABSTRACT

At the request of the Govemment of Democratic People's Republic of Korea, UNIDO sent a service mission (SI/DRK/93/802) titled "High level Advisary Service to the Korean Technical Centre for Traditional Medicine (KTCTM) for the improvement of the production and quality of plant-based pharmaceutical formulations. The job commensed on August 22, 1994 and ended on October 21, 1994. The job description is given in Annex 1.

The mission worked in collaboration with the counterpart staff at the Centre, visited UNDP office in Pyongyang, Sangwon State Farm for Medicinal Plants, Pyongyang Drugstore for Traditional Medicines, two hospitals and four pharmaceutical factories which are under the technical guidance of the Centre. The mission also met the famous scientists and professors working at Korean Medical Academy of Sciences, Pyongyang Medical University and State Institute for Quality Control of Drugs, and discussed the present situation and future prospects of Traditional Korean Medicines (TKM).

Having finished these activities, the mission came to the following conclusions and recommendations:

(1) DPR Korea is rich in natural resources of medicinal plants. Some of the medicinal plants are cultivated in twelve state farms according to the Government's plan.

(2) There are 203 pharmaceutical factories for TKM, distributed in every region of the country, manufacturing more than 230 kinds of commonly used traditional medicines which account for 50% of the medicines used clinically in the country. Most of the equipment for production are rather old and backward and the methods used are traditional and need improvment. The formulation of medicines need modernization.

(3) The KTCTM is the state key institution for development of traditional medicines in DPRK. It is the Centre for R & D of new products, development of process parameters, formulation technologies, quality assessment methods and specifications of traditional medicines. But good process parameters and international and standard quality specifications cannot be developed in the

Centre because of the lack of a modern pilot plant and some very necessary analytical instruments such as HPLC, GC etc.

(4) Methods for improving the formulation of dosage forms were demonstrated by the consultant using video-shows, lectures and explanation of methods.

(5) Assistance for the development of process and quality assessment protocols was given by the mission. The methods for processing 15 kinds of medicines were given to the Centre and some quality standards and specifications were also developed and replenished.

(6) Four analytical instruments provided by UNIDO have reached the Centre. The mission trained counterpart staff in the use of new methods and equipment.

(7) A second project for technical assistance to KTCTM was recommended to both UNIDO/UNDP and the Government. Strengthening the Centre with a modern pilot plant and some necessary laboratory instruments will be of great importance to the health care of this country.

INTRODUCTION

A. Objectives of the mission

The objective of the mission was to provide high level advice to enable the Korean Technical Centre for Traditional Medicine for the improvement of produced traditional medicinal formulations, their quality assessment, research and development of new products, and manufacturing practices to meet internationally accepted standards. The job description of the consultant is given in Annex 1.

The programme concerning places and institutions to be visited was drawn up by the host institution, the Korean Technical Centre for Traditional Medicine. Some modifications were requested by the consultant in order to assess the manufacturing practices in the factories.

As soon as the consultant arrived in Pyongyang, the consultant visitied the UNDP office in Pyongyang. Mr. G. Faruq Achikzad, the Resident Representative of UNDP and UNDP System Resident Coordinator, and Mr. Li Song Ho, the Programme Officer, kindly welcomed the consultant and discussed the work and scheduled arrangements for the mission.

Before leaving Pyongyang, the mission visited UNDP-office once more to finilize the job in DPRK. The mission's work was greatly appreciated.

Thanks to the valuble assistance offered by UNIDO and UNDP officers and the cooperation of the Korean people, the objectives were successfully attained.

B. Brief information on Korea

Korea is the biggest peninsula situated in Eastern Asia, together with 4198 islands. It covers an area of 222,209.231 square kilometers. Korea stretches about 1,144.59 kilometers from the west to the east, and is bounded on the north by the People's Republic of China and on the northeast by the Russion Republic. To the east, south and west of Korea, are the seas.

Korea is a mountainous peninsula with an average altitude of 440 meters above the sea level. It's geography is characterized by great diversity. In the northern and eastern part, the mountain ranges are overgrown with wild

forests including many medicinal plants. In the west and south, there are many plains, such as Riangchen plain, Yunjon plain, etc. Between the plains and mountains are many plateaus, such as Gaema plateau, etc.

The northern half of the peninsula is the Democratic People's Republic of Korea (DPRK). The population of DPRK is twenty millions. Pyongyang, the capital of DPRK, has a poulation of about two millions, accounting for one tenth of the total population. It is also the political, economic and cultural centre of DPRK.

C. Traditional Medicines in DPR Korea

Due to the great diversity of geography, DPR Korea has 1200 species of medicinal plants grown in the mountain regions, plains plateaus and the seas. Many wild indigenous plants are abundantly found as natural resources. In addition, 100 kinds of medicinal plants are cultivated at twelve State Farms for Medicinal Plants and some small cultivation stations. 330 kinds of commonly used crude drugs are included in the DPRK Pharmacopoeia.

DPRK has a long history of extensive use of traditional medicines and a well established national system for research and production of traditional medicines. Traditional Korean Medicines (TKM) account for 50% of medicines used clinically in the country. There are 203 pharmaceutical factories of traditional medicines in DPRK, situated in Pyongyang and every region of the country. About 230 kinds of TKM are produced in these factories. Most types of dosage forms, such as tablets, granules, teas, tinctures, mixtures, honey pills, dans (small pills), powders and injections, are formulated.

Some medicines, for example, Korean ginseng and its products are exported abroad in large quantities. Although many types of medicines are produced in factories, most of the equipment used are old and primitive and some of the processes need upgrading. The formulation of medicines need modernization. GMP is not in place in these factories.

There are many research institutions for traditional medicines in DPRK, such as Korean Medical Academy of Sciences, Research Institute for Natural Medicine, Research Institute for Traditional Korean Medicine, Koryo Pharmaceutical University, Pyongyang Medical University and 12 other colleges of pharmacy or faculties of pharmaceutical sciences in medical universities. Some achievements have already been obtained in the study of chemical constituents and pharmacological activities of commonly used crude drugs. The

study on P-polysaccharide prepared from peat has achieved outstanding results. It has already been used for the industrial production of P-polysaccharide injection. Studies on Lycoris have led to elucidation of an anti-infantile-paralysis compound dihydrogalanthamine. Some marine and animal drugs were successfully researched and developed. These are used for the treatment of cerebral thrombosis and sequela of cerebral hemorrhage.

The mission identified KTCTM as the only institution in this country with a clear mandate for the development of modern processing parameters, formulation technologies, quality control methods and standardization. KTCTM is the state institution for development of traditional medicine industry because it is technically responsible for all of phytopharmaceutical factories in DPRK. The Centre has qualified manpower and has achieved a lot of applied research results. KTCTM has some laboratory equipment. It is now constructing a building for a modern pilot plant. The building will be completed by the end of this year. The mission recommended a new project for strengthening the Centre.

I. INSTITUTIONS VISITED

A. Ministry of Health, Korea (MHK)

In the Ministry of Health, Korea, there are two pharmaceutical administration agencies: General Bureau for Administration of Modern Medicine and General Bureau for Administration of Korean Traditional Medicines (GBAKTM). The consultant met Mr. Kim Guan Heng, the vice-Head of GBAKTM and Mr. Han Bo Guk, the Director of Technical Department. Mr. Kim made a brief introduction to Korean traditional medicine. He said "There are 250 Korean traditional hospitals and 203 traditional pharmaceutical factories in Korea. Majority of Korean people use Korean traditional medicines and like to be treated by using traditional medicine". Mr. Kim emphasized the policy of the Korean Government for the improvement of traditional medicine which established the Korean Technical Centre for Traditional Medicine in June 1992 for R & D, standardization and validation of traditional medicines and for development of modern processing parameters in order to improve the quality and production of traditional medicines.

B. State Institute for Quality Control of Drugs (SIQCD)

State Institute for Quality Control of Drugs (SIQCD) has following departments:

1. Department for traditional Korean Medicines
2. Department for new medicines (synthesized medicines)
3. Department for biological studies
4. Department for standardization of drugs

There are 130 staff members working in this institute. The main task of SIQCD is to control the quality of drugs used in this country, especially to control the quality of medicines that are to be exported. Another task of this institute is to develop standard specifications for drugs. There are some neccessary analytical equipments in SIQCD, such as spectrophotometers, HPLC-GC and a TLC scanner.

Under the SIQCD, there are 12 provincial institutes for quality control of drugs distributed at the capitals of each province (Dou).

C. Sunchan Pharmaceutical Factory (SPF)

Sunchan Pharmaceutical Factory (SPF) located in Sunchan City, about 50 km from Pyongyang was established in 1992. The factory has a new building of 2400 m^2 construction area. There are 100 staff members working in SPF, including eight pharmacists and engineers, ten technicians and 82 workers. The main departments in SPF are as follows:

1. Extraction department: Some simple equipment, such as extractor, evaporator, are used for extraction of crude drugs.

2. Formulation development: 86 kinds of Traditional Korean Medicines which are formulated into tablets, pills, liquid extracts, mixtures, granules and injections are manufactured in this department.

3. Health food department.

4. Analytical department: There are two technicians working in quality control of raw materials, intermediates and finished products. Some

simple intruments, such as spectrophotometer, balance and a few glassware are used for the analysis of medicines.

5. Cultivation department: SPF has a cultivation department with four hectares of land where twelve kinds of medicinal plants are cultivated.

The consultant gave the following advice:

- To pay more attention to manufacturing practices to meet GMP standards.

- To use haw leaves in addition to haw fruits for manufacturing injections, and other medicines as given in some reports from UK, Germany, China and Japan.

- Comprehensive utilization of fruits of Schizandra chinesis which are used for producing injections. The mission suggested that the fruit pulp is good for making syrups. Seed coat contains lignans, such as schizandrin, which possess tonic activity and anti-hepatitis effect. A tonic agent is made from the seed coat in Russia. And an anti-hepatitis medicine is also produced by using the seed coat as raw material. The seed kernel is a good raw material for producing oil.

D. Pyongyang Jangsudongyak Factory

Pyongyang Jangsudongyak Factory (PJF) in Pothonggang District of Pyongyang city is the most advanced phytopharmaceutical factory, the consultant has ever seen in DPR Korea. All equipment in PJF for formulation of dosage forms were imported from Japan and Germany. The main task of PJF is production of traditional medicines for export. The TKM manufactured in PJF were exported to over 30 countries, some of which are China, Japan, Canada, USA, Nigeria and southeast Asian countries. Some raw materials (crude drugs) used in PJF, such as liquorice, rhubarb, are imported from China.

In PJF there are 212 staff members, including 32 qualified engineers and pharmacists graduated from colleges and universities, 40 technicians and 140 workers, most of whom are female workers.

