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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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INDUSTRIAL UTILIZATION OF MEDICINAL AND AROMATIC PLANT RESOURCES FOR THE PRODUCTION OF PHARMACEUTICALS

US/GUA/84/282/11-51

THE REPUBLIC OF GUATEMALA

Technical report: Galenicals Production*

Prepared for the Government of the Republic of Guatemala
by the United Nations Industrial Development Organization

Based on the work of E. Lörincz, expert on galenical productions

Backstopping Officer: T. De Silva, Chemical Industries Branch

* This document has not been edited.

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C O N T E N T S

EXPLANATORY NOTES:

Abbreviations:

CAPROFIT:	Comisión Asesora de Productos Fitoterápeuticos (MSPAS)
CEGIMED:	Centro Guatemalteco de Información de Medicamentos USAC
CEMAT:	Centro Mesoamericano de Estudios sobre Tecnologia Apropiada
CONAPLAMED:	Comisión Nacional para el Servicios Aprovechamiento de las Plantas Medicinales
DRCM:	Dirección General de Servicios de Salud Division de Registro y Control de Medicamentos (MSPAS)
GEXPRONT:	Gremial de Exportadores de Productos No Tradicionales
ICTA:	Instituto de Ciencia y Tecnologia Agricolas
LAPROMED:	Laboratorio de Producción Medicamentos
LUCAM:	Laboratorio Unificado de Control de Alimentos y Medicamentos, MSPAS
MSPAS:	Ministerio de Salud Publica y Asistecia Social
USAC:	Universidad de San Carlos de Guatemala

I. INTRODUCTION

This report is written by: Éva Lőrincz (Hungary)
The period of mission: 10. February 1992 - 9. March 1992.
Site: Guatemala City, CONAPLAMED, GEXPRONT (Annex VI.),
Different Companies.
The aim of project: Industrial Utilization of Medicinal and
Aromatic Plant Resources for the Production of
Pharmaceuticals.
Job description (Annex I.)

On the basis of available literature and the discussions and negotiations with different companies and institutes moreover with the Ministry of Health it is safe to state: the Guatemalan ethnobotanics/ethnomedicine uses such type of medicinal plants (e.g. Tagetes lucida, Psidium guajava, Smilax lundellii, etc.) which are not used in Europe. While these plants are used for centuries, their benevolent effect is proved statistically, however not scientifically, it is necessary to support by all means the development of a stable, exactly dosable pharmaceutical product made from them.

It gives more support to the above reasoning that these plants, the teas and tinctures produced from them show no toxic effect at all.

At present the product based on medicinal plants produced in the country, do not have analytical neither pharmacological neither clinical approvements. So far only microbiological purity was demanded for permission.

There is a very expressed interest for the analytics of medicinal plant products, for the technology of extract preparation, and for the solid forms of medicines.

According to my estimations only a couple of small firms are able to manufacture solid medicine forms (like tablets and capsules), they know well however, that the stability of liquid forms is always in doubt.

The Ministry of Health and the LUCAM started the creation of norms and pharmacopoeias for medicine products of plant origin.

The work for the permission processes of manufacturing and marketing of the above products is going on.

A. Summary

1. Twice a week, in cooperation with CONAPLAMED and GEXPRONT, I held a two hours lecture in the Industrial Chamber, about the different technologies of pharmaceutical products applied mainly to the preparations of medicinal plants. (Annex II.; VIII.)
   In these lectures I dealt with
   - chemical analytical methods
   - the importance of stability in medicine
   - GMP systems
   - the construction of norms and pharmacopoeias
   - permission processes also.

2. I was invited to 9 pharmaceutical companies and laboratories, where I provided help to their problems. (Annex III.; VII.)

3. I took a part on CAPROFIT talks, about the construction of pharmaceutical norms, pharmacopoeias, and the permission processes. (see technical report)

4. I took part in the creation of GMP prescription for the production of medicines of plant origin. (see technical report)

5. I visited the Barefooted Doctors, and discussed the conditions and requirements for the planned productions of medicines of plant origin (GMP), and the types of the necessary equipment.

B. Conclusion

1. The equipment at LUCAM (instruments, laboratory setup) are on a higher level, than the one's at USAC, or at any other producer.

