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GUIDELINES FOR THE CHEMICAL AND BIOLOGICAL ASSESSMENT OF HERBALS AND HERBAL PREPARATIONS *

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Introduction and scope

Medicinal plants and parts thereof represent a primary source of products for the pharmaceutical field.

Greater and greater amount of medicinal plants are used by the pharmaceutical industry for the production of high content standardized extracts, of chemically pure active constituents and of intermediates for the semi-synthesis of rare natural products or of new active compounds.

At the same time, the traditional use of vegetable drugs and preparations thereof has increased too, both in developing countries, where traditional medicine is still of great therapeutical, social and economic importance, and in industrialized countries, where an over-growing proportion of the population is using vegetable drugs "derivatives" for self-medication.

In order to avoid that this increasing traditional use of medicinal plants takes place unmethodically, beyond the rules that govern each product intended to the therapeutical field, it is necessary to settle some guidelines for testing vegetable drugs, vegetable drug preparations and formulated herbal preparation, which are at the same time simple and reliable.

The purpose of this document is just to suggest a whole of controls which allow the standardization of vegetable drugs, of vegetable drug preparations and of formulated herbal preparation.

On this purpose, some general considerations must be stated:

a) the guidelines for the control of a vegetable drug and therefore of a

vegetable drug preparation and of a formulated herbal preparation must take into account that the material to be examined has a complex and "incostant" composition.

Due to this:

- the analytical limits cannot be so strict as in the case of chemically pure products.
- the identification tests must be specific and extended to several groups of substances so as to attain a cross-evidence of the composition. The importance of a specific identification involving several groups of substances is clear: it allows to highlight adulterations and degradation of the test material. Moreover, in the case of vegetable drug preparations a cross-identification allows to ascertain the "reconstruction" of extracts, the latter being attained by diluting an extract with a high content of a given constituent with large quantities of excipients.

b) the standardization of a vegetable drug and of a preparation thereof is not a mere analytical operation, i.e. it cannot be limited to the identification and to the assay of an active constituent or of a marker.

Standardization means the whole information and controls which can be useful to guarantee the constancy of composition - hence the standardized quality - of vegetable drugs and preparations thereof.

For instance, in case of an alcoholic fluid extract, the standardization controls must include the determination of physico-chemical characteristics. These are not just routine tests: each has its own value and importance as concerning either the

stability (pH, alcohol degree) or the constancy of content of total extractive material (total solids).

c) because of the complex nature of the vegetable drugs, the process of manufacture of a vegetable drug preparation is crucial to constancy of quality. For this reason, the standardization of a vegetable drug preparation must include the description of its manufacturing process (extraction solvent, particle size, type of extraction, concentration details, possible purification, etc.) which must be kept constant because only through a constant extraction procedure it is possible to obtain, from a standardized vegetable drug, a standardized vegetable drug preparation.

d) vegetable drugs are, inevitabily, "inconstant" because several elements affect their composition: age and origin, period of harvest, method of drying, etc. In order to by pass some of the causes of incostancy, cultivated plants should be used instead of spontaneous plants which are often heterogeneous as far as the previously cited elements and, consequently, the active constituent content.

Cultivated plants offer many advantages in terms of quality, in addition to the ecological ones:

- cultivation can be carried out under homogeneous climatic and soil conditions.
- the age of the plants and exact information on their active constituent content, and therefore on their period of harvesting, are readily available data.
- they can be picked "at the right time" and quickly.
- they can be dried under controlled conditions of time and

temperature. It should be never forgotten than a homogenenous and correct drying often represents the most delicate and essential step in the entire manufacturing process.

Besides proposal on how to standardize vegetable drugs and their derivatives intended to the therapeutical use, this document gives also a model of documentation for introduction of herbal medicines into health care delivery.

AN OVERVIEW OF DIFFERENCES IN REGULATORY REQUIREMENTS BETWEEN COUNTRIES

The problem of the harmonization of the regulatory requirements for obtaining a marketing authorization for proprietary medicinal products has been faced by the countries of the European Economic Community with surely positive results as nowdays the application for marketing authorization follows precise and clear rules concerning the type and the quality of the documentation to be submitted to the Health Authorities.

At the present moment, no special rules have been settled - at Community level - for the herbal remedies and so they must comply with the general regulatory requirements as any other proprietary medicinal product.

