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Reflection paper on the level of purification of extracts to be considered as herbal preparations

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Reflection paper on the level of purification of extracts to be considered as herbal preparations

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1. EXECUTIVE SUMMARY

This reflection paper applies to extracts used as active substances in herbal medicinal products (HMPs) both for human and veterinary use and in traditional herbal medicinal products (THMPs) for human use.

The purpose of this reflection paper is to consider aspects related to the different levels of purification of extracts and to provide criteria to distinguish between those extracts that may be considered as herbal preparations and those that might be, more correctly, classified as isolated herbal constituent or purified mixtures of herbal constituents, taking into account that the final decision has to be taken on a case by case evaluation.

The aim is to provide clarification on which existing guidance documents should be used for different herbal refined extracts in order to assist applicants in identifying the most appropriate authorisation/registration procedure.

2. INTRODUCTION (Background)

The Directive 2001/83/EC as amended provides definitions for HMPs, herbal substances and herbal preparations. The same basic legislation applies to both HMPs and other medicinal products[1]. An additional simplified registration procedure has been established for THMPs.

According to these definitions a herbal medicinal product is any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

THMPs may contain also vitamins and minerals, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients.

Many chemical moieties are obtained by extraction and purification from plant material and it has been clarified[2] that products containing isolated chemically defined constituents (irrespective of whether they are of natural or synthetic origin) or a mixture thereof are not HMPs.

HMPs have a number of characteristics that differentiate them from medicinal products containing isolated chemically defined active substances and therefore specific guidelines have been established, which cover particular aspects that general guidelines do not address. It should be noted that herbal substances and herbal preparations are complex mixtures of natural constituents which altogether form the "active substance"**.** This includes those constituents that may arise from natural transformations.

3. PROBLEM STATEMENT

The definition for herbal preparations covers not only simply processed preparations obtained by one step extraction but also purified and concentrated preparations such as refined extracts. Extraction with a given solvent leads to typical proportions of constituents in the extractable matter. Unwanted matter may be removed after extraction for safety reasons and/or to improve the pharmacological activity of extracts and also for quality reasons.

1 Directive 2001/83/EC as amended

2 CPMP/QWP/2819/00 Rev 1 Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products; "Products containing chemically defined isolated constituents or a mixture thereof are not herbal medicinal products."

In the case of standardised and quantified extracts, purification procedures may be applied with the aim of increasing the content of constituents with known therapeutic activity or active markers. Such extracts are referred to as "refined" in the European Pharmacopoeia.

In some cases the purification of a herbal extract is so substantial that it is questionable whether the resulting preparation may still be considered as a highly purified herbal preparation or whether it should be regarded as an isolated herbal constituent or a mixture of closely related herbal constituents.

In other circumstances the extract may have been previously fractionated and/or refined and then mixed again to form the final preparation.

There is a broad range of possibilities for refining of extracts, including blending and mixing different fractions. In most cases the classification is clear and the purification does not change the status of the extract as a "herbal preparation" even for substantially refined and concentrated herbal preparations.

However, a grey area remains both for highly refined, concentrated extracts and for extracts consisting predominantly of mixtures of related constituents which do not comply with the general quality guidelines[3] on substances for pharmaceutical use.

Therefore a careful evaluation of the borderline is needed to ensure the correct category is assigned in order to establish the appropriate specifications and regulatory status.

The purpose of this reflection paper is to consider criteria to discriminate between highly purified extracts which can still be considered as herbal preparations and other preparations which should be considered as isolated herbal constituents or mixtures of related herbal constituents.

4. DISCUSSION

The quality of a medicinal product is independent of its use and therefore all general principles of quality and quality guidance documents also apply to HMPs.

Due to their complex nature, specific herbal guidelines provide further information on how the quality issues should be addressed in the case of herbal substances/herbal preparations/HMPs.

For single, isolated constituents from herbal origin (e.g. morphine) adherence to the general quality guidelines for chemically defined active substances is required.