2. It is necessary to help Analytic and Plant Chemistry Department of USAC to the level of LUCAM, to enable them to develop new technologies and to file new medicinal products.

3. USAC should take part in developing norms and pharmacopoeias.

4. The new technologies developed by USAC should be marketed as know-how's or a contract-work construction should be developed.

5. The participation of the most developed companies in the process of norms and pharmacopoeias is desired.

C. Recommendations

1. To carry out the requirements as per the conclusions, a coordinator should be installed, who will negotiate the differences emerging.

2. USAC should be supported financially to purchase some important instruments and machines. (Annex IV.)

3. A professional help is needed to the working out of norms, pharmacopoeias and permission processes, the sooner the better.

4. USAC's Institute of Pharmaceutical Technology should participate in the working out of compositions containing active substance of plant origin.

II. TECHNICAL REPORT

A. Assessment of the situation of Galenic products

I was invited by 9 pharmaceutical companies, we discussed mainly analytical, technological and GMP questions. The experts of these companies took part on my lectures and the problems important for them were discussed. According to the program made by CONAPLAME) I spent generally two days at a company.

I have studied the issue "Preliminary plan for the production and the marketing regulation of phytoterapeutic products" assembled by CAPROFIT existing in the frame of the Ministry of Health, and I have recommended the following alterations:

The above plan should contain:

1. The description of the living plant.
2. The description of the dried plant material.
2.1. Morphological description.
2.2. Microscopic identification.
3. The maximal water content of the dried plant material in %.
4. Content of ash in %.
5. Content of acid insoluble ash in %.
6. Foreign organic matter (the proportion of stems, browned leaves, flowers and other foreign organic matter in %)
7. Content of water or alcohol extract in %.
8. Active substance content in mg/g.

9. Assay (determination methods).
10. Usual dose (single, daily).
11. Stability data, storage condition.

We have agreed that the limit values of the Guatemalan medicinal plants and the European or North-American requirements surely will not be the same, therefore the investigation methods could be adarted, but the results most probably will be dissimilar.

The other prepared plan, which we have discussed was the work titled as "The rules of registration of phytoterapeutic products".

I have recommended alterations to the prepared plan, which were accepted. At the starting material should be investigated the presence of:

1. Heavy metal
2. Herbicide
3. Pesticide

On the other hand I considered as unnecessary the statement of structural form and physico-chemical constants of the active substance. I recommended only a literature reference.

We have discussed the plan titled as "The conditions of creating companies for the production of phytotherapeutic products".

In this subject we assembled, the description:

- for buildings and rooms
- for starting materials and other materials
- for machines and instruments
- for persons concerned

prescribed also in GMP. We have dealt by documentation systems required in GMP too.

We have dealt separately with the working and of requirements for the manufacturing of galenics based on medicinal plants of trusted quality. With the aim of providing medicine to the villages far from the cities.

I have discussed in the individual laboratories by their experts the problems of quality control and technological parameters of pharmaceutical products already in production at the companies.

Whenever the required instrumentation was available, I demonstrated the investigation, but in many places the equipment is backing or nil. In this case I could recommend methods, recipes and literature.

Information about the companies are the following:

1. LANCASCO SA

According to their information they produce about 100 different medicines and cosmetics, mainly based on foreign patents. Only four of their products contains plant extract. About 130 people are working in the production, 10 white collar.

The analytical and production equipment are modern, their application is high level.

To the products containing medicinal plant extracts they buy active substance concentrate, or they produce it in part.

I provided advices to the solution of two of their technology problems. They had a syrup filtration problem, for which I recommended, that the filtration should have been done at a previous phase. The plant extract should have been filtered clear, thus after clarifying, the sugar syrup should have been filtered hot, and the two solutions unified.

Then the several raised analytical questions we have solved the determinations of the added Iodine in their preparation containing also raw plant extract.

They took it well and kept it afterwards.

2. IMPRO

The company produces 36 medicines and medicinal cosmetics developed on their own. They also manufacture their plant extracts. They have their own plantation, where they cultivate Aloe vera. They export the fresh gel and partly use it themselves. They plan to market a new antiinflammatory ointment containing Aloe gel. I supported them by advices to the technology.
Referring to their intentions of producing new pharma-cosmetics I have recommended the application of the extract of Urtica dioica, because this plant contains a large variety of vitamins and minerals.