The PJF has two buildings of about 3,500 m^2 construction area. It posseses following departments:

1. Extraction department
2. Formulation department
3. Quality control department
4. Administration department

More than 40 kinds of traditional medicines and health foods are manufactured in this factory. Almost all dosage forms with the exception of injections are produced here. The consultant saw how the workers were producing " Koryo insam indan" made of ginseng, "Koryoinsam jongaek" (tincture of ginseng) and "Tonicum cervi parvi" in the formulation department of KJF. The total output per year is about 10,000,000 Korean wons.

The quality of the products manufactured in PJF was controlled mainly by the Korean Technical Centre for Traditional Medicines. The products for exporting abroad were quality controlled by the State Institute for Quality Control of Drugs.

The manufacturing practices were not good enough to meet the GMP standards. The mission advised on the improvement of manufacturing practices.

E. Junggu Pharmaceutical Factory

Junggu Pharmaceutical Factory (JPF) is a small phytopharmaceutical factory which is situated in Junggu district of Pyongyang city. There are 60 staff members,including 11 pharmacists and engineers graduated from colleges or universities, 9 technicians and 40 workers.

The main departments of the JPF are as follows:

1. Extraction department: industrial extraction of medicinal plants are conducted in this department. There is only a few very simple and old equipment for extraction and concentration.

2. Formulation department: 70 kinds of traditional medicines are manufactured in this small factory. The main dosage forms produced here are extracts, powders (tea), pills, tablets, mixtures, tinctures and injections. The mission saw a group of workers who were producing "Aloe injection". The aloe leaves were extracted with hot water and filtered. The filtrate was concentrated and then alcohol was added to the concentrate. The precipitate formed was removed by filtration and the alcoholic liquid was concentrated. The concentrate obtained was diluted with distilled water and formulated into ampoules. Aloe injection is used for the treatment of nephritis.

3. Analytical department: quality control of products is performed here. A few instruments available such as vis- photometer along with some glassware are far from enough for ensuring the quality of raw materials, intermediates and finished products.

The consultant was impressed by the contribution made by the JPF and the staff inspite of lack of proper facilities.

F. Sangwon Pharmaceutical Factory

Sangwon Pharmaceutical Factory (SPF) located in Sangwon Gun of Pyongyang is a newly established phytopharmaceutical factory, the building of which is a three floor construction of 2000 m^2. There are one hundred people working in SPF, including ten engineers and five pharmacists.

The main departments in SPF are as follows:

1) Extraction department: There are three extractors, each of which can process 150kg of medicinal plants per batch by using water as solvent. The vacuum evaporators are linked to these extractors. Extraction with organic solvents, such as alcohol, cannot be performed in SPF.

2) Formulation department: The main dosage forms manufactured here are powders (teas), tablets and pills. Ten kinds of traditional medicines are produced in this department.

3) Quality control department: There are only few instruments, such as balance, visual photometer and some glassware, which are far from enough for quality control of the products manufactured in this factory.

SPF is a middle scale phytoparmaceutical factory in DPRK. The total output value per year is five million Korean Wons.

All equipment for extraction, concentration and a pill - making machine were designed by the engineers of this factory and were produced by the Pyongyang Machinery Factory.

G. Pyongyang Maternity Hospital

Pyongyang Maternity Hospital (PMH) was established in January, 1981. This modern hospital with its construction area of 60,000 square meters is special for lying - in woman, woman and children. The main departments in this hospital are as follows:

1. Department for maternity (Obstetrical Dept.)
2. Department for woman
3. Department for children
4. Department of pharmacy
5. Laboratory

There is a staff of 400 persons, including professors, doctors, pharmacists technicians, working in this big hospital. The wards can hold 1,500 patients, all of them enjoy free public health services.

The department of pharmacy is divided into two units: New Medicine Unit and Korean Traditional Medicine Unit. There is a small traditional pharmaceutical factory which produces about 100 kinds of Korean traditional medicines, including different sizes of pills, powders, tablets, liquids and injections. Most of these medicines are used within this hospital.

H. Kim Man You Hospital

The largest hospital in Asia, Kim Man You Hospital (KMYH), which is situated in the bank of the beautiful Daedonggang river, is composed of seven buildings of 105,000m² construction area. There are 1,100 staff members working in this big hospital, including 500 doctors.

The main departments in this hospital are diagnosis department, therapy department, ward department, pharmacy department, research department and administration department.

Most of advanced medical instruments and equipment, such as CT. X-ray etc. have been imported from Japan and Germany.

The pharmacy department has two units: new drugs unit (modern style medicines) and traditional medicine unit. About 50% of medicines used

clinically in this hospital are traditional Korean medicines, part of which is obtained from the State Goverment, and the other part is manufactured by the small factory under the pharmacy department. The small factory can produce 150 kinds of traditional medicines which are mainly used within this hospital.

The consultant was convinced that this hospital and Pyongyang Maternity Hospital used traditional medicines to the extent of 50% for treatment.

I. Pyongyang Drugstore for Traditional Medicines

Pyongyang Drugstore for Traditional Medicines (PDTM) is the largest drugstore in DPRK, which is located at the eastern bank of the beautiful Daedonggang river.

There are 120 kinds of commonly used traditional Korean medicines in this drugstore. In addition, more than 300 kinds of crude drugs are also sold for composing prescriptions.

J. Sangwon State Farm for Medicinal Plants

Sangwon State Farm for Medicinal Plants (SSFMP) located in the eastern suburbs of Pyongyang city was established in 1968 with a cultivating area of 340 hectares. Common farming machines are used for cultivation of medicinal plants. 21 species of commonly used medicinal plants are cultivated including Astragalus membranaceus, Rehmannia glutinosa, Platycodon grandiferum, Paeonia lactiflora, etc.

The species of medicinal plants to be cultivated and the cultivating area for each plant are decided by the State General Bureau for Administration of Korean Traditional Medicine, Ministry of Health. All crude drugs harvested should be handed over to the State Commune of Materia Medica (SCMM). The crude drugs will then be distributed to traditional pharmaceutical factories and hospitals by SCMM, according to the State's plan.

There are thirteen similar state farms for medicinal plants, distributed in different regions of DPRK.

II. DISCUSSION WITH LEADING SCIENTISTS AND PROFESSORS IN FIELD OF TKM

A whole day discussion about Traditional Korean Medicine was held between the consultant and six leading scientists and professors in the field of TKM. They were Prof. Mun Guan Xim, the Chairman of Society of Traditional Korean Medicine and fellow of Korean Medical Academy of Sciences (KMAS), Prof. Chui Long Sam of KMAS, Prof. Cha Jit. Hon, Vice-chairman of the Society of Traditional Korean Medicine, and Professor of Pyongyang Medical University (PMU), Prof. Kim Chang Gun of PMU, Prof. An Chol Gol of PMU and Mr. Han Chang Gun, Scientist and Director of KTCTM. The officer, Mr. Han Bo Guk, who is in charge of TKM in the Ministry of Health, also took part in the discussion.

The talk was concentrated on R & D, processing, fomulation, quality control and manufacturing practices in Traditional Korean Medicine. The consultant obtained the following information through this discussion:

1. Natural resources of medicinal plants are very rich in Korea. Over 1200 species of medicinal plants are growing indigenously in different parts of this country. Among them, 330 kinds of crude drugs were included in the Korean Pharmacopoeia.

2. Research on chemical constituents and pharmacological activities of commonly used crude drugs are being carried out. The study on liquorice led to the elucidation of an anti-infantile-paralysis compound, dihydrogalanthamine which was shown to be ten times stronger than galanthamine. Some marine and animal products were also studied. The civetta injection made of animal drug civetta was successfully researched and developed. Now it is used for the treatment of cerebral thrombosis and sequels of cerebral hemorrhage. The main institutions for R & D of Traditional Korean Medicines are Korean Medical Academy of Sciences, Korean Medical Institute, Korean Technical Centre for Traditional Medicines and 12 colleges of pharmacy or faculties of pharmaceutical sciences of medical universities.

3. There are 203 pharmaceutical factories for manufacturing Traditional Korean Medicines in DPR Korea. Every region in this country has its own production units. About 230 kinds of Traditional Korean Medicines are produced for clinical use. Some medicines such as ginseng and ginseng products are exported abroad in large quantities.

4. Quality control of Traditional Korean Medicines is performed by laboratories of pharmaceutical factories, Korean Technical Centre for Traditional Medicine and the state Institute for Quality Control of Drugs. Analysis is performed according to the specifications of the Korean Pharmacopoeia.

5. GMP and GLP are not in place in the phytopharmaceutical factories.

In the discussion, the mission made a brief introduction on R & D, production, quality control and manufacturing practices in Japan, USA and China.

III. ACTIVITIES

The consultant spent most of the time working at the Korean Technical Centre for Traditional Medicine and carried out the following duties.

A. Evaluation of the activities perfomed by the Centre

Korean Technical Centre for Traditional Medicine was established in June, 1992. The Centre has four research divisions and seven technical units.

Research Divisions:

1) Traditional Medicine
2) Biotic Medicine
3) Modernization of equipment for production
4) Pharmacological and Toxicological Testing

Technical Units:

1) Designing Unit for Packing
2) Investigation Unit for Data
3) Analysis and Control Unit
4) Health Foodstuff Unit
5) Trial Production Unit
6) Screening and Introduction Unit for New Technology
7) External Affairs Unit for Exchange of Technical Information

The Centre has strong manpower consisting of 78 staff members including a professor, qualified scientists (20), doctors (6), engineers (10) and phamacists (12).

The Centre has some laboratory glassware and instruments, such as digital electronic balance, analytical balances, centrifuge, UV - Vis Spectrophotometers, TLC - scanner, fraction collectors for column chromatography, pH - meter, rotary vacuum evaporators, vacuum drying oven, computers, vacuum pumps, IR - moisture - analyzer, IR - spectrophotometer, Potentiometric titrator. The Centre had an old pilot plant with old and primitive components. Processing parameters for scaling up to the industrial level could not be obtained by using such an old pilot plant. Experimentation at pilot plant level is very necessary. The Centre has decided to establish a modern multipurpose pilot plant. The building for housing the pilot plant equipment is under construction with in the premises of the Centre. KTCTM hopes that UNIDO/UNDP can provide the necessary equipment for the pilot plant.

Mr. Han Chang Gun, the director of the Centre is a very intelligent and energetic leader. He successfully researched and developed a new medicine "P - polysaccharide" which is menufactured industrially in large quantities for clinical use. Under his leadship, all staff members work very hard, and fruitful results have been obtained in the two years since the Centre was founded.

