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Issue Paper I

SOME KEY ASPECTS IN THE INDUSTRIAL UTILIZATION OF MEDICINAL PLANTS: TRANSFER OF TECHNOLOGY FOR GENETIC IMPROVEMENT; FACTORY-PRODUCED HERBAL MEDICINE; AND PROCESS TECHNOLOGY DEVELOPMENT AND PRODUCT STANDARDIZATION

Prepared by

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I. BACKGROUND

1. The importance of medicinal plants as a source of drugs and therapeutic agents in contributing to the health-care programmes and economies of developed as well as developing countries is well-established. Medicinal plants are utilized in three main ways: (a) they can be used unmodified as therapeutic agents; (b) they provide natural products for direct use or for the partial synthesis of drugs; and (c) they provide molecular models used by scientists to synthesize new drugs.

2. In order to improve the economics of the subsector, there is a need to upgrade cultivation techniques and improve production technologies of pharmaceuticals derived from plants. The operations for the attainment of such development are:

(a) Agronomic activities relating to the improvement of the percentage yield of the required active principles within the plant itself, i.e. genetic improvement;

(b) Technological activities, which are primarily directed towards generating technologies appropriate for the processing of each plant species. Considerable research and development efforts go into these activities. The process of extraction, isolation, formulation and where relevant synthetic manipulation becomes the acquired knowledge and property of the technology holder who has carried out such developmental efforts;

(c) Chemical activities pertaining to the isolation and characterization of the chemical structure of individual phytochemical constituents of the plant. They also include the development of quality-control methods and the chemical modification of structures so as to obtain the desired biological effects. These chemical activities are characteristic of the established approach to industrial drug development;

(d) Biological activities covering the main operations designed to ensure the safety and efficacy of drug preparation, including toxicological testing etc. to meet pharmaceutical regulatory requirements.

3. In order to improve the supply of medicinal plants as raw materials or as processed products, guidelines have been prepared by the United Nations Industrial Development Organization (UNIDO) with the aim of assisting developing countries in this regard.

4. Keeping in view the significant role of medicinal plants and the important areas of activities related to their utilization, there is an urgent need for developing countries to begin generating some of the needed technologies themselves. An expert group meeting convened by UNIDO to discuss this topic recommended that UNIDO should discuss the industrial utilization of medicinal plants at the Third Consultation on the Pharmaceutical Industry, focusing attention on the following main areas: 1/

(a) Technology for the genetic improvement of medicinal plants;

(b) Factory-produced herbal medicine;

(c) Process technology development and product standardization.

5. Background papers covering these three main areas for the industrial utilization of medicinal plants have been prepared to facilitate the presentation and discussion of this issue at the Third Consultation. 2/

II. ISSUE 1

6. Participants at the Third Consultation are invited to discuss and consider actions to be taken on the three main areas under issue 1: Industrial utilization of medicinal plants.

A. Technology for genetic improvement of medicinal plants

7. There is a general need to transform the practice of collecting wildly grown plants into a standard method of cultivation of medicinal plants in order to stabilize supply, maximize effective chemical contents and improve economic returns in developing countries embarking on the cultivation of these plants with a view to industrial processing. This calls for concerted efforts in improving knowledge about natural occurrences of medicinal plant species, their physical and chemical properties, agro-techniques concerning their cultivation and the genetic improvement of plant species through the use of conventional as well as new techniques. It also entails: the analysis of factors having a bearing on the choice of medicinal plants for genetic improvement; the improvement of selected medicinal plant species at national and regional levels; the collection, maintenance and long-term preservation of the genetic diversity of medicinal plants; selection; and the conventional breeding of priority plant species. Work should cover such techniques as: mutation and ploidy breeding; in-vitro culture techniques and the micropropagation of genetically improved medicinal plants; and protoplast fusion and recombinant DNA transfer techniques for the genetic improvement of medicinal plants.