3. ICA

About 25 different products based on plants are marketed. They produce the extracts by traditional extraction methods (macerations). At present 25 people are employed. They have granulation and tableting equipment. They have plans for capsulation of dried plant extracts. We discussed the requirements for this. They do analytical examinations only partially. The measurements of refractory indices and tablet solidness are continuous.
To the planned capsulation of the dried extracts I have recommended the addition of colloidal SiO_2, which was tested by us in laboratory scale, and the result was found as satisfactory.

4. FARMAYA

8 people in the laboratory do mainly research, documentation and microbiological work.
They market one component and multi component tea-mixtures, infusions, elixirs and tinctures. These are self-developed.
They provide their own starting goods for their farmers. Also provide advices to drying. The quality of their products is good and stable.
They do microbiological tests for others too and participate in development of new products on the ground of their ethnomedicinal knowledge.
Instead of the presently used maceration, I recommended a more effective and quicker percolation for the production of tinctures.

5. LUCAM

It is properly equipped and the staff is well trained for examining the drugs and food-products in circulation.
There is a lack of practice, some minor equipment (for example extractors) and of standards materials for testing galenics of plant origin.
For preparing the standard materials and for determining the effective substances proposal was made.
During my visit at LUCAM, the question of quantitative determination of medicines made by extracts from multi component medicinal plant was raised.
I answered the problem as follows, which gives reasons for purchasing some instruments.

Preparative thin layer chromatography seems to be the best method for separating the characteristic active substances in the different plants. This way the substance of unknown structure can be qualitatively identified.
If quantitative determination is required, a known quantity of standard substance should be runned on the thin-layer chromatogram, parallel with the plant extract, and the relative R_f values and the active substance content of the plant extract could be determined by densitometry.

6. ICTA

The institute located in Chimaltenango considers it as its main object and has it actually done, the exact identification and cultivation of plants used in ethnomedicine. One of their successful areas is the research of economical and non destructive drying. For the exact evaluation of their results, the analytical investigation of the plants is also needed.

7. THOMAE DRMANN HERVALL

The plant has 14 employees, 4 of them graduated. They produce c psules, tinctures and elixirs. At the present they work on a anti-psoriasis ointment and have some problems with its stability.
Their presently developed ointment preparation contains the water extract of Swetia humilis. We have changed the composition of the so far unstable preparation. We have concentrated the water plant extract added an emulgeator, and stabilized by colloidal SiO_2. The product showed an excellent stability afterwards, the sample prepared that time is perfect even today.

8. LAPROMED

The products are manufactured by 3 teachers and 12 pharmacy-students. At present they are working an 2 new preparations: an anti-fungus ointment and a spasmolytic, antibacterial syrup. Both of them contain concentrated plant extracts. At the development of the two products they incurred solubility and homogeneity problems. By dilution with the original solvents we have solved the problem in laboratory.

9. SIERRA

The firm is more than 100 years old. They manufacture their preparations according to old French Pharmacopoeias. They market mainly tinctures and medicinal cosmetics. At the present they do not intend to modify their used technologies.

10. Barefooted Doctors

On my assessment the clinical trials of medicinal products of plant origin will represent a lot of difficulties. I mean here the organizing job and the provision of financial background. I recommend for this aim the participation of Barefooted Doctors, who can provide an assessment about the preparations activity, after the chronic toxicity examinations and pharmacological tests of the prepared products.

11. PILOT PLANT

On the day of my last lecture series, we organized a demonstration at the experimental plant located at USAC, for the participants, where they studied the different extraction, concentration and aromatic oil preparation processes.

Due to the lack of laboratory equipment I was able to do a short manual work, common practice only in a few cases. The analytical equipment is incomplete at most of the companies. The LANCASCO company has the highest level.

I got the majority of the question from the area of the development of analytical determinations, the technological steps (extraction, concentration) and the realization of solid pharmaceutical forms.