The main activities of the Centre are as follows:

1) Research and development of new products:

Many new products including traditional Korean medicines, health foods and drinks etc. were researched and developed. For example, a series of health foods, teas and drinks were developed by using ginseng and rhodiola.
P - polysaccharide and civetta injections have been industrially manufactured and used clinically. The chemical constituents and pharmacological activities of Thymus japonica Hara. were studied and the academic results were rapidly transfered into applied research. Finally a new drug made of this plant was developed and manufactured for treatment of hepatitis.

2) Development of process technologies:

The research results obtained in laboratories should be scaled up into industrial operation. But this important function of the Centre has not been in practice due to the lack of a multipurpose pilot plant. A new method for

extraction called "Cellulase Extraction Method" was developed at the Centre. The key point of the method is to destroy cell walls with cellulase so that the extraction efficacy is greatly enhanced so that energy costs can be reduced.

3) Development of formulation technologies:

Modernization of dosage forms of traditional medicines is a very important task of the Centre. A number of new preparations of traditional medicines have been formulated and the technologies have been transfered to factories for manufacturing.

4) Quality control and standardization of traditional medicines:

Development of new quality control methods and standardization of traditional medicines manufactured in factories are carried out at the Analysis and Control Unit of the Centre. Now the Centre is in the process of developing standard specifications for 50 kinds of medicines prepared from medicinal plants. During the period of UNIDO project (SI/DRK/93/802) standard specifications for two traditional medicines were completed and introduced into the use for quality control of industrial products. But most of the methods currently used are still old and lack the accuracy, precision and sensitivity needed for the development of modern specifications. HPLC and GC are absolutely necessary for this Centre to carry out its duty on quality control.

5) Technical advice for all traditional medicine factories in the country:

All new products developed in the Centre and all new methods, technologies for processes, formulations and quality control methods are transfered to the pharmaceutical factories for industrial use. The technical problems in these factories are also being solved by the Centre. The Centre is also responsible for the quality control of traditional medicines manufactured in these factories.

6) Other activities performed by the Centre:

The following activities are also performed by the Centre.

- Collection of information on traditional medicines
- Screening and introduction of new technologies
- Exchange of technical information and development of cooperation with other countries. Cooperation with Sri Lanka, China and Egypt are

progressing

- Personnel training for pharmaceutical factories

It can be concluded that the Centre is: the key base for scientific development of traditional Korean medicines, modernization of industrial processes and formulations, and the unit for technical advice for 203 pharmaceutical factories producing TKM in DPRK. Therefore, strengthening the Centre by provision of a modern pilot plant and some necessary instrument is very significant for the further development of traditional medicine industry in DPRK. The consultant recommended that the Goverment and the Centre seek funds for second project for strengthening the Centre.

B. Assessment of the methods of production and advice on improvement

The commonly used methods for production in DPRK are as follows:

1) Crude drugs are pulverized into powder which is then mixed with honey to produce "Honey Pills". Honey pill is an old traditional dosage form of 10 - 20mm in diameter. The medicines in this dosage form are difficult to store. In some cases, the pulverized powder is directly packed into small bags called "medical teas".

2) Crude drugs are cut into pieces or slices and then extracted with water. The extract obtained is concentrated and dried. The dried extract is then formulated into tablets or small pills. The concentrate obtained can also be formulated into mixtures or liquid extracts.

3) Some injections are manufactured by using so called "water - alcohol method" as follows: crude drugs are cut into pieces and then extracted with hot water. The liquid extract is concentrated. The concentrate obtained is then mixed with alcohol for precipitating polar impurities, such as proteins, water - soluble starch etc. Removal of the precipitate by filtration affords aqueous- alcoholic extract, which is concentrated to remove the alcohol. The water solution is then adjusted to certain volume and divided into ampoules. Many injections, such as ginseng injection, aloe injection, haw injection are manufactured by this "water - alcohol method ".

Nearly all of the equipment used in the factories for extraction and concentration have been designed by the factories themselves and manufactured by a machinary factory in Pyongyang. Most of these equipments are old, simple and primitive. No spray drying or freeze drying is used in the factories. What

is more, there is no modern pilot plant in the Centre (KTCTM). The bench-scale research results obtained in the Centre as well as in other institutions can not be scaled up into industrial operations. The validation of processing is not in place due to the lack of pilot plant which could develop process parameters. The methods of production need upgrading.

The consultant advised on the improvement of production as follows:

a) A pilot plant is very essential for the Centre to develop process parameters which could then be transfered to the factories for production of medicines.

b) The Centre developed an injection called Civetta injection which is made of civetta, the secretion of civet cats raised in Ethiopia. Civetta is very precious and its effective constituents are volatile. So the consultant suggested that supercritical fluid extraction with liquid CO_2 at very low temperature can reduce the loss of volatile oil as compared to the extraction with acetone.

c) The mission highly evaluated the "Cellulase Method" developed at the Centre and suggested that further investigation into this method is still neccessary in order to validate its scope of appilications. Any good method cannot be used universally. More attention should be payed to the compounds which are insoluble in water at a comparative low temperature and to the compounds which are liable to decompose during long periods of incubation with the cellulase.

C. Assessment of the methods of quality control and advice on improvement

The quality control of traditional medicines is conducted by institutions at three levels in DPRK: factory level and at KTCTM and the State Institute for Quality Control of Drugs. There is a laboratory for quality control of raw materials, intermadiates and finished products in each factory. But the manpower and the facilities in factory laboratories could not meet the needs of quality assurance. The principal institution for quality control is the Centre (KTCTM). The difficult samples of raw materials, intemediates and finished products are sent by the factories for analysis. The Centre is the authorized unit for controlling the quality of traditional medicines produced by 203 pharmaceutical factories in this country. Analysis of imported and exported traditional medicines is performed by the State Institute for Quality Control of Drugs which is directly under the Ministry of Health. The identification and analysis are performed according to the regulations of

Korean Pharmacopoeia. They include macroscopic and microscopic examination, physico - chemical determination, chromatographic analysis, quantitative determination and microbiological analysis.

In addition to the routine analysis of traditional medicines produced in the 203 factories, the Centre is in the process of developing standard specifications for 50 kinds of medicines prepared from medicinal plants. But methods currently used are old and lack the accuracy, precision and sensitivity needed for the development of modern specifications.

The consultant advised KTCTM on improvement of quality control as follows:

1) Strengthening of the laboratories in the 203 factories:

To increase the staff members of the laboratories. To improve the facilities in these laboratories. At the present time, some common methods should be utilized fully by these laboratories, for example chemical reactions, titrations, TLC and so on. TLC is one of helpful methods for quality control. But most of factory laboratories have not used this method due to the lack of Merck - made precoated thin layer plates. The consultant recommended a good method for preparing silica gel thin layer plates by using 0.1 - 0.3% of Carboxy Methyl Cellulose (CMC) as the binder. The plates obtained in this way are very cheap and can be used widely in the laboratories.

2) Establishment of a modern laboratory for standardization and quality control at the Korean Technical Centre for Traditional Medicine (cf: Recommendations).

D. Assessment of the methods of formulations and advice on improvement

Two hundred traditional medicines commonly used clinically are produced in pharmaceutical factories in DPRK. The dosage forms which can be formulated in the country are powders, granules, honey pills, small pills, tablets, tinctures, mixtures, liquid extract, injections and medical wines. Capsules cannot be manufactured yet in the country due to the lack of medical gelatin, but an effort is being made to solve this problem. The granules made directly from water extract of crude drugs were not found in DPRK. This kind of granules is very popular in Japan and China. It is very convinient for oral administration due to the small volume of powder. It is also easy to transport and store. The consultant suggested KTCTM to develop this kind of granules in DPRK.

Most equipments for formulations are old and simple. Only a few equipment, such as tablet machine, mixing - machine used at PJF were imported from Germany and Japan. In addition, different types of packing machines are not readily available in DPRK.

The mission gave KTCTM the following advices on improvement.

1) To develop new types of formulations, such as capsule, extract - granule.

2) To develop new kinds of traditional medicines. The consultant recommended 15 plant-based medicines which were new to DPRK, which are produced abroad (cf:subchapter D of this chapter).

3) To reduce the kinds and volumes of honey pills which are difficult to store.

4) To improve packing methods.

E. Assessment of manufacturing practices and advice on improvement

Most of the factories in DPRK payed attention to administration of production and quality control of raw materials, intermediates and finished products. The directors or managers of the factories are familiar with technology for production. Most of them are graduates from colleges of pharmacy or faculties of pharmaceutical sciences of medical universities. They have strong capabilities to organize and lead the activities of factories. Analysts in laboratories of pharmaceutical factories and in the KTCTM are qualified specialists for quality control. There is a general engineer in each factory, who is in charge of the administration of production activities. Although efforts have been made for good manufacturing practices, the present situation in these factories is far below the GMP standard. In production zones, there is no air - purifying equipment. People and materials move together in same corridor even in the zone which should be extremely restricted, such as the workshop for production of injections. Quality control of production is performed at low level due to the lack of analytical instruments.

In order to advise on improvement of manufacturing practices, the mission showed two videos titled "GMP in Japan", and "Pharmaceutical Industry in Shenyang". The The mission discussed with 40 related persons about the GMP. More effort should be made to meet the GMP standards in DPRK.

F. Demonstration of methods for improving the formula of dosage forms and their testing

In order to demonstrate methods for improving the formulation of dosage forms and their testing, the following activities were carried out by the consultant.

1. A lecture was given about the new progress in formulation of plant-based medicines in Japan and China. The mission emphasized the form of extract-granule which has become the main dosage form of compounding preparations in Japan and China.

2. The consultant explained the technology for manufacturing extract-granules and demonstrated the method for formulating the extract-granule "Hachimijio-gang" which is well known in Japan as well as in China. It is a good example for formulating compound traditional medicines.

3. Method for manufacturing ginsenosides powder was also shown to the staff members of KTCTM. The famous medicinal plant, Panax ginseng C.A. Meyer is cultivaled in DPRK on a large scale. Every year DPRK exports roots of ginseng to Hong Kong, southeast Asia and China in large quantities. But the leaves, flowers and fruits of the plant have not been utilized industrially in DPRK. The mission showed how to extract ginsenosides, the major effective fraction, from leaves of Panax ginseng and how to formulate it into ginsenosides powder.

This kind of formulation is very suitable for those crude drugs whose effective constituents or active fractions have already been known. The medicines made by formulation of the effective fraction are very easy for transportation and storage. They are also convenient for administration. The mission demonstrated how to test the product, for example, how to identify it by using chemical reaction, TLC, and how to quantitatively determine the ginsenosides by using a spectrophotometric method.

In China, particularly Sanchakou ginsenoside factory has well developed know how for manufacturing ginsenosides from the leaves of Panax ginseng. Every year this factory produces tons of ginsenosides which are sold not only within China, but also exported abroad. The consultant recommended to establish a joint - venture company between Sanchakou ginsenoside factory and KTCTM.