Active substances in HMPs consist of complex mixtures of phytochemical constituents. For many herbal substances and herbal preparations, the constituents responsible for the therapeutic activity are not known. In addition, there are herbal preparations where neither constituents with known therapeutic activity nor active markers are known. These herbal preparations are characterised by their production process and their specifications. They are described as "other" extracts in the European Pharmacopoeia.

Refining extracts may aim to reduce problematical constituents or to increase the content of active constituents (standardised extracts and quantified extracts with reference to the European Pharmacopoeia). During the refining process the composition of the final preparation may vary to a

3 CHMP/QWP/297/97 Rev 1 Summary of Requirements for Active Substances in the Quality Part of the Dossier
CPMP/QWP/130/96 Rev. 1 Chemistry of New Active Substances.
CPMP/ICH/ 2737/99-ICH Q3A (R2) Impurities Testing: Impurities in New Drug Substances (ICH Q3A)
CPMP/ICH/ 367/96-ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (ICH Q6A)
European Pharmacopoeia General Monograph "Substances for pharmaceutical use" 01/2008:2034
European Pharmacopoeia General Chapter "Control of impurities in substances for pharmaceutical use" (5.10) 01/2008:51000

greater or lesser extent but in general the refined extracts no longer have the total spectrum of constituents present in the original extract.

The different purification steps lead from "total extracts" (natural multi-component mixtures) via "refined extracts" (including mixtures of closely related constituents) finally to "isolated single constituents". Increasing the purification of total extracts converges the active substances more and more towards isolated chemically defined substances. Sometimes the herbal matrix of natural concomitants is completely removed, even though the level of purification achieved is not the same as a single chemical entity.

Although the final evaluation has to be made on a case by case basis, the following aspects which characterise the different extracts should be taken into account for the assessment: level of refinement, purification level with regard to the presence of residual concomitants, method of purification.

4.1. Level of refinement

DER_{native} and level of refinement are important factors to define the preparation, but they do not determine per se the classification as a herbal preparation. Methods used in refining and purification may be more relevant for this purpose.

It is worth noting that even for some chemically defined active ingredients, especially of natural/biological origin, the standard degree of purity NLT 95% is not applied, where justified (e.g. antibiotics).

Concerning refined extracts, the critical threshold for the case by case evaluation is generally considered to be above 70% of active constituent(s).

4.2. Presence of concomitant constituents

With HMPs, the whole herbal preparation is considered to be the "active substance" and all constituents originating from the plant material (concomitant constituents) are considered to be part of the active substance and not impurities. However, if the active substance is classified as an isolated chemically defined compound, all other constituents originating from the herbal substance would be considered as impurities.

4.3. Methods of extraction / refining

Chemical modifications of original constituents may occur during the extraction process or following refining and it is not infrequent that artefacts are present in the extract, e.g. as a consequence of fermentation, heating, hydrolysis, etc.

Naturally occurring changes in the original composition of the plant material during the manufacturing process are acceptable, provided that they are consistently controlled.

Several refining processes exist. Appropriate justifications are needed for the methods employed.

4.4. Examples of categories of preparation of herbal origin

In relation to the composition of the preparation of herbal origin, the following different categories can be identified:

a) Isolated constituent (e.g. morphine) for which a characteristic impurity profile may be established and the purity has to be proven within the usual margins of acceptance for chemical substances.

b) Mixtures of purified constituents obtained by specific processing methods (e.g. precipitation of sennosides as calcium salts). Concomitant constituents have been removed or are present at insignificant levels.

c) Mixtures of chemically defined substances with related chemical structures extracted from herbal material. These may be difficult to separate (e.g. alkaloid fraction not containing N-oxides or quaternary alkaloids, saponin fraction containing only monodesmosides saponins). Concomitant constituents have been removed or are present at insignificant levels.

d) Chemically defined compounds extracted from herbal material and partially purified, e.g. 85%, but where the remaining part is represented by concomitant constituents.

e) Isolated class of constituents (e.g. total alkaloids, total saponins fraction) maintaining the natural variability for which identification of the main constituents in the mixture is possible.

f) Standardised extracts adjusted to a specified content of constituents with known therapeutic activities (e.g. sennosides). Natural concomitants are present.

g) Quantified extracts with a specified content of constituents considered as active markers (e.g. quantified Hypericum extracts). Natural concomitants are present.

h) Purified extracts neither standardised nor quantified for which the pattern of active constituents has to be determined.