Only the "Part II C - Control of starting materials" of the chemical and pharmaceutical documentation prescribes additional requirements for herbal remedies.

Nevertheless, in spite of this Communitary situation which does not provide special rules for the herbal remedies, in each EEC country the situation is not so uniform.

All the EEC countries agree upon the necessity of a chemical and pharmaceutical documentation including the detailed description of all the controls carried out on starting materials, intermediates, finished products, of the manufacturing process, of the stability studies. Just because they contain active ingredients of "complex and inconstant" nature, the herbal remedies must meet severe - and realistic - quality controls, in order to guarantee constancy of quality and therefore of activity.

Different and not heterogeneous is the situation adopted by national authorities vis-à-vis the pharmaco-toxicological and clinical documentation.

Beside countries which consider the herbal remedies as usual medicinal specialities and therefore subjected to the Communitary general rules, there are others that allow to use a "semplified" dossier as far as pharmaco-toxicology and clinics.

This occurs mainly in France, and in part in West Germany, U.K. and Belgium, where the Health Authorities accepted the principle that "the traditional use of a vegetable drug or of a vegetable drug preparation can be accepted as an evidence of its safety and therapeutical activity and makes not compulsory the submission of new clinical data with the proviso that the requested indications correspond to the traditional use of the vegetable drug or of the relevant preparation".

Of course a new indication, not corroborated by a traditional experience, must be supported by pharmacological and clinical data.

We consider this philosophy "traditional use allows traditional indications" adopted by the French Ministry of Health (1, 2) particularly interesting and such to constitute a basic model to be followed.

GENERAL DISCUSSION ON METHODS OF ANALYSIS OF RAW MATERIALS, INTERMEDIATES AND FINISHED PRODUCTS

The standardization is the whole of information and controls which guarantee the constancy of composition - hence the constancy of activity - of a vegetable drug or a vegetable drug preparation or a formulated herbal preparation.

The chemical analysis, even if represents the most important part of the standardization, must be completed:

- for the vegetable drugs, with information on site and period of harvest, stage of vegetation, treatment during growth (use of pesticides), method of drying, storage (use of fumigation agents).
- for vegetable drug preparation, with information on the process of manufacture (type of extraction, solvent, particle size, conditions of concentration, possible purifications, possible addition of excipients to adjust the vegetable drug preparation to a certain level of constituents with known therapeutic activity or for any other purpose) and on storage conditions.
- for formulated herbal preparation, with information on storage conditions and validity period.

We list hereunder the controls to be carried out, unless justified, on vegetable drugs, vegetable drug preparations and formulated herbal preparations.

Vegetable drugs: macroscopical and microscopical characters; foreign matters; total ash; toxic metals; moisture; pesticide residues;

fumigation agent residues; swelling index (for some drugs); foaming index (for some drugs); hemolytic activity (for some drugs); identification of the main constituents; quantitative determination of constituents with known therapeutic activity or of the main markers; total aerobic microbial count.

Vegetable drug preparations: characters; solubility; total solids; alcohol degree; residual solvents; water; pH; toxic metals; qualitative and quantitative chemical profile; total aerobic microbial count; pesticide residues; stability studies in normal and stressed conditions.

Formulated herbal preparations: qualitative and quantitative chemical profile; disaggregation time (for solid formulations); stability studies in normal and stressed conditions.

Rather than divide the methods of analysis into chemical and instrumental methods, it is more realistic to divide the methods used for the qualitative identification and the quantitative determination into specific and nonspecific methods.

For the identification tests of vegetable drugs, vegetable drug preparations and formulated herbal preparations, the chromatographic techniques now available (TLC, HPLC, GLC) supply results that one may regard as truly satisfactory.

We repeat here again that the chromatographic identification must not be confined to a single product but extended to several groups of substances so that a better evidence of the composition of the vegetable

drug can be attained. In addition, cross-checks on several substances are a prerequisite for an objective study of the stability of a vegetable drug preparation and of a formulated herbal preparation.

Some chromatographic techniques, especially HPLC and GLC, have to be considered as the most suitable also for the quantitative determination of vegetable drugs and derivatives thereof.

Nevertheless, not always these techniques are available: for a quantitative determination equally satisfactory results can be obtained from a combination of nonspecific methods with specific chromatographic techniques.