G. Assistance in the development of process and quality assessment protocols

1. Assistance in the establishment of a pilot plant

KTCTM wants to install a pilot plant in the premises of the Centre. A two-floor building for housing the pilot plant is under construction. The construction area is 630 m^2. The consultant adviced KTCTM on the selection of equipment for extraction, concentration and distillation and handed the UNIDO publication on "Design Options for a Polyvalent Pilot Plant Unit for the Distillation and Extraction of Medicinal and Aromatic Plants". "Technical Proposal of a Poly-functional Pilot Plant for Extraction of Medicinal Plants with a capacity of 200 kg per day" prepared by Shanghai Pharmaceutical Industry Design Institute was also given to the Centre.

2. Assistance in the development of plant-based medicines

Now 230 kinds of traditio. al medicines are produced in DPRK. The number of the traditional medicines produced is far from enough for the treatment of common diseases in this country. KTCTM wants to introduce some new plant - based medicines into DPRK. The consultant assisted in providing some technologies for producing the following plant medicines:

1) Extraction of berberine from Berberis amurensis: Korea is rich in the natural resource of Berberis amurensis. The root of the plant contains berberine up to 3%. The consultant showed the method for extracting berberine from the roots. Berberine can be formulated into tablets for the treatment of dysentry. Berberine, as a chemical raw meterial, can be exported abroad.

2) Production of tasteless berberine: Berberine with its bitter taste is disliked by patients, particularly by children. A tasteless form of berberine is berberine tannate. During oral administration of this medicine, it does not taste bitter because berberine tannate is insoluble in water. As soon as the medicine enters the small intestine, it is decomposed into berberine and tannic acid by the alkaline medium of the intestine. The berberine freshly released acts on dysentry bacteria. So the tasteless berberine is more effective than berberine alone for the treatment of dysentry. The consultant demonstrated the method for producing tasteless berberine to the KTCTM staff members. Shenyang Pharmaceutical University (SPU) posseses the advanced

technology for production of tasteless berberine. The consultant suggested KTCTM to contact SPU for this technology.

3) Production of ginsenosides from the leaves of Panax ginseng C.A Meyer: The total ginsenosides obtained from the leaves of Panax ginseng are used as a tonic and a detoxifying agent, such as anti-alcoholism, detoxifying agent for reducing toxicity of anti-cancer drugs. Total ginsenosides are exported to USA.

4) Production of Dioscin from the rhizomes of Dioscorea nipponica Maxim. Dioscin, a kind of steroid saponin, is the major effective component of Discorea. Dioscin is formulated into tablets for treatment of coronary heart disease. The consultant explained the method for producing dioscin from the rhizomes of the title plants.

5) Extraction of matrine and oxymatrine from Sophara flavescens Ait. Korea has very rich resource of Sophara flavenscens. But the major constituents, matrine and oxymatrine have not been extracted industrially and used clinically in this country. The consultant gave some information about the R & D of matrine and oxymatrine in Japan and China. The two alkaloids have anti-cancer activity and anti-arrythmic effect as well as anti-dysentry action. The consultant explained the method for isolating and purifying oxymatrine which is formulated into tablets for treatment of cancer and dysentry.

6) Industrial utilization of Epimedium Koreanum Nakai: Medicinal plant, Epimedium Koreanum Nakai is widely distributed in this country. The consultant recommended the industrial utilization of the plant. The extract obtained from the leaves of this plant can be formulated into tablets for the treatment of coronary heart disease and bone spongy (Cancellous bone) which are very common diseases in aging people.

7) Extraction of schizadrin lignans from Schizandra chinensis Baillon: The schizandrin lignans obtained from the seeds of this plant are formulated to tablets for treatment of hepatitis. The consultant gave a lecture on the method for producing the schizandrin lignans from this plant.

8) Utilization of chrysanthemum boreale Makino: The essential oil prepared from the flowers by steam -distillation is used to treat

common cold and influenza with good therapeutic effect. The consultant suggested to utilize industrially this plant for medicine.

9) Processing of haw leaves. There is a lot of haw trees (Crataegus pinnatifida Bge.) growing in the Korean peninsula. Haw fruits are used to manufacture medicines in DPRK. The leaves of this plant have not been used yet. The consultant suggested to use the leaves for manufacturing medicines for the treatment of some blood-vessel diseases. The method for extracting total flavonoid compounds was given to the KTCTM staff by the consultant.

10) Production of medicinal extract from Ginko biloba: Medicinal extract obtained from Ginko biloba is widely used in France and Germany and in many other countries for the treatment of heart and vessel diseases, senile dementia. Many preparations, such as tablets, tinctures, oral liquids, capsules, granules and injections are made from the medicinal extract which contains about 24% flavonoids and 6% ginkolides. The consultant gave relevant information on the methods of extraction and standardization.

11) Production of drunkenness dispeller. Many Korean men like to drink wines. Some persons are suffering from alcoholic intoxication. The consultant gave an introduction to the recent advances in R & D of drunkenness relieving agents. The method for producing "Shingjiuling", a kind of drunkenness relieving medicine was taught to the KTCTM staff by the consultant.

12) Application of reticular resins in production of saponins from crude drugs: This method is widely used in China and Japan for isolating saponins from extracts, such as ginsenosides from ginseng, Saikosaponin from Saiko etc.

13) Production of Taxol from Taxus cuspidata Sieb et Zncc: Taxol is a new type of anti-cancer drug for treatment of ovisac cancer with higher therapeutic index and lower toxicity than other known anti-cancer drugs. Korea is rich in the natural resource of Taxus cuspidata, so the consultant recommended to produce taxol from this plant. The produced taxol could be used domestically or exported. The consultant gave some information about the taxol.

14) Industrial utilization of Acer ginnala Maxim: Acer ginnale Maxim grows everywhere in DPRK. The branches and leaves of this plant can be industrially used for the production of gallic acid which is an important raw material in the pharmaceutical industry to synthesize Trimethoprim and other medicines. The consultant recommended to establish a joint venture company with Harbin pharmaceutical company of China in "the Golden Triangle Free Economic Zone" of DPRK. The product could be exported to China or used in DPRK.

15) Production of Urone from Quercus dentata Thumb: Urone is used for treatment of urine stone in many countries, such as Japan, China etc. It is prepared from Quercus dentata Thamb which is found in DPRK. The consultant gave some information about the effective fractions of this plant and the method for the preparation of them.

H. Assistance in quality assessment protocols

Now the centre is in the process of developing standard specifications for 50 kinds of medicines prepared from medicinal plants. The consultant worked in collaboration with the related staff members of the Centre and assisted in developing quality assessment protocols.

In the original standard specification of "Tincture of Ginseng and Acanthopanax" prepared by the Centre's staff, there were only three test reactions for identification: a) Liebermann-Buchard reaction for testing ginseng saponins. b) Ninhydrate reaction for testing amino acids. c) NaOH reaction for testing some phenolic compounds which turn yellow upon alkali addition. The consultant explained that these three reactions are not enough for the identification of both ginseng and Acanthopanax (sibirian ginseng). TLC for analysis of ginsenosides in Ginseng and syringin in Acanthopanax was suggested to be added to the standard specifications. In addition quantitative determination of ginsenosides and syringin in the tincture are also necessary for assuring the quality of the product. In collaboration with the related staff the standard specification for this product was supplemented by adding TLC analysis for ginsenosides and syringin, and quantitative determination of ginsenosides by a photometric method. HPLC analysis could not be used for analysis of this product due to the lack of HPLC instrument at the Centre.

The following activities were also undertaken by the consultant for assisting KTCTM in quality control of traditional medicines.

1) Method for the preparation of silica gel thin layer plates was suggested to the Centre. Thin layer chromatography is frequently used for indentification of traditional medicines, but the precoated TLC plates produced by Merck company are too expensive for KTCTM to use them in large quantities. The researchers at the Centre tried to make TLC plates by themselves with silica gel G. The problem was the poor quality of the produced plates, because the thin - layer of silica gel was liable to strip from the glass plate. The consultant demonstrated a good method for producing stronger TLC plate by using 0.3% CMC solution in water as the binder.

2) A lecture on quality control of traditional medicines in China and Japan was presented by using slides. In his lecture, the consultant gave some examples to show the application of advanced equipment in the quality control of plant-based medicines, such as HPLC, two-dimensional TLC scanning, spectrophotometers etc.

3) Advice on authentic samples. Authentic samples play a very important role in quality control activities. The consultant suggested that State Institute for Quality Control of Drugs and KTCTM should prepare some pure compounds from commonly used crude drugs, and exchange authentic samples with the related institute in other countries.

I. Training of counterpart staff in the use of new methods and equipment

The quality requirements of internationally acceptable products have to be determined by using modern methods and instruments which are more accurate and precise. UNIDO provided the Centre with four new equipment: M-500 Infra Red spectrophotometer, electronic balance, titrator of voltage difference and an IR moisture analyzer. These instruments reached the Centre fifteen days before the consultant arrived in Pyongyang. The consultant worked in collaboration with the engineers and pharmacists in the Analysis and Control Unit of the Centre. He read the related installation and instruction manuals and commissioned these instruments. Then the consultant trained the counterpart staff how to use these instruments. Finally, the consultant wrote procedures of operations for the instruments.

The consultant specially explained the application of IR spectra in the identification of known compounds and structural elucidation of new compounds. For example, the absorption around 3000 cm^{-1} indicates the existance of -CH-,

$-CH_2$ - and $-CH_3$ structures, while the absorption at around 1650 - 1750cm^{-1} shows the different kinds of carbonyl groups (>C=O). The consultant also gave information about the application of IR spectra in identification of traditional medicines by using the additive property of IR spectra. An IR spectrum obtained using the equipment and the procedure of operation for M-500 IR spectrophotometer are given in Annex.

Some important accessories are very necessary in order to utilize these instruments fully. A hydraulic press is needed to make solid sample containing KBr tablets (pellet) for measuring IR spectra. The 12 ton Mini "C" Hydraulic press is a widely used piece of standard laboratory equipment and is used with the evacuable 13 mm KBr Die for pressing KBr pellets. This piece of equipment belongs to a part of M-500 IR spectrophotometer. In addition, there was no Printer P22 for the titrator TR 154. Urgent purchasing of the hydraulic press, Printer P22 and Drip glass are recommended.

The Centre bought some equipment from China, such as water pumps, oil pumps and rotatory evaporators. The consultant advised the counterpart staff on rational use of the equipment. For example the consultant explained that good water-circulation is essential for water pump to work well. A buffer (empty) bottle and silica gel-containing dryers (two bottles containing silica gel for drying) were suggested to be connected before the oil pumps. The shortage of some parts which are necessary to these instruments were recorded and will be informed to the manufacturer by the consultant.