A preparation of herbal origin may fall into more than one of the above mentioned categories. Specific examples are reported in Annex 1.

5. CONCLUSIONS

The definition of herbal preparations includes not only extracts made by simple processes where the full spectrum of extractable plant constituents is present but also purified/refined extracts which may consist solely of mixtures of related herbal constituents. In the latter case, the full spectrum of plant constituents may no longer be present as certain concomitant constituents have been removed in the purification processes.

In some cases the purification of the herbal extract is so substantial that it is questionable whether the resulting preparation may still be considered as a highly purified herbal preparation or whether it should be regarded as an isolated herbal constituent or a mixture of closely related herbal constituents.

The following aspects should be considered in designating the extract as a 'herbal preparation':

1. Definition is in accordance with Directive 2001/83/EC as amended and Ph. Eur.
2. Complex mixture of constituents extracted from plant material is present in the preparation.
3. Proportional content of constituents in the preparation may vary from batch to batch due to the natural intrinsic variability.
4. The preparation is a mixture of related constituents reflecting the natural variability during the extraction process, but the mixture may be standardised or quantified.

At least one of the following criteria would exclude the material being designated as a 'herbal preparation':

1. Extracts subjected to chemical processes where the chemical modifications may be comparable to a partial synthesis. These preparations should be assessed case by case.
2. Extracts enriched with isolated compounds.

Some refined extracts can only be evaluated taking into account additional information such as the manufacturing process.

6. DEFINITIONS

Constituents with known therapeutic activity: are chemically defined substances or groups of substances, which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.

Drug extract ratio (DER): means the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

Extracts: are preparations of liquid (liquid extracts and tinctures), semi-solid (soft extracts and oleoresins) or solid (dry extracts) consistency, obtained from herbal drugs (or animal matter) which are usually in a dry state.

Extraction solvents: are solvents which are used for the extraction process.

Genuine (Native) herbal preparation: refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

Herbal medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

Herbal substances: all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal preparations: preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Impurity:

(1) Any component of the herbal substance, which is not the entity defined as the herbal substance.

(2) Any component of the herbal preparation/herbal medicinal product that is not the entity defined as the herbal substance/ preparation or an excipient in the herbal preparation/herbal medicinal product.

Markers: are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if that marker has been quantitatively determined in the herbal substance(s) or herbal preparation(s) themselves.

There are two categories of markers:

Active markers: are constituents or groups of constituents, which are generally accepted to contribute to the therapeutic activity.

Analytical markers: are constituents or groups of constituents that serve for analytical purposes.

Other extracts: extracts essentially defined by their production process (state of the herbal drug to be extracted, solvent, extraction conditions) and their specifications.

Quantification: means adjusting the herbal substance or herbal preparation to a defined range of constituents (active markers) exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extract).

Quantified extracts: extracts adjusted to a defined range of constituents (active markers).

Ratio of herbal substance to genuine herbal preparation (DER genuine): is the ratio of the mass of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

Refined extracts: standardised or quantified extracts submitted to purification procedures that increase the typical proportions of characterised constituents in the extractable matter with respect to the values expected by means of the extraction with a given solvent.

Refining: means purification of quantified or standardised extracts, which increases the typical proportions of characterised constituents in the extractable matter with respect to the expected values of pharmacologically or therapeutically active constituents obtained by means of the extraction with a given solvent.

Specification: a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance and / or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Standardisation: means adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts).

Standardised extracts: extracts adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity.

Traditional herbal medicinal products: are medicinal products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

Unidentified impurity: an impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

7. REFERENCES

1. 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00, current version).
2. 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2820/00, EMEA/CVMP/815/00, current version).
3. European Pharmacopoeia General Monograph "Extracts" 04/2008:0765
4. European Pharmacopoeia General Monograph "Substances for pharmaceutical use" 01/2008:2034
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6. use" (5.10) 01/2008:51000
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12. Gaedcke F. Contribution to the discussion of the "Reflection paper on level of purification of extracts to be considered as herbal preparations" (EMEA/HMPC/186645/08).

