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Medicinal Plant Derivatives: Regulatory and Economic Aspects (**)

The new European Economic Community rules cover all aspects of the applications for marketing authorizations for proprietary medicinal products: chemistry, toxicology, pharmacology and clinics.

While some countries, like the United Kingdom and France, have provided themselves with special regulations for the registration of medicinal plants and their derivatives, allowing the use of simplified dossiers for the toxico-pharmacological and clinical aspects, all countries seem to be moving towards a "reasonable" acceptance of the EEC regulations on the chemical side (see the end of this paper).

Let us now see, point by point, how one can "reasonably" comply with the new multistate procedure of the EEC when it comes to registering a proprietary medicinal product whose active constituent is an extract or other derivative of medicinal plants that is not a chemically pure product.

Total or purified extracts, tinctures, fats and essential oils may be grouped in a single category definable as "preparations from vegetable drugs": whatever their content of active or characteristic constituents, they are all more or less complex mixtures of natural products.

These preparations from vegetable drugs thus range from traditional total extracts through increasingly purified extracts to products with a high content of active constituents, which are actually marketed under names that suggest pure products. The most well-known case is certainly silymarin, a natural mixture of several products whose three principal constituents, silybin, silydianin and sylicristin, are present in high percentages and practically constant reciprocal ratios.

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1) Regulatory Aspects

Nomenclature

The problem of a rational, standardized nomenclature has been satisfactorily solved for pure products, whether synthetic or extractive.

In the case of extracts, the situation is quite different and, unfortunately, confused, because there is no single, universally accepted way of naming an extract.

This situation creates confusion and uncertainty: it prevents the comparative assessment of the pharmacological and clinical results obtained by different teams of researchers and makes it impossible for the health authorities to compare proprietaries containing extracts of a given drug on the basis of rational and homogeneous names, thereby involuntarily backing wrongness in doses and prices. All this, let us make no bones about it, throws discredit on an entire sector that is of no mean therapeutic — and market — importance.

It is therefore necessary to lay down rules that will ensure clear, simple and rational naming of extracts.

Let us make some proposals.

In the case of a total extract, it is essential to specify the name of the medicinal plant, the part of the plant used (drug), the physical form of the extract and, if possible, the extraction solvent used.

The medicinal plant must be uniquely defined by the botanical name (genus and species) and authority. Exceptionally, one can use the name cited in a well-known Pharmacopoeia.

As to specifying the drug — that is, whether leaves, roots, flowering tops, seed or other part — there can be no uncertainty. There is no point in stating that it is the dry drug because drugs are customarily used in the dry state. When a fresh drug is used, this must be stated, because this factor is crucial to the composition of the extract.

The physical form of an extract leaves no room for uncertainty either, since total extracts are only either fluid or dry or soft extracts.

With regard to the nomenclature of purified extracts, it is necessary to frame rules requiring that it be stated explicitly that the extracts have undergone a process of purification with a consequent increase of the contents of a given group of active constituents.

It must be made clear at the start that purification is not a simple defatting operation but a process that is far more important in regard to the content of active principles, in order to increase it appreciably above that in a total extract.

One proposal might be to have the name of the medicinal plant and of the drug followed by terms such as "anthocyanoside or flavone or alkaloid complex" or "liposoluble fraction (or complex)".

As per the purified extracts, the indication of the physical state may become superfluous, because they are practically always in the dry state or are, in the case of "liposoluble fractions", oily products.

The names of total or purified extracts must always be complete with the

statement of content of active or principal constituents. Since these data must appear also on the label of the proprietary medicinal product, they must be brief and clear.

Current practice here again is very varied: in many cases the generic extract/drug ratio is still used, in other cases the content of a given extract is expressed in various ways, while in others nothing at all is said. In yet other cases the names suggest mixtures of pure products rather than extracts, as for example with "total alkaloids of Belladonna", "*Vaccinium myrtillus* anthocyanosides". Failure to state the percentages of alkaloids or anthocyanosides may lead to serious errors of evaluation or rather to overvaluation.