IV. RECOMMENDATIONS

A. Recommendations for the improvement of processing, quality control, formulations and manufacturing practices including safety measures

1. Methods for improvement of processing

1) Establisment of a modern pilot plant in the Centre.

KTCTM is a technical Centre that should instruct technically the industrial production conducted in the 203 pharmaceutical factories under the Centre. KTCTM is responsible for changing laboratory research results into industrial operations. So a pilot plant is very necessary for the Centre, to develop process parameters for scaling up the bench-scale research results to the Industry. Knowing the importance of a pilot plant, the Centre is in the process of constructing a 630 m^2 - building for housing the pilot plant.

2) Strengthening R & D for improving processes

3) Enhancement of kinds and types of traditional medicines through:

a) Studies on chemical constituents, pharmacological activities and clinical usage of medicinal plants and developing them into new drugs.

b) Introduction of some good plant-derived medicines from abroad.

c) Establishment of joint-venture phytopharmaceutical factory with China or other countries (cf.subchapter D of chapter III).

2. Methods for the improvement of quality control

1) Modernization of laboratory for quality control.

There are some instruments for quality control, such as TLC scanner, UV spectrophotometer, Vis-spectro-photometer, balances, which are utilized for quality control as well as R & D of new drugs. Recently UNIDO provided the Centre with four advanced instruments: M-500 IR Spectophotometer, TR-154 Titrator with pH meter CG804, Misture-Analyzer (Satorius MA40) and a

electronic balance. These instruments are very necessary for the center to strengthen its ability to do quality control work. But certain analytical instruments such as HPLC and GC are requierd as the Centre is responsible for the quality control of products manufactured in 203 factories. So the consultant strongly recommended to equip the Centre with at least two HPLC and one GC instruments.

2) Standardization of raw materials, intermediates and finished products.

Now the Centre is in the process of developing standard specifications for 50 kinds of medicines prepared from medicinal plants. The Centre is recommended to pay more attention to the standardization of raw materials, intermediates and finished products. The Centre should strengthen its ability to develop new or improved quality control methods, quality standards and specifications for the products and for use in the manufacture of phytopharmaceutical products.

3) Training of personnel for quality control

The extreme lack of qualified analysts and technicians in the pharmaceutical factories drew the consultant's attention strongly. Qualified analysts should be in charge of the laboratories in the factories which are the first key-points for quality control of raw materials, intermediates and finished products. Training of personnel for quality control was strongly recommended to the Centre and the Government. Some high level analysts working at the Centre should be sent abroad for training. The analysts working in the factories could be collected to the Centre and trained by the Centre's high level analysts.

4) Preparation and exchange of authentic samples

Authentic samples are very necessary for qualitative and quantitative determination of chemical compounds in the raw materials, intermediates and finished products. The consultant recommended to the Centre and the State Institute for Quality Control of Drugs to prepare some authentic samples. Some samples could also be obtained from related institutions of other countries.

3. Methods for improvement of formulations.

1) Modern modification of old formulations

Although some old dosage forms, such as honey pills, have been used for thousands of years in China, Korea, Japan and other countries, its weakness is too obvious to continue developing it. Its cost is greatly increased due to usage of large quantities of honey which are not essential for therapeutic purposes in most of cases. In addition, honey pill is poor in stability because it is liable to contamination with bacteria and fungi. The honey pills are hardly used in Japan now. Instead, the extract granules which are derived from honey pills and Kampo decoctions are very popular in Japan. In China, more and more honey pills are being replaced by tablets, granules. So the consultant recommended to the Centre and the Government to pay attention to modification of old formulations, especially to that of honey pills.

2) Development of new formulations

Some dosage forms of plant-based medicines, such as capsules, extract-granules, aerosols, adhesive plasters etc, are well manufactured and used in China, Japan, and other countries. These formulations are seldom produced in DPRK. The consultant recommended to the Centre and the Government to introduce some of these formulations. Especially, the extract-granule could be thought to the major dosage form of traditional medicines in the 21st century. Aerosol is a good form for some traditional medicines used for treatment of asthma and diseases of the respiratory tract. Adhesive plaster of traditional medicine is commonly used for treatment of external injury.

3) Improvement of filling and packing methods for traditional medicines:

Some advanced filling and packing machines are recommended to be introduced into the factories. The consultant saw that ampoules of injections were filled and closed by hands in the factories. There were no PTP packing machines used for traditional medicines. So the consultant suggested to import some advanced filling and packing machines for equiping the planned preparation workshop of the Centre.

4. Methods for the improvement of manufacturing practices including safety measures:

1) GMP

The consultant found that many directors of phytopharmaceutical factories did not know what are the principles and main contents of GMP. So the consultant suggested to conduct GMP education among the directors, engineers and chief-analysts. The consultant showed a video titled "GMP in Japan" to the staff members at the Centre and gave a detailed explanation on GMP. The consultant emphasized the importance of GMP for producing high quality medicines. Let every director, engineer, analyst know what is GMP and the basic requirements of GMP. Construction of new factories, reformation of old factories should follow the requirements of GMP.

2) Establisment of a small model phytopharmaceutical factory according to the requirements of GMP

The planned pilot plant building which is to be built contains several preparation laboratories. The consultant suggested that they be built taking into account GMP requirements. Then this factory will become a model for all other pharmaceutical factories in this country to meet the GMP standards.

3) Air-purification and safety measures

At the present stage, air-purification and safety measures should be taken as the first step to meet GMP standard for some factories. There is no air-purifying equipment in any of the pharmaceutical factories visited. The units preparing injections in the factories should have air-purifying equipment as soon as possible. Attention must be also payed to safety measures. In Pyongyang Jangsudongyak factory, the consultant saw a group of workers who were producing "Insam Indan" (Ginseng pills) by using alcohol, as the moistener. The room was full of alcohol vapour which is a very dangerous because of inflammable property of alcohol. So the consultant strongly recommended to the factory director and related persons to take some safety measures, for example, to build a draft or fix up an exhauster.

B. Recommendations of other equipment and training required for strengthening the Centre

1) Equipment for pharmacological and toxicological experiments:

Pharmacological and toxicological experiments are very essential for research and development of new medicines as well as for validation of existing traditional medicines. The newly established "Research Division for toxicity Testing" in the Centre, which is in charge of not only toxicological testing, but also pharmacological study, lack the necessary equipment. The consultant recommended to the Centre and the Government to strengthen this division by providing certain instruments. Some of them are urgently required by the division. They are listed in Annex 3.

2) Personnel training

Qualified analysts, chemical engineers and pharmacologists are recommended to be trained abroad. KTCTM should be responsible for training more personnel from factories in quality control and production activities.

C. Recommendations for strengthening the Centre through a new project

A comprehensive consideration of the recommendations mentioned above led the consultant to suggest a new project for strengthening the Korean Technical Centre. The key point of the project are as follows:

Title: Technical assistance for strengthening the Korean Technical Centre for Traditional Medicine

1. Background and Instification

The Korean Technical Centre for Traditional Medicine was established in June, 1992 for R & D, standardization and validation of traditional medicines and to develop modern peocessing parameters in order to improve the quality and production of traditional medicines. The Centre is going to transfer the processes and quality specifications developed, to 203 pharmaceutical factories which are under the technical direction of the Centre. The Government of the Democratic People's Republic of Korea has invested 520,000 Korean won for the construction of the Centre. Now the Centre has four research divisions and seven technical units. On the request of the DPRK Government, a UNIDO's project (SI/DPK/802) for technical service to the

KTCTM was carried out. The UNIDO's project has achieved very active results as follows: a) Three qualified staff members including the Director of the Centre updated their knowledge on production, formulation, quality control and good manufacturing practices by the study tour to Sri Lanka, India and China. The study tour was a good oppotunity for the project anthorities to identify the types of machinary needed for research and production. b) Four testing equipments, IR spectrophotometer, electronic balance, titrator of voltage difference and IR moisture analyzer, were provided through the project. All of these instruments have already reached the Centre and are being used for quality control. c) High level advisory service to the Centre has been completed by the UNIDO consultant. This advisory service was highly recognized by the Centre and the Government for improvement of technology, quality assessment, formulations and manufacturing practices.

These active results achieved by completion of UNIDO's project have led to a more significant action. The project anthorities including the related leader of Ministry of Health and the Director of the Centre have been greatly encouraged and therefore they have prepared a plan for the Centre's further development to serve the health care needs of the country. The Centre has and will have the following functions:

1) Research and development of new traditional medicines

2) Development of processes and formulations, scaling up bench - scale research results into industrial operation by experimentation at pilot plant scale.

3) To develop new or improved quality control methods, quality standards and specifications for the products and use in the processes of manufacture of pharmaceutical products.

4) To transfer the technologies developed in the Centre to the 203 pharmaceutical factories distributed in different regions in the country.

5) To direct the production and quality control conducted in all phytopharmaceutical factories in DPRK.

From the Centre's function, we can know the importance of the Centre to the health care of the country. The Centre is different from other institutions (research institutes or colleges of pharmacy) where academic research is being carried out, as it is a focal point to combine academic research with applied research and finally transfer these results into

industrial use. KTCTM is the key and the authorized institution which is technically responsible for all of phytopharmaceutical factories in DPRK. So strengthening the Centre is of great significance to the industrial utilization of medicinal plants in DPRK. It is also meaningful to the development of traditional Korean medicines.

In order to conduct R & D of new drugs (function 1), some equipments for pharmacological and toxicological experiments are necessary.

In order to scale up bench scale research results into industrial operations (function 2), experimentation at pilot plant level is very necessary. A pilot plant capable of carrying out various unit operations such as extraction, distillation, fractionation, evaporation, etc. can be suitably used to derive necessary process parameters for scaling up to the industrial level. There is, at present, no multipurpose pilot plant in DPRK. The Centre has decided to install a true multifunctional pilot plant. Now the building for housing the pilot plant equipment is under construction (see the photo in Annex 7).

In order to carry out the function 3 (quality control), a modern laboratory equipped with advanced analytical instruments such as HPLC, GC, etc. is necessary.

The provision of a multifunctional pilot plant for the extraction and distillation of medicinal and aromatic plants and some equipment for quality control, pharmacological and toxicological experiments are seen as a right step to strengthen the Centre. UNIDO's long and proven experience in this field could successfully assist the Government to strengthen the Centre.

As a result of the project implementation, the technological processes for productior and formulation of traditional medicines will be further improved. The phytopharmaceutical industry in DPRK will develop more rapidly and more scientifically and best quality medicines could be offered to the population of Korea.

2. The Project

1) Immediate Objective

The objective of the project is to improve the production and research on medicines using modern experiments by strengthening its capability for developing methods for production, formulations, quality assessment, R & D of

new products, and manufacturing practices to meet internationally accepted standards.