Due to the fact that only a few have tableting and capsulating machines, in the case of medicinal plants used in ethnomedicine or having only a mild effect, I recommended the simple granulation.

B. Personal part

1. I recommend the nomination of 1-1 persons from the USAC-LUCAM-Ministry of Health and the ONUDI, who would create the organization structure of the second phase, and half-year plans about the jobs to be done.

2. USAC takes up the provision of personnel to the research works on:

   plant analytic,
   phytochemistry,
   pharmacognosy,
   pharmacology,
   pharmaceutical-technology.

3. LUCAM works out and gets the permissions, provides personnel to the requirements of official permissions and marketing.

4. USAC, LUCAM, Ministry of Health and the leading pharma-companies work out the pharmacopoeia paragraphs of medicinal products of plant origin.

C. Technological recommendation

A financial support should be extended to the successful completion of the second phase to the research and development institutes. In the Annex V. attache the list of basic instruments and equipment.

I recommend the exact working out of the rules of the permission and filing process for one plant, and for the therefrom produced preparation, and to send this document as an example to every pharma-manufacturer.

Éva Lőrincz

ANNEX I.

Job description:

Post title: Consultant in Galenicals Production

Duties: The expert will be formally attached to the organization CONAPLAMED - the National Commission for the Utilization of Medicinal and Aromatic plants. He will be responsible to UNIDO and the National Project Director under whose guidance he will carry out the following:

- Assess the available facilities and the current methods used in the production of galenicals and suggest improvements.
- Assist the laboratories to improve the production of creams, ointments, syrups, liniments, tablets and capsules incorporating plant extracts.
- Develop quality control profiles for the galenicals prepared.
- Train local personnel in all aspects of the production of galenicals.
- Recommend new and improved technologies to be introduced including any equipment and training.

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

ANNEX II.

Lecture content:

Course: The theory of preparation of Phytogalenic medicines.
Organizer: CONAPLAMED and GEXPRONT
Site: Industrial Chamber
Date: 20^{th} of Feb. - 13^{th} of March 1992
Thursday and Friday 8^{30} - 10^{30}

1. The role of pharmaceutical technology in medicine and the place of galenics in it.
2. The personnel, objective and in site requirements of the preparation of phytogalenics.
3. The division of plant based galenics according to the different pharmaceutical forms.
4. The preparation of raw materials and technological processes (from the preparation of medicinal plant to the industrial processes).
5. Liquid medicinal forms (solution with water, alcohol, oil etc).
6. Ointments (gels, creams, pastes etc).
7. Solid medicinal forms (tea-mixtures, powders, granule, tablets etc).
8. Storing, conservation, stability.
9. Quality control of starting materials, process and end products (norms, pharmacopoeias)
10. The documentation of raw materials, processes and end products of phytopharmaceuticals.
11. Authority permissions, packaging, marketing.

On every Thursday after the lecture consultations according to personal needs.

ANNEX III.

The visited companies and laboratories:

LANCASCO
IMPRO
ICA
FARMAYA
THOMAE DRMANN HERVALL
LAPROMED
SIERRA
DEPARTAMENTO DE FARMACIA INDUSTRIAL
LUCAM
ICTA
CEMAT
DRCM (Sessions of CAPROFIT)

ANNEX IV.

Important instruments for USAC:

1. Complete thin layer chromatographic equipment.
2. Densitometer.
3. Laboratory equipment for determination volatile oils from plants (e.g. apparatus according DAB 9.).

ANNEX V.

Basic instruments and equipment:

1. Laboratory equipment for different type extractions of medicinal plant or galenical preparations (20-100 g).
2. Thin layer chromatographic apparatus for qualitative analysis.
3. UV lamp (dual wavelength type, 254,365 nm).
4. Analytical balances.
5. Vacuum distillation apparatus.

ANNEX VI.

Senior counterpart staff:

Dipl. Armando Caceres, Nacional Director, CONAPLAMED
Dr. Amarillis Saravia Gómez, President of CONAPLAMED
Eng. Francisco Solorzano, GEXPRONT

ANNEX VII.