8. The Consultation may wish to consider whether additional work should be undertaken by the pharmaceutical industry, specialized agencies such as UNIDO, the Food and Agriculture Organization of the United Nations (FAO), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Health Organization (WHO), the International Atomic Energy Agency (IAEA) and other international organizations such as the International Union for Conservation of Nature and Natural Resources (IUCN), as appropriate, in the following areas at national and international levels:

(a) Identifying the areas of maximum genetic diversity for selected plants and their near-wild relatives. Collection and conservation and exchange of gene-pool material from geographic regions by linking national efforts, supplemented, where necessary, through international funding;

(b) Adopting a programme for the improvement of a selected plant species by conventional and modern breeding methods;

(c) Initiating a pilot project for the improvement of 5-10 selected priority species in scientifically recognized centres in developing countries to demonstrate the techniques and methodology to other developing countries;

(d) Establishing national systems to ensure the continuous flow of propagating materials needed for the culture of medicinal plants as raw materials for industrial processing;

(e) Facilitating the production of nucleus breeders, aiming for the free flow of genetic stock and improved cultigens;

(f) Publishing of documents on available cultigens.

B. Factory-produced herbal medicine

9. Traditional herbs and medicinal plants are widely grown and used in developing countries. They are also a source of important export earning. The most immediate objective in this field is to transform traditional products into scientific formulations that could be prescribed and administered according to accepted professional practices. Furthermore, there is a need to apply modern scientific procedures in the extraction of active principles and in the development and registration of marketable, safe, efficacious and stable formulations.

10. Thus, a modern industry could emerge that is based on sound scientific principles and adapted for use in developing countries. In Asia, Africa and Latin America successful methodologies have been developed to utilize modern science and technology in the improvement of traditional pharmacopoeial preparations. The pre-eminent case is in China where the successful integration of improved traditional preparations into current therapy is evident. A case study of factory-produced herbal medicine in China has been prepared to serve as an example in this regard. The methodology for cultivation, processing, clinical trials and dispensing is available. The model may be of interest to developing countries where the necessary level of infrastructure is available.

11. UNIDO has acquired extensive experience in technical co-operation with developing countries in the industrial utilization of medicinal plants. From this experience, the following criteria appear to be most crucial to the success of technology transfer in this field:

(a) Social acceptance of traditional therapies;

(b) Political will to utilize and improve these therapies using the techniques of modern science;

(c) The availability of an appropriate infrastructure: scientific research personnel, technicians, artisans, farm managers, agro-techniques etc.;

(d) A nucleus of committed multidisciplinary goal-oriented development personnel to commence activities;

(e) Concepts and initiatives in marketing new products both locally and outside the country;

(f) The potential for entrepreneurship.

12. Accordingly, UNIDO would like to continue to contribute to the achievement of health-care objectives through promoting the production of standard-quality herbal medicines made in factories in accordance with the principles of good manufacturing practice.

13. The Consultation may wish to consider whether any action should be taken on the following:

(a) The Chinese model based on the development of drugs through industrial processing and clinical trials may be considered for application in other areas where the necessary level of infrastructure is available. Other models may be studied, and information may be made available to developing countries;

(b) Techno-economic benefits and barriers associated with the establishment of this industry may be studied;

(c) International organizations may consider collaboration with the Chinese authorities in holding a series of practical workshops to enable interested developing countries to familiarize themselves with the methodologies involved in developing this industry. Additional work will have to be considered in the adaptation of such a model to the specific conditions of each interested country. Further work may also be considered to study other relevant models in this field;

(d) International co-operation may be encouraged in the establishment and continuous updating of a statistical data base to monitor the development of herbal medicine on national, regional and international level;

(e) Consideration may also be given to the possibilities of co-operation between industrialized and developing countries in the preparation of documentation for the registration and approval of phytotherapeutic specialities as well as in industrial research and development projects when preliminary scientific evidence warrants detailed pharmacological investigations.