As a rule, vegetable drugs contain several products with similar structure: in the lack of a specific HPLC or GLC assay, other methods (spectrophotometry, colorimetry, gravimetric determinations, ester or acid or hydroxyl or iodine values) must be used: in this particular "complex" situation these methods give only "global" results and they must be combined with specific chromatographic identification.

This is for instance the general practice of many Pharmacopoeias: the quantitative determination of total alkaloids, hydroxyanthracene derivatives, total anthocyanosides, etc. is always combined with specific TLC identifications.

As far the biologic methods is concerned, nowdays they are essentially confined to the microbial contamination control according, for instance, to the procedure of the European Pharmacopoeia, 2nd ed., V.2.1.8 for the products not required to comply with the test for sterility.

The acceptable limits for vegetable drug preparations are:

- bacteria less than 10^4/g

- fungi, moulds and yeasts, less than 10^2/g
- Coliform bacteria, Salmonella species, Staphylococcus aureus, absent.

In the case of vegetable drugs, broader limits must be accepted. Proposed limits could be:

- bacteria, less than 10^7/g
- fungi, moulds and yeasts, less than 10^4/g
- Coliform bacteria, Salmonella species, Staphylococcus aureus, absent.

DOCUMENTATION REQUIREMENTS FOR INTRODUCTION OF HERBAL REMEDIES INTO HEALTH CARE DELIVERY (a) NON-PRESCRIPTIVE, (b) PRESCRIPTIVE

a) A realistic model of documentation requirements for the introduction into health care delivery of non-prescriptive herbal remedies is represented by the present French situation.

In 1986 and 1987 the French Ministry of Health published two papers, the one (1) concerning the application for marketing authorization of medicinal proprietary products containing vegetable drugs and the other (2) concerning the application for marketing authorization of medicinal proprietary products containing vegetable drugs endowed with laxative activity.

The first document contains both a list of 112 plants largely used in traditional medicine and a list of 20 "traditional" indications relating to these drugs or to the relevant derivatives (extracts, powders, tinctures).

Each therapeutic indication is introduced by "Traditionally used in ..."

For obtaining the marketing authorization for these non-prescriptive medicinal proprietary products, the French Ministry of Health asks for a "simplified" dossier containing mainly a chemical and pharmaceutical documentation whose requirements correspond roughly to the EEC ones.

As far as pharmaco-toxicology and clinics, no particular documentation is required with the proviso that the indications required for the non-prescriptive medicinal speciality must

correspond to one of the 20 indications listed in the document.

The only exception as concerning the toxicological documentation is represented by the requirements for any alcoholic preparation obtained with an alcohol strenght of more than 30° and that has not been used traditionally in that form. For these vegetable drug preparations the results of specific toxicological studies (DL_{50} in the rat, 4 week toxicity by oral route in the rat) have to be submitted.

Also in the case of laxative vegetable drugs and relevant preparations a "simplified" dossier is admitted, according to the general rules published in the first documents: it is important to put into evidence that in the case of laxative drugs, rules are given also for dosage and posology.

b) For prescriptive herbal remedies containing as active ingredients vegetable drug preparations either not traditionally used in the requested indications or never previously used in therapeutics, a "complete" dossier must be submitted: a totally satisfactory model is represented by a recent EEC document (3) which contains also some specific requirements for the control of vegetable drugs, vegetable drug preparations and formulated herbal preparations.

Definition of major terms

For the purpose of this study, certain repeatedly used terms are defined as follows:

VEGETABLE DRUGS are fresh or dried plant materials used for medicinal purposes.

VEGETABLE DRUG PREPARATIONS are powdered or comminuted vegetable drugs, extracts, tinctures, fatty or essential oils, juices expressed from fresh vegetable drugs. The production of some vegetable drug preparations, e.g. extracts, fatty and essential oils, can involve a fractionation, purification or concentration process. However, chemically defined mixtures of constituents or isolated constituents of vegetable drugs are not vegetable drug preparations.

Vegetable drug preparations can contain other substances (diluent, preservatives): they form part of the vegetable drug preparation and must be mentioned (see "Vegetable drug nomenclature").