2) Outputs

Output 1 A fully operational multipurpose pilot plant with GMP requirements including a formulation unit

(a) Staff Composition

1 Chemical engineer
1 Pharmacist
5 Labourers

(b) Premises

These will be made available by the Centre

c) Equipment

The necessary equipment are listed in Annex 3.

Activities for Output 1

The following activities will be carried out for the achievement of the abovementioned output:

1.1 Recruitment of NPC, preparation of detailed workplan for project activities
1.2 Assignment of international expert (chemical engineer)
1.3 Assignment of national expert (chemical engineer)
1.4 Placement of order and installation of equipment
1.5 On-the-Job training for the Centre staff
1.6 Drawing up of standard procedures for the operation of the plant
1.7 Commissioning and use of pilot plant

Output 2 A full operational modern laboratory for quality control of traditional medicines

This laboratory should be established by strengthening the existing laboratory facilities of the Centre through provision of equipment, such as HPLC, GC.

(a) Staff Composition

2 Analytical chemists
3 Laboratory assistents
3 Technicians

(b) Premises

The rooms to house the laboratory facilities will be provided by the Centre as the Government input.

(c) Equipment

The main equipment are given in annex.

Activities for Output 2

2.1 Assignment of international expert (Analyst)
2.2 Review and elaboration of specification of equipment
2.3 Placement of order and procurement of equipment for the laboratory
2.4 On-the-job training of the Centre staff (by expert)
2.5 Drawing up of standard operations (by expert)

Output 3 A modern laboratory for pharmacological and toxicological testing.

This laboratory should also be established by strengthening the existing laboratory facilities of the Centre through provision of equipment.

D. Summary of recommendations

Identification of the problem	Action to be taken	Responsible party
1. DPRK is rich in natural resources for plant medicines. There are 203 pharmaceutical factories for traditional medicines. Although many types of medicines are produced in these factories, the methods used are traditional and need improvement. The equipment are rather old and need modernization.	Methods and equipment used for production should be modernized	The Ministry of Public Health is expected to pay more attention to improvement of processing methods and modernization of equipment. KTCTM should develop new methods for production.
2. Many kinds of dosage forms can be formulated in these factories. But there is only a few kinds of capsules, extract, granules, pastes for external use, aerosol. Good packing machine, such as PTP packing machine, is not found	Research and development of these useful dosage forms for production of more traditional medicines should be carried out. Good packing machines should be introduced.	KTCM should pay more attention to the research and development of these useful formulations. Ministry of Health to introduce advanced packing machines into traditional medicine industry.

3. Quality control in pharmaceutical factories is weak due to the lack of some instruments and qualified analysts.	The laboratories for quality control in the factories should be strengthened by provision of analytical equipment and enhancement of the number of analysts whose level should also be raised by training.	Ministry of Health to strengthen the laboratories for quality control in the factories by provision of some analytical equipment and enhancement of the number of analysts.
4. GMP is not in place for most traditional medicine pharmaceutical factories	GMP in pharmaceutical factories must be stressed from now on.	Ministry of Health, State Institute for Quality Control of Drugs and KTCTM to draw a plan and take necessary measurements for introducing GMP.
5. KTCTM is a key institution for improvement and prospect of traditional medicine industry. But KTCTM lack a modern pilot plant and some necessary equipment for quality control and pharmacological experiments	Effective measurement should be taken for strengthening KTCTM by provision of a modern pilot plant along with some necessatry instruments such as HPLC, GC, etc.	The pilot plant equipment and necessary instruments should be provided. UNIDO could be made responsible for selection of international experts, personnel, training, etc.

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Annex 1

JOB DESCRIPTION

Project in DPR Korea
SI/DRK/93/802/11-01

Post Title: Chemical Technologist

Duration: 2.0 m/m

Date Required: ASAP

Duty Station: Korean Technical Centre for Traditional Medicine and travel in the country as appropriate.

Purpose of Project: To advice the Traditional Medicine Centre on the improvement of processes, formulations of dosage forms, quality assessment and manufacturing parameters in the production of traditional medicines.

Duties: The expert will be required to work in collaboration with counterpart staff at Traditional Medicine Centre in carrying out the following duties:

- Evaluate the activities performed by the Centre.
- Assess the methods of production, quality control and formulations and manufacturing practices and advice on improvement.
- Demonstrate methods for improving the formulation of dosage forms and their testing.
- Assist in the development of process and quality assessment protocols.

- Train counterpart staff in the use of new methods and equipment.

- Recommend methods for the improvement of processing, quality control, formulations and manufacturing practices including safety measures.

- Recommend other equipment and training required for strengthening the Centre.

Finally, the expert will furnish a report enbodying his findings and progress made and outlining his recommendations to both UNIDO and the Government.

Annex 2

LIST OF PEOPLE MET

UNDP

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Mr. Kim Guan Heng, Vice - Head of General Bureau for Administration of Korean Traditional Medicine, Ministry of Health.

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Ms. Jong Yong Hui, Director of Traditional Medicine Unit, Department of Pharmacy, PMH.

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Mr. Kim Do Bin, Director of SSFMP

Mr. Kim Lak Won, General Agroengineer of SSFMP

SPF

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Mr. Cha Kuang Hui, General Engineer of SPF

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Ms. Liang Gyong Suk, General Engineer of JPF

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Mr. Kim Yun Gi, General Engineer of KJF

Mr. Li Hao Gol, Director in Production of KJF

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Mr. Cha Jin Hon, Professor of Faculty of Pharmaceutical Sciences, PMU. Vice- Chairman of Society of Traditional Korean Medicine, Vice director of Division for Traditional Korean Medicine of Korean Pharmacopoeia Committee.

Mr. Kim Chang Gun, Professor of Faculty of Pharmaceutical Sciences, PMU.

Mr. An Chol Gol, Professor of Phytochemical Department, Faculty of Phramaceutical Sciences, PMU.

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Ms. Gang Bo Yong, Scientist of Traditional Medicines Division, KTCTM.

Ms. Pak Zheng Gil, Scientist of Traditional Medicine Division, KTCTM.

Ms. Kim Jing Ok, Scientist of Traditional Medicine Division, KTCTM.

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Ms. Li Sun Dok, Scientist of Biotic Medicine Division, KTCTM.

Ms. O Son Nyo, Scientist of Biotic Medicine Division, KTCTM.

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Ms. Li Bok Hui, Scientist of Analysis and Quality Control Unit, KTCTM.

Ms. Go Myong Hui, Scientist of Analysis and Quality Control Unit, KTCTM.

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Mr. Kim Yong Sob, Pharmacist of Healthy Foodstuff Unit, KTCTM.

Ms. Mo Yong Suk, Pharmacist of Healthy Foodstuff Unit, KTCTM.

Ms. Choe Kum Ok, Engineer of Healthy Foodstuff Unit, KTCTM.

Mr. Gang Jing Wan, Head of Screening and Introduction Unit for New Technology, KTCTM.

Ms. Choe Sun Sil, Scientist of Screening and Introduction Unit for New Technology, KTCTM.

Ms. Choe Yong Sil, Head of Trial Production Unit, Pharmacist.

Mr. Sok Kum Bok, Head of Modernization Division, MD. Engineer.

Mr. Jo Myong Kuk, Researcher of Modernization Division.

Ms. Zhang Jong Suk, Pharmacist of Investigation Unit for Data, KTCTM.

Ms. Pak Un Sil, Pharmacist of Investigation Unit for Data, KTCTM.

Ms. Kim Ok Sun, Head of Foreign Affairs Unit, KTCTM.

KMAS

Mr. Mun Guan Xim, Prof. Dr. Head of Department for Traditional Korean Medicine. Institute of Pharmacy, KMAS; Chairman of Society of Traditional Korean Medicine; Director of Division for Traditional Korean Medicine of Korean Pharmacopeia Committee.

Mr. Chui Long Sam, Professor and Head of Department for Anti - Cancer Medicine, Institute of Pharmacy, KMAS.

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Mr. Kim Hong Bae, Director and engineer of SCPF.

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Ms. Lyom Song Ok, Director of Pharmacy Department, KMYH.

Annex 3

List of equipment, instruments and needs for strengthening the Centre

A. Provisional list of industrial equipment (pilot plant)

1.Multifunction extractor,	200 kg/day,	1,	70,000
2.Triple effect evaporator,		1,	30,000
3.Drying box with hot air circulation,	0.45kW	3,	30,000
4.Highy performance vacuum dryer,	6kW	1,	30,000
5.Freeze dryer (volume of 1m),		1,	30,000
6.Spray dryer,	1kg/h	1,	30,000
7.Tablet PTP packing machine,	5kW, 40,000T/h	1,	50,000
8.Bag-packing machine for powder,tablet,	1.5kW	1,	10,000
9.Electric steam generator,	35kW	1,	30,000
10.Tablet-pressing machine,	1.5kW, 5,000-10,000T/h	2,	50,000
11.Granulating machine,	1.5kW	1,	10,000
12.Coating machine,	1.1kW, 30kg/h,	2,	5,000
13.Pill-making machine,	4kW, 2,800 pills/h,	1,	15,000
14.Shaking granule-selector,	30-50kg/h,	1,	7,000
15.Multi-layer plate frame filter,	0.5-1m^3/h,	1,	2,000
16) Membrane filter,	5.5dm^3/min,	1,	2,000
17) High speed mixing granulating machine,	50-60kg/h,	1,	10,000

18) Stainless centrifugal pump, 0.75kW, 3m³/h,		2,	6,000
19) Air-purifying apparatns, 40-8-W,		3,	15,000
20) Central air-purifying equipment,		1,	20,000
21) Centrifugal separator, 1.5kW,		1,	10,000
22) Water-distillator, 100 L/h,		1,	10,000
23) Multifunction sterilizing dryer, 1kW,		1,	10,000
24) Ampoule-washing machine,		1,	10,000
25) Ampoule-pouring and enclosing machine, 380W,		1,	15,000
26) Raw material cutting machine (cutter) 80kg/h,		1,	2,000
27) Coarse granular mill 50-100kg/h,		1,	3,000
28) High speed pulverizer, 1.5kW,		1,	3,000
29) Refrigerator (Box-type), 1,000*1,000*500mm,		2,	20,000
30) IBK personal computor, with Cpu intel 80486 or 80586, 150Mbyte Hard disk, imagine scanner, laser printer		1 set,	18,000
	Total	$	553,000 USD