Expressions like:

— *Aesculus hippocastanum* L. seeds, dry hydroalcoholic extract containing 20% total saponins calculated as escin;

— Cascara bark, fluid extract containing 3% hydroxyanthracene derivatives calculated as cascaroside A;

— *Prunus africana* (Hook.) Kalkm. bark, liposoluble fraction containing 10% of β-sitosterol;

— *Ribes nigrum* L. fresh fruits, anthocyanoside complex containing 15% of anthocyanosides;

would be sufficient to supply the elements for a basic knowledge that would permit "homogeneous" comparisons of content between similar products.

Manufacture

The description of a manufacturing procedure, involving either traditional methods of extraction or special technologies, raises no particular problems. It must specify the extraction solvent(s), any purification procedures, any particular requirements to be complied with to avoid the risk of degradation, any inert material that may need to be added to "adjust" the content or to improve the usability or the extract.

The additions of the so-called inert material must be always justified by "adjustment" of the content of active or characteristic constituents or by real technological requirements and must be always limited to the least.

Needless to say that "adjustment" of the active constituent content means variations, in fact reductions, of modest value.

"Adjustments" greater than 10-15% should be more realistically called "adulterations".

The preparation of an extract is always a tricky operation that requires a whole set of analyses and operating tests, which are the only guarantee of constancy of quali- and quantitative composition. It is because the composition of an extract is less easy to control than a pure product, that the process of manufacture, meaning the combination of controls and operating stages, *is crucial to constancy of quality*.

Quality Control During Extraction

The subparagraph "Starting materials" is undoubtedly a new element since it requires data on the quality control of the drugs.

This does not mean that drugs were not controlled before the new EEC multi-state procedures came in. There would be no point in speaking of control of an extract if the drug is not controlled: we must never forget that the extract must be made "in the image and likeness" of the drug. The new element is that, along with the scientific data, the tests that the extract producer conducts on the drug before it is extracted have to be reported.

Some member States of the EEC, i.e., United Kingdom and France, gave much weight to this control, with specific guidelines for its execution.

First there must be a general introduction stating the scientific name of the plant (genus, species, variety and so on), the parts used (vegetable drug), the habitat, place of harvesting. It is also useful to state whether the plant is wild or cultivated.

This general introduction should be accompanied by a brief description of the composition of the drug, according to the most up-to-date published findings.

The purpose of this information on composition is, *inter alia*, to explain the knowledge base on which the analyses of the drug and of the extract derived from it are founded.

A drug intended for the production of extracts must be examined or tested for the following purposes:

— macroscopic and microscopic characters;

— identification by chromatography of the principal constituents or groups of constituents;

— assay, preferably specific, for the principal constituents; if there is no specific method of assay, the combination of non-specific assay (colorimetry, spectrophotometry, volumetric and gravimetric analysis) and chromatographic identification may supply satisfactory results;

— moisture, a very important point indeed, because a high moisture content may jeopardize the stability of a drug;

— heavy or toxic metals.

The subparagraph "Tests on intermediate products" requires the description of the tests done to check the exhaustion of the drug and to ensure the rational trend of the various phases of extraction, of any purification and concentration. These intermediate tests range from the testing of the pH (essential to avoid possible degradation) to the titration of the percolates before concentration or purification. These are tests that we consider absolutely normal and logical. They anyway show that the preparation of an extract is something quite different from a simple percolation and concentration.

Development Chemistry

Of all the requirements of this paragraph only the last two are relevant to extracts: physico-chemical characterization and analytical development.

The physico-chemical characteristics of an extract are essentially the pH value (for all types of extract), solubility (for soft and dry extracts), miscibility (for fluid extracts) in solvents commonly used in formulatoin of finished product, total solids (for fluid or soft extracts), alcohol degree (for fluid extracts), loss on drying for dry extracts).

The are not just routine tests. Each has its own value and importance as concerning either the stability (pH, loss on drying, alcohol degree) or the constancy of content of total extractive material (total solids) or the usability (solubility and miscibility).

An additional control must be carried out, i.e., the test for microbial contamination. Acceptable limits are:

bacteria, 1,000 to 10,000/g;

moulds and yeasts, less than 100/g.