FORMULATED HERBAL PREPARATIONS are pharmaceutical preparations containing as active ingredients exclusively vegetable drug preparations.

A vegetable drug preparation is regarded as one active ingredient in its entirety, regardless its constituents with therapeutic activity are known or not.

ACTIVE CONSTITUENTS are chemically defined substances or group of

substances which determine the therapeutic activity of a vegetable drug and/or of a preparation thereof.

INDICATORS (or MARKERS) are chemically defined constituents of vegetable drugs and/or preparations thereof which are of interest for control purposes.

The problem of a rational nomenclature for vegetable drugs and for vegetable drug preparations is of fundamental importance for the researchers and the health authorities to compare scientifically and economically herbal remedies containing the same active ingredient(s).

VEGETABLE DRUG NOMENCLATURE. A vegetable drug must be uniquely defined by its correct botanical name and authority and by the part of the plant actually used. Example: Cinchona succirubra Pavon, bark.

When a fresh drug is used, this must be stated, because this factor is crucial to the composition of the vegetable drug. Example: Vaccinium myrtillus L., fresh fruits.

If the constituents which determine the therapeutic activity are known, their quantity may be given. Example: Atropa belladonna L., leaves, containing ...% of total alkaloids calculated as hyosciamine.

VEGETABLE DRUG PREPARATION NOMENCLATURE. As a vegetable drug preparation (see previous definition) may be either a powdered vegetable drug, or an extract, a tincture, etc., a unique nomenclature for so different preparations may not be adopted.

a) In the case of powdered or comminuted vegetable drugs the same nomenclature as the vegetable drug must be adopted.

If any other substance is added during the manufacturing to adjust the vegetable drug preparation to a certain level of constituents with known therapeutic activity, or for any other purpose, the added substance(s) must be mentioned as "other ingredient(s)" and the vegetable drug as "active ingredient". Example:

Active ingredient	
Atropa belladonna L., leaves, corresponding to 3 mg of total alkaloids calculated as hyosciamine	900 to 1000 mg
Other ingredient	
Dextrin	0 to 100 mg

b) In the case of total extracts, the vegetable drug name must be followed by the extraction solvent used, the ratio of the vegetable drug to the extract and the physical form (fluid, soft and dry). Example:

- Rhamnus purshiana D.C., bark, 1:1, 20% ethanolic fluid extract
- Rhamnus purshiana D.C., bark, 6:1, 60% ethanolic dry extract.

If the constituents which determine the therapeutic activity are known, their quantity may be given instead of the ratio vegetable drug/extract (see example).

If any other substance is added during the manufacturing of the extract to adjust to a certain level the active constituent contents, or for any other purpose, the added substance(s) must be mentioned as an "other ingredient(s)" and the extract (genuin extract) as the "active ingredient". Example:

Active ingredient	
Rhamnus purshianus D.C., bark, 60% ethanolic dry extract corresponding to 10 mg of hydroxyanthracene glycosides, calculated as cascaroside A	84 to 100 mg
Other ingredient	
Dextrin	0 to 16 mg

c) Purified extracts. The manufacturing of a purified extract involves fractionation or purification steps (generally protected by a patent) which are not simple defatting operations but processes that are far more important as per the content of active constituents, in order to increase it appreciably above that in a total extract. For these extracts, the general nomenclature previously reported for the total extracts can not be adopted.

A satisfactory nomenclature may be the vegetable drug name followed by terms such as "anthocyanoside complex" or "liposoluble fraction (or complex)" or "total alkaloids". The indication of the physical state may become superfluous, because these purified extracts are practically always in the dry state or, in the case of liposoluble fraction, oily products.

The nomenclature of a purified extract must always include the statement of content of the active constituents. A brand name, in brackets, may be added. Examples:

- Vaccinium myrtillus L., fresh fruits, anthocyanoside complex containing 35% of anthocyanosides (Myrtocyan^{R})

- Atropa belladonna L., leaves, 90% total alkaloids calculated as hyoscyamine.
- Serenoa repens, seeds, liposoluble fraction, containing 90% of C_6 to C_{20} linear chain fatty acids.

d) Tinctures. The vegetable drug name must be followed by the extraction solvent used and by the ratio of the vegetable drug to the tincture. Example:

Valeriana officinalis L., roots, 1:10, 70% hydroalcoholic tincture.

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