B. Provision list for laboratory equipment

1.	Preparetive HPLC with UV and RI detector, gredient pumps, programmer and record paper.	45,000
2.	HPLC with UV detector, automatic injector, thermostatic chamber, Data-chromatipak.	35,000
3.	Gas chromatography with TCD, FID FPD detector, capillary tubes (column) * 2. Hydrogen generator, Programmer, record paper and necessary parts.	15,000
4.	Low pressure chromatograph (for Labor Column chromatography) with UV detector, record paper and necessary parts. Labor columus RP-18, RP-8 each 2.	5,000
5.	Electrophoresis equipment.	5,000
6.	TLC spreader 2.	1,400
7.	Dryer 1501 (40-120 m).	1,500
8.	Incubator, two seta.	2,600
9.	Rotary evaporator , 2 with vacuum pumps , 4 sets	4,400
10.	Water-purifying appartus on table NRK-RO-5 type (NRK Catalogue).	2,700
11.	Laboratory grinder (Small type).	1,000
12.	Laboratory vacuum distillator (stainless) 2 sets.	9,600
13.	Laboratory ball miller, 1 set.	1,000
14.	Laboratory granulating apparatus, 1 set.	700
15.	Laboratory plastic bag encloser, 4 sets	2,000
16.	Universal pulverizer for laboratory use, 2 sets	2,000

17. Automatic mixer.	2,000
18. Centrifuge, 3,000-5,000 r/m (2)	4,000
19. Centrifugal filter (3)	4,050
20. High pressure steam sterilizer.	3,000
21. Jafameter (for tissue culture) 10 L.	5,000
22. Shaker (for tissue culture) 2 L (10hrs).	2,500
23. Vacuum dryer (laboratory use) with vacuum pumps 300W (3)	6,000
24. Spray dryer (laboratory use) (3)	6,000
25. Freeze dryer (lab. use) (3)	6,000
26. Sugarometer (2)	1,500
27. Glass cutter (for TLC [illegible]e) (1)	300
28. Dryers (2)	2,000
29. Working table for designing (1)	1,000
30. Vacuum pump (1)	700
31. Bacteria-free operational apparatus (purifying table).	2,000
32. Electric mortar (1)	1,500
33. PH meter for industrial use (1)	1,400
34. Laboratory tables (3)	4,500
35. Laboratory draft (1)	2,000
36. Sugar coating machine (Lab use) (1)	1,000
37. Animal Environment controlling Apparatus (2) With 60 plastic cages for mouse housing 60 plastic	26,000

cages for rat housing and filter materials. 2,000

38. MR spectrometer (use for measuring Blood deficient level in vivo, fatigue speed and recovery, muscle movement, pharmacological effect, metabolism of cancer cells). 30,000

39. Mouse and rat auto balance (2) 1,900

40. Animal thermometer (for rabbit, mouse and rat use) (5) 250

41. Glass metabolic cage for rat (1) 2,500

for mouse (1) 1,800

42. Laboratory animals

Mouse ICR, C 57 DBA/2 BALB
each 10.

Rats wistar Donryu
each 10.

43. Tumor cell lines

Mouse L 1210 Leukemia P-388,
S-180, Lewis peumoma.
Erlisch cell, B-16 Belonoma
each 5.

Rats Ushita sarcoma, Walker-256,
hepatoma
each 5.

44. Necessary parts for following instruments:

(1) for M-500 IR spectrophotometer:
Record paper 100
Pens 10

NaCl window disk
38*19*4mm, 10
25*4mm, 10

Hydrastic press apparatus,
KBr 2kg (each pack 100g*20) 1,000

(1) UV spectrophotometer (Shimatzu UV -160 A)

Cell	10mm	10,	
record paper	(FTP-040)	50,	
Halogen lamp RJ 5012,		5,	
H.lamp Ds-350V,		5,	
fuse 3A 200 -240V,		5.	1,000
		Total	$ 256,800 USD

C. Provisional list of chemicals for laboratory use

1.	$Na_2WoO_4 . 2H_2O$,	AR	500g,	1,000
2.	$NaMoO_4 . 2H_2O$,	AR	500g,	1,200
3.	$NaHAsO_4 . 7H_2O$,	AR	500g,	800
4.	Silica gel for Column chromatography		3kg,	300
5.	Silica gel G. for TLC.		3kg,	500
6.	Reticular Resin D101,		10kg,	200
			Total	$ 4,000 USD

Annex 4

Procedure for Operation of M-500 IR Spectrophotometer

1. Turn the M - 500 on and let it stabilize for 1 hour.

2. Set scan time, gain and pen response. The typical setting for low energy loss samples are 3 minute scan time, gain 0 and pen response 1 seconds (cf. Note 1)

3. Push the scan/stop button (for storing reference data into memory). After reset, the M - 500 changes to the ratio mode and a true %T can be observed.

4. Turn the recorder on.

5. Set the range selector (9) to var (red) Volts (cf. Note 2)

6. Set the voltage selector (10) to 1 (red) Volt (cf. Note 2)

7. Block the beam and use the zero point potentiometer (8) to set zero %T on the chart paper (cf. Note 2)

8. Unblock the beam and set 100%T with the potentiometer for variable range expansion (7) (cf. Note 2)

9. Set the chart speed selector (3) to ext (cf. Note 2)

10. Index the pen to 4000 cm^{-1} by using the direction switch (2) and the fast speed buttion (5).

11. Set the direction Switch (2) to forward.

12. Put the sample in the M - 500's beam and push start/stop button. The recorder will draw the spectrum (cf. Note 3)

Note:

1. High energy loss samples may need a higher gain, slower speed and higher pen response time for better results.

Scan time	gain	pen responce
3	0	0.1
12	0	0.8

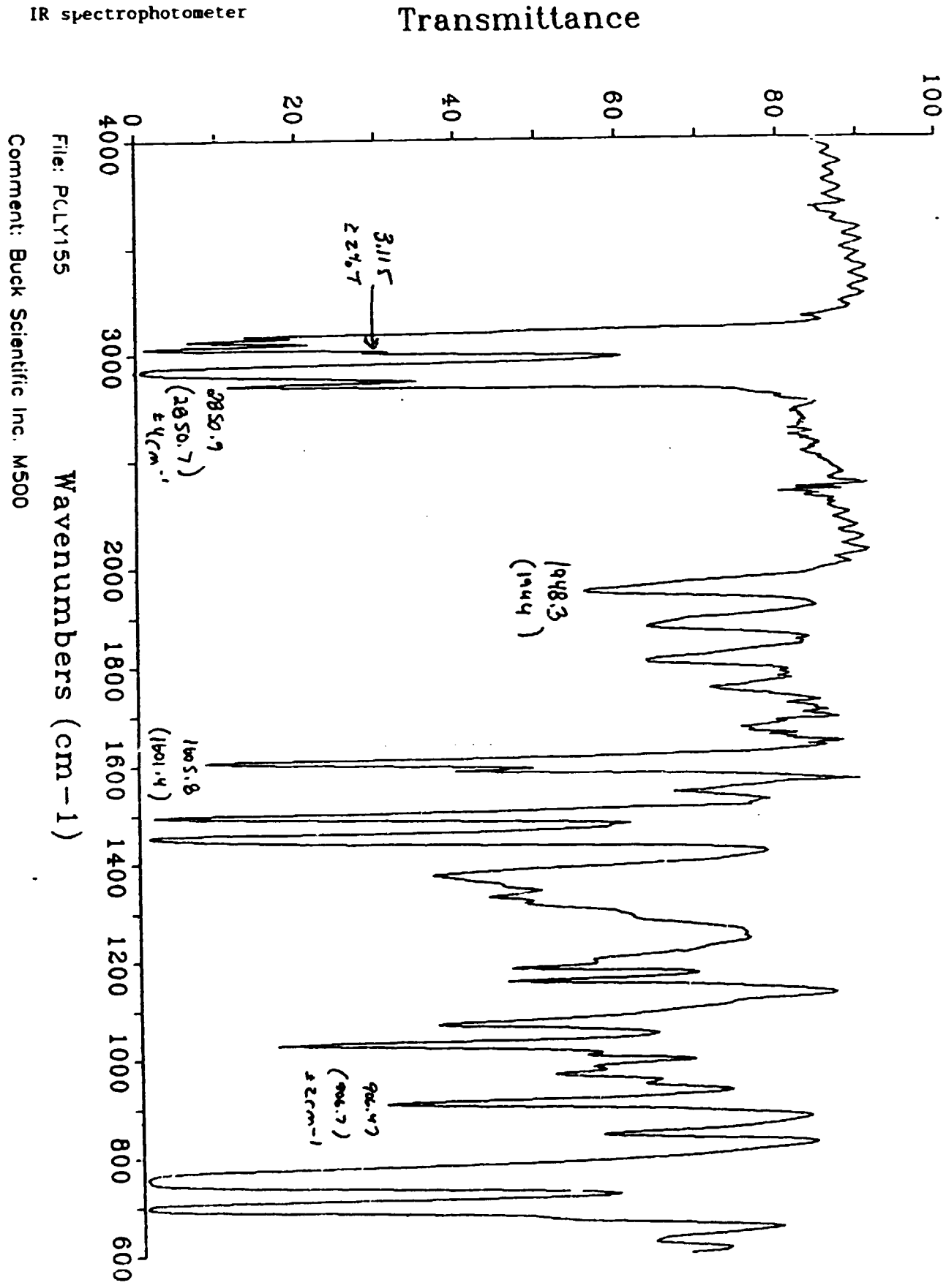
2. As routine operation, the steps 5, 6, 7, 8 and 9 can be omitted.

3. Continue to run samples with the start/stop button. For the highest performance scans, restore the reference run.

4. Place the IR instrument on a level, firm work surface, free from vibration, r. f. energy sources and excessive heat.

Annex 5

Copy of a IR spectrum measured with the M-500
IR spectrophotometer



Annex 6

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1. Introduction to Korea (in Japanese). Pyongyang, DPRK, 1982.

2. Choi Tae Sob: Tonic Traditional Medicines (in Korean), Pyongyang, 1980.

3. Korean Health Adiministration Agency: Standard Specifications of Health Foods (in Korean), Pyongyang, 1990.

4. Processing of Traditional Korean Medicines (in Korean), Pyongyang, 1975.

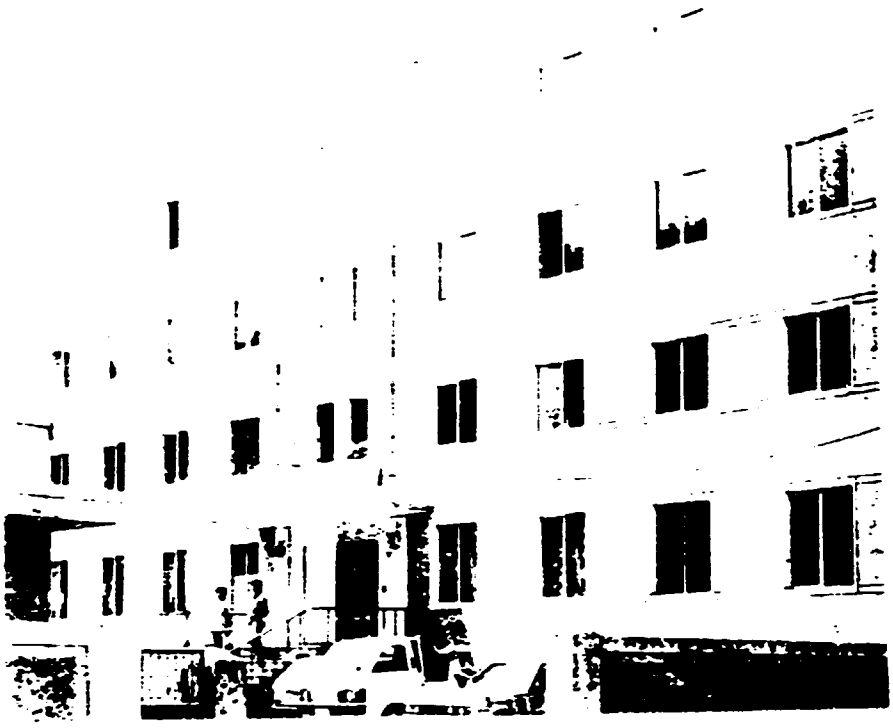
5. Animal - origin Traditional Medicines (in Korean), Pyongyang, 1991.