C. Process technology development and product standardization

14. A considerable amount of research has been carried out on the phytochemical constituents of medicinal plants indigenous to several developing countries. There is a need to make use of the results of this research with a view to developing standardized, safe and stable preparations from medicinal plants for primary heath-care use as well as some products with export possibilities. This need is best served by enabling the developing countries to have access to suitable pilot-scale facilities for technology adaptation and development. It requires a pilot-processing facility capable of carrying out a multiplicity of unit processes as and when each or several of them are needed.

15. A versatile model pilot-plant assembly could be designed to serve such a purpose and would have the advantage of being constructed and installed relatively cheaply in selected developing countries. The specifications for a versatile poly-functional pilot plant assembly would include, for example:

Plant capacity. Model I: 80-100 kg per charge, dry-weight basis; model II: approximately 150-250 kg per charge, dry-weight basis.

Characteristics of raw material to be processed. Plant material (usually in dried condition): leaves, woody stems, barks, wood, roots, rhizomes, fruits nuts, whole shrubs. Density of material: between 0.2-0.3.

Final products. Aqueous extracts; dried extracts; solvent extracts (polar and non-polar solvents of a volatile and inflammable nature, as well as those which may be toxic e.g. benzene); alcoholic and aqueous alcoholic extracts; steam distillates of essential oils.

Specific operations to be carried out. Comminution of plant material (crushing, pulverizing to the appropriate dimension); percolation with water or organic solvents at ambient as well as higher temperatures; batch-wise aqueous/agareous alcoholic extraction; continuous extraction with organic solvents; removal of solvents and solvent recovery; drying of products; steam distillation of volatile constituents; separation of volatile, water-immiscible oils; filtration and purification by crystallization; fractional distillation.

Major components of the pilot-plant assembly. One extractor vessel, fitted with heating device (steam jacketed), inside working pressure atmospheric, with loading device including perforated grids or wise-mesh basket; one (condenser) tubular-type heat-exchanger suitable for solvent recovery and distillation of essential oils; one Florentine vessel for separation of oil heavier than and lighter than water; one reduced-pressure solvent evaporation system consisting of reboiler with matched capacity (or design possibility to utilize extractor vessel itself) with steam-heating device (including one packed column with reflux exchanger, cooling device, receiving vessel with matched capacity and a safety filter for miscella); one compatible vacuum pump with explosion-proof motor; one crusher with a capacity of approximately 30-50 kg/h for model I and 100 kg/h for model II.

Notes: All pipelines and valves and all parts of the pilot-plant assembly in contact with the solvent or product must be of high-grade stainless steel. Water and steam pipelines may be of galvanized steel or other suitable material. All service requirements and other information should indicate the following:

Steam consumption (kg/hour)
Water consumption (m^3/hour)
Scaffolding and foundation requirements
Dimensions of assembly and layout plans
Line diagrams of all individual items and total assembly

16. In addition to pilot-plant facilities, it is necessary that developing countries should have the benefit of modern analytical instrumentation in order to provide the basis for quality assurance to ensure compliance with regulatory standards and to monitor procedures for isolation, separation and assay in the case of the products developed.

17. The Consultation may wish to consider the following:

(a) International organizations such as UNIDO may be requested to prepare a set of designs with adequate practical details for the establishment of a versatile pilot plant at three alternative capacity levels. Countries having the ability to design and equip such pilot plant may assist UNIDO in this effort. Advice on the steps to be taken in this regard may be considered by the Consultation;

(b) Developed countries may be requested to contribute, through international organizations, by providing information required for the elaboration of a compendium of monographs on selected plant-derived preparations with international market potential. These monographs should include the required quality standards, together with all necessary analytical parameters.

Notes

1/ "Report of the Expert Group Meeting on Medicinal Plants and Other Issues" (IPCT/20/SPEC.).

2/ "Process technology development and product standardization" (ID/WG.466/13(SPEC.)); "Transfer of technology for the genetic improvement of medicinal plants" (ID/WG.466/14(SPEC.)); and "A Study on Phytopharmaceutical Supply System in China".