List of people met:

Dipl. Armando Leiva, LANCASCO
Dipl. Norma Gladys Contreras, LANCASCO
Hector Adolfo Ruiz Godoy, tecnical director, LANCASCO
Rafael Felipe Solares Riepele, president, LANCASCO
Dipl. Vilma Judith Solórzano, IMPRO-Aloederm
Eng. Jorge Nadalini, general director, ICA
Dipl. Gladys Rodas, ICA
Dipl. Lidia Girón, FARMAYA
Dipl. Elsa Jauregui, FARMAYA
Dipl. Dennis Santizo, FARMAYA
Dipl. Aracely de Leon, Departamento de Farmacia Industria
Dipl. V. Eugenio Cordero, Departamento de Farmacia Industria
Vicente Martinez, ICTA
Francisco Vasquez, ICTA
Enrique Godoy Duran, director, THOMAE DRMANN HERVALL
Dr. Byron E. Godoy Guiterrez, manager, THOMAE DRMANN HERVALL
Dipl. Lucrecia Pérez, THOMAE DRMANN HERVALL
Dipl. Victor Manuel Molina Cruz, general director, SIERRA
Dipl. Marta Sardá, SIERRA
Eng. Byron Baldizon, Pilot Plant, USAC
Edwin Fuentes, Pilot Plant, USAC
Carlos Cardona, Pilot Plant, USAC
Antonio Medrano, Pilot Plant, USAC
Dipl. Sergio Ortiz, Professor of Phytochemistry, USAC
Dipl. Beatriz Medinilla, Professor of Pharmacognosy, USAC
Eng. Williams G. Alvarez Mejia, Professor of Chemical Engineering USAC
Dipl. Roberto Benavides, LUCAM

barefooted Doctors :

Dr. Anne Bourgey, doctor
Christine Masse, academy of hygiene
Thierry Muller, chemical engineer
Jean Pierre Nicolas, botanist

ANNEX VIII.

List of participants of lectures:

Jiménez, Beatriz B. de, CEGIMED-USAC
Cáceres, Armando, CONAPLAMED
Muller, Thierry, CONAPLAMED/Med.Des.
Fernández, Marta Regina, DGSS
López, Marta Elena, DGSS
Sesam, Sandra L., DGSS
De León, Aracely, Esc. Farmacia
Saravia, Amarillis, Esc. Farmacia-CONAPLAMED
Estrada, Patricia, Escuela Química, USAC
Guzmán, Nora, Escuela Química, USAC
Montenegro de Scheel, Flora, Escuela Química, USAC
Solis, Jorge, Facultad AGRONOMIA
Girón, Lidia, FARMAYA
Jaruegui, Elsa, FARMAYA
Santizo, Dennis, FARMAYA
Rodas, Gladys, Laboratorio ICA
Solórzano, Vilma, Laboratorios IMPRO
Gonzáles, Alba, Laboratorios PROM
Orellana, Carlota, Laboratorios SIERRA
Sardá, Marta, Laboratorios SIERRA
Herrera, Rodrigo, Laboratorios THOMAE
Pérez, Lucrecia, Laboratorios THOMAE
Contreras, Norma Gladys, LANCASCO
Leiva, Armando, LANCASCO
Recinos de Barrera, Alba Nory, LAPROMED
Aguilar, Olga L., LUCAM
Benavides, Roberto, LUCAM
de Beltrán, Beatriz Estrada, LUCAM
Santo de Girón, Aída, LUCAM
Sierra L., Jorge, STCC
Carolina Perrot de Molini, Laboratorios PROM

T. De Silva/jbg
1 July 1992

Backstopping Officer's Technical Comments
based on the work of Ms. E. Lõrincz
US/GUA/84/282/11-51

The consultant has carried out the duties as per job description. The galenicals production in Guatemala has encountered many problems for which the consultant has suggested remedial action. She has also adviced the national quality control laboratory of LUCAM on how to improve the monographs preparation and specifications for plant products.

A course of lectures conducted by the consultant has enriched the know how of the scientific staff of a number of different institutions. Furthermore this course has strengthened the scientists' knowledge on basic principles thereby increasing their confidence and abilities in problem solving.

The account of activities in terms of product development is very concise. The report therefore cannot serve as a means of dissemination of know how to readers. This may be to safeguard the interests of the different private companies assisted by the consultant.