6. The Chemistry of Traditional Medicines (in Korean), Pyongyang, 1991.

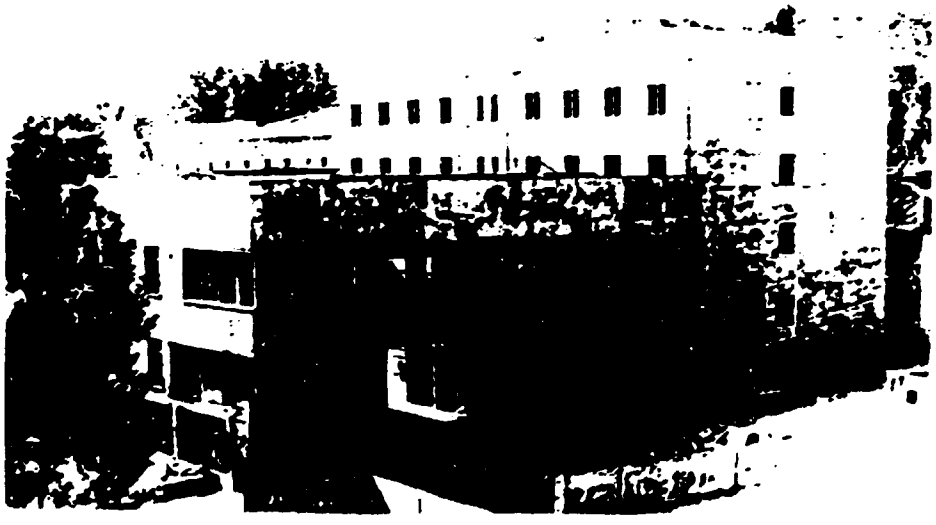
7. An Introduction to Traditional Korean Medicines (in Korean), Pyongyang, 1993.

Annex I

PHOTOGRAPHS OF THE CENTRE

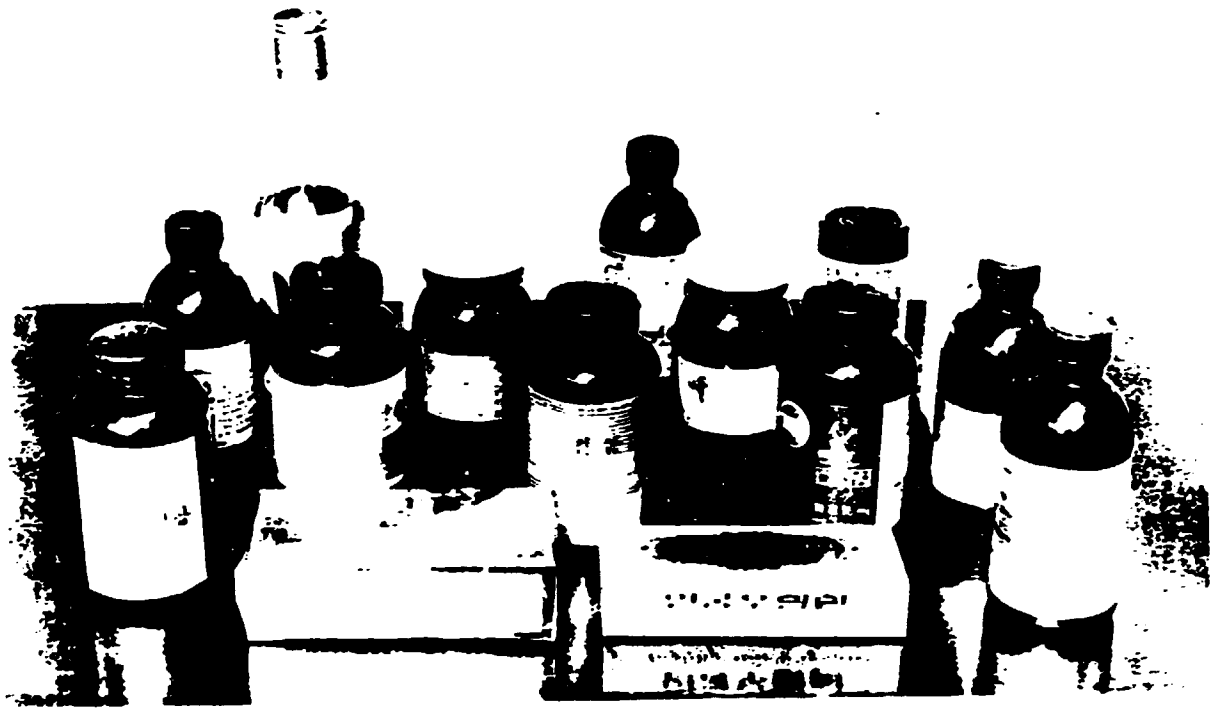


The main building of KTCTM

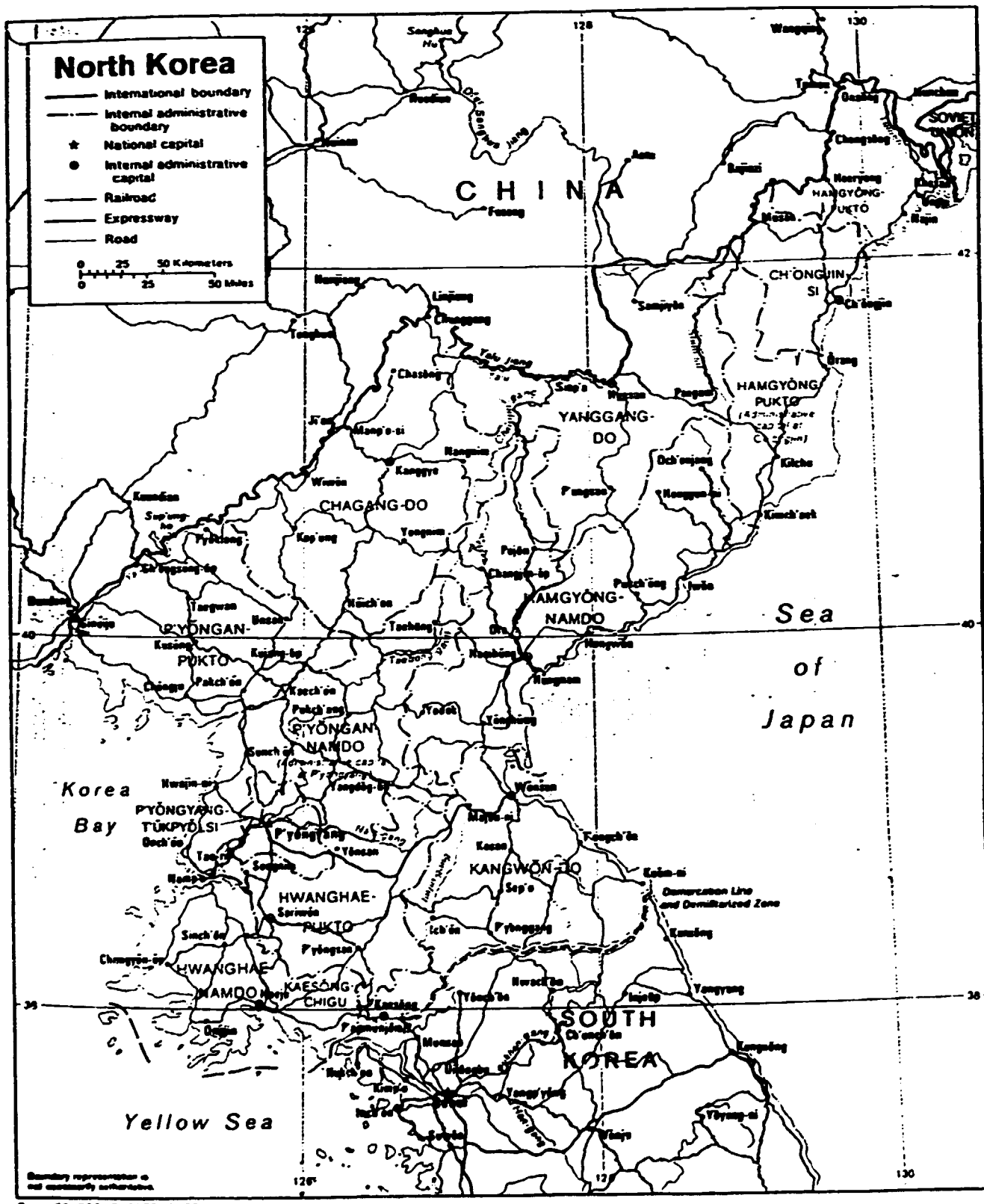


A building for housing pilot plant is under construction in front of the main building of the Centre.

The traditional Korean medicines developed by KTCTM



Annex 8



Base 504883 (546979) 3-82

The boundaries and names shown ... maps do not imply official endorsement or acceptance by the United Nations.

Annex 9

Backstopping Officer's Technical Comments
based on the work of Prof. Y.J. Chen, SI/DRK/93/802/11-01

This comprehensive report contains a review of the state of development of the manufacture of traditional medicines in DPRK and recommendations for the development of the Traditional Medicine Centre. The expert has performed his duties very well and gone beyond the scope of his mission in preparing a project document for technical assistance on the request of the Director of the Centre.

The use of testing equipment have been demonstrated and the counterparts trained in the quality control of preparations. New formulations have been developed and many new products have been recommended. The know how for the production of those has been imparted.

The GMP and quality requirements have been stressed and it is hoped that the Government will implement these recommendations soon. The requirements of equipment and training have been indicated. The consultant has imparted much know how and new methods for the development of new products and the development of the Centre.