Coliform bacteria, Salmonella species, Staphylococcus aureus, absent. The point "analytical development" includes descriptions of the methods of identification and assay used to "know" the extract in all its aspects.

Although some chromatographic techniques, especially HPLC, have to be considered as the most suitable for solving complex problems of analysis, such as those that confront one in the control of an extract, equally satisfactory results can be obtained from a combination of nonspecific methods with specific identification techniques. This is, for instance, the general practice of many Pharmacopoeias.

Unlike a pure product, which has its own well-defined analytical pattern, an extract is something more complex, whose physiognomy is never unitary: the analytical control of an extract *must* pin down this non-unitary physiognomy at several points. In other words, there must be cross-checks on several substances, because only by so doing is it possible to have elements that permit a serious study of the stability of an extract and of the pharmaceutical formulation in which the extract is used.

Impurities

If the search for, identification of, and assay for impurities that may be found in a pure product constitute no simple problem, with extracts the problem becomes a headache.

Actually, as long as one does not expect to obtain, in terms of identification and accuracy, something that the complex nature of an extract cannot yield, even in the case of extracts the problem of impurities can be tackled successfully.

A) *Potential impurities originating from the extraction process.*

Two classes of impurities must be envisaged:

a) *products of degradation.* This search can only be carried out on the major components, those that on the pharmacological or chemical plane can be considered as markers and whose structures are obviously known. To take an example, if a given drug contains saponins or hydroxyanthracene derivatives or anthocyanosides or esters, it is "possible" during the various stages of preparation of the extract (extraction, concentration, purification, if any, drying) for degradations to occur (enzymatic or chemical hydrolyses due to the working pH and temperature conditions, fermentations), with formation of the corresponding aglucones, of their products of polymerization or of further degradation.

b) *residual organic solvents.* Here one is concerned mainly with dry or soft extracts and oily extracts.

The preferable method of analysis is definitely gas chromatography, given its specificity and accuracy. The limits of organic solvent residues vary with the solvent: in the case of ethanol, high values can be accepted, whereas for other solvents (methanol, acetone, chloroform, ethyl acetate) the limits must be much lower, even of the order of a few tens of ppm.

However, it should be reasonable to accept that residual organic solvent limits are not fixed but can vary from product to product according to its dosage.

B) *Potential impurities originating from degradation as evidenced by exposing the extract to stress conditions (heat, light, acid, bases, etc.).*

This study is of great importance because it enables one, firstly, to identify the changes that the markers may undergo in the course of formulation or during the validity period of the finished product unless specified rules regarding pH, temperature, exposure to light and so on are complied with. Secondly, it enables one to define the physical state (fluid, dry or soft) of the extract and of the finished product in which the extract is used. In other words, if the stress study demonstrates that a fluid extract or a liquid formulation (syrup, drops) is not stable, it will be wise to opt for a dry extract or even a soft one and prepare solid formulations (tablets, capsules). If bioavailability of marketing considerations make a liquid formulation preferable, one can reconcile these requirements with that of stability by preparing granules for instant solution.

C) *External contaminants*

Given the extensive use of weed-killers and pesticides in agriculture, it is essential to test all products of vegetable origin for them. This applies both to cultivated plants, which may have been subjected to disinfestation, and to wild plants, which may have been contaminated by weed-killers and/or pesticides administered to adjacent crops.

Gas chromatography is sufficiently selective and sensitive for this purpose.

And here we have to mention a very important point: although the health authorities all demand testing for foreign contaminations, there are as yet no precise rules with regard to tolerated limits.

Since a solution to this problem has to be found, inspiration may be sought in the food industry, where the problem has been solved, in that limits have been established for a whole series of weed-killers and pesticides tolerated in foodstuffs.

These limits need to be transferred from the food sector, obviously allowing for the fact that a pharmaceutical product is consumed in tiny quantities compared to fruit and vegetables and that therefore, percentagewise, the limit of external contaminants tolerable for an extract can safely be higher than for food, consumption of which is measured not in milligrams but in hundreds of grams or more.

D) *Heavy or toxic metals*

This item ends the list of potential impurities in an extract.

Testing is done by colorimetry against lead reference standard: the values normally found do not exceed few tens of ppm. Nevertheless, more specific methods would be better, so as to determine exactly some toxic metals (cadmium, chrome, etc).

Reference Substances

The identification of a pure product or an extract presupposes comparison with a reference standard. While for a pure product the problem does not exist in practice, in the case of an extract the choice of the reference standard must take account of the fact that it is a complex product, essentially a mixture.

An example: fresh *Vaccinium myrtillus* fruits contain numerous anthocyanosides, 15 to be precise. In a purified extract defined as "Anthocyanoside complex of *Vaccinium myrtillus* containing 36% anthocyanosides", they should clearly *all* be present, in the same reciprocal ratio as they are found in nature.

For a correct identification of this "anthocyanoside complex" will it be sufficient to use as a reference substance one or other of the anthocyanosides present in the bilberry fruit, or will it not be better to use a reference extract that permits a global comparison, not confined to a single constituent, even if this is one characteristic of the drug?

The answer is obvious: given the complex composition of an extract, its identification, to be correct, must be performed against another extract, which, to be accepted as a reference substance, must comply with the following requirements:

— it comes from a drug that complies with all the prescribed requirements of identity, content of active constituents, etc.;

— it must have been prepared in conditions that prevent any alteration of the original components of the drug;

— all its major components must be identified either as definite chemical entities or as chemical families (alkaloids, flavones, saponins, cardioglucosides, etc.) so that a precise map of the base composition of the reference extract is established, which will act as a fingerprint for the extract under study in all routine tests.

2) Economic Problems

The new EEC regulations have two signal consequences: improvement of quality and increased production costs of the proprietary medicinal products.

I have deliberately said "production costs" to highlight the fact that I am not referring to the costs of preparaing the registration dossier and hence once-off, but to costs arising from the variety of quality control tests to be conducted on the active constituents, intermediates and finished product, which will be a charge on the products as long it is marketed.

The increase in production costs applies to every drug, to every active principle and *a fortiori* to extracts. Let me recall that in the '60s and thereabouts anthraquinone drugs with a laxative action were identified by a colorimetric test that was absolutely devoid of specificity: acid hydrolysis, extraction with ether, violet coloring of the ethereal layer after treatment with ammonia. And, apart from a few physico-chemical tests of scant value, the testing was over.

Present requirements include specific methods of identification and assay, testing for various impurities, microbiological control, and stability data: a set of tests that ensure really satisfactory standardization of extract quality.

All this obviously has a cost, which must inevitably work through to the price of the active constituent.

What we ask is that the health authorities — both those that judge the quality and those that examine the economic aspects — should understand this new situation and allow adequately for the large volume of analytical research and the intricacies of production that underlie a standardized extract.

ANNEX I

PRESENTATION OF APPLICATION FOR MARKETING AUTHORIZATION

Part II C: *Control of starting materials*

- Omissis -

1.2. Active constituents (scientific data)

1.2.1. Nomenclature

— International non-proprietary name (INN)
— Chemical name
— Other name(s)
— Laboratory code

1.2.2. Description

— Physical form
— Structural formula
— Molecular formula
— Molecular weight

1.2.3. Manufacture

— Name(s) and address(es) of the manufacturing source(s)
— Synthetic route
— Description of process
— Solvents and reagents
— Catalysts
— Final purification

1.2.4. Quality control during synthesis

— Starting material
— Intermediates tested

1.2.5. Development chemistry

— Evidence of chemical structure (synthetic route, key intermediates, elemental analysis, mass spectrum, NMR, IR, UV, other)
— Potential isomerism
— Physico-chemical characterizaiton (solubility, physical characteristics, polymorphism, pKa and pH values, other)
— Analytical development

1.2.6. Impurities

— Potential impurities originating from the route of synthesis
— Potential impurities originating from degradation as evidenced by exposing the material to stress conditions (heat, light, acids, bases, etc.)

1.2.7. Batch analysis

— Batches tested (date of manufacture, place of manufacture, batch size, and use of batches)
— Results of tests
— Reference Standard (results of tests)