ANNEX 1

Examples considered as herbal preparations

Example 1

A highly concentrated ethyl acetate extract of milk thistle fruits (*Silybum marianum)* specified to contain 65% of silymarin according to Ph. Eur., which is variable in its composition and contains between 20-45% of silycristin and silidianin, 40-65% silibinin A and B and 10-20% isosilibinin A and B. The extract is standardised and assayed by:

Silymarin, calculated as silibinin, related to the dried extract 30-65%

Sum of contents of silibinin A and silibinin B, calculated as silibinin with reference to total silymarin 40-60%

Sum of contents of silicristin and silidianin, calculated as silibinin with reference to total silymarin 20-45%

Isosilibin A and isosilibin B, calculated as silibinin with reference to total silymarin 10-20%

Example 2

Extract of Serenoa repens. The herbal preparation is characterized by:

Free unsaturated and saturated fatty acids and respective methyl- and ethylesters, triglycerides, determined after methanolysis and calculated as the sum of the derivatised fatty acids: 85.0-95.0%

Sterols: 0.2-0.4%

Long chain alcohols: 0.15-0.30%

Example 3

Ethanolic extract of soya beans. The extraction is followed by purification steps (removal of lipids, filtration, preparative column). The extract is characterised by isoflavones content of 36-44% with respect to dried extract.

Example 4

Deoiled, enriched phospholipids from soya beans. The phospholipids are manufactured by hexane extraction of soya beans, purified (e.g. filtration, degumming, bleaching, hydration), enriched by ethanolic extraction and adsorption on a silica gel column. The obtained herbal preparation is characterised by phosphatidylcholine content of 73-79%. Other phospholipids present in preparation: phosphatidylethanolamine (max. 7%), phosphatidylinositol (max. 0.5%) and phosphatidic acid.

Example 5

A mixture of isolated flavones manufactured by water extraction of Scullcap Baical (*Scutellaria baicalensis*) and purificated (filtration, acidification, ethanolic extraction). The extract is characterised by baicalin content min. 75%. Other flavones present in the extract: baicalein and wogonin.

Example 6

Aescin is a mixture of over 30 related saponins, manufactured by methanolic extraction of horse chestnut seeds with subsequent purification (acidification, activated charcoal, crystallisation, dissolution in ethanol and drying). Purity: 96-103%.

Examples not considered as herbal preparations

Example 7

Mixtures of active constituents derived by chemical treatment of natural compounds with methanesulfonic acid such as e.g. ergoloid mesylates.

Justification: This preparation is not a herbal preparation because the chemical treatment is comparable to a partial synthesis (criterion of exclusion 1) and has to be treated as a chemically defined mixture of active constituents.

Example 8

A highly purified extract, fractionated into triterpenic acid and triterpenic sugar ester fractions to reach about 40% of asiaticoside and about 60% of the triterpenic genins: asiatic acid and madecassic acid. Processing of this extract involves many purification steps of the crude ethanolic extract (70 % V/V), including also chemical hydrolysis and leading to two highly purified fractions, the genins fraction (purity ≥ 75%) and the pure asiaticoside (purity ≥ 95%), which are then mixed in the ratio 60:40.

Justification: Taking into consideration its production process and its specification, this preparation cannot be considered as a herbal preparation because the purification steps are extreme and involve chemical treatments that remove the matrix of natural concomitants, so that the final extract is a recombination of a highly refined extract with an isolated constituent (asiatic acid) and the natural proportion of the components is not maintained (criterion of exclusion 2).

Example 9

Calcium sennosides from senna leaves and/or pods. The plant material is extracted and the extract is evaporated and concentrated. The dry extract is subjected to chromatographic or other appropriate purification methods to separate the refined extract containing the hydroxyanthracenic glycosides (sennosides). The sennosides are precipitated as calcium sennosides by using a calcium salt solution. The precipitate is dried to obtain the final calcium sennosides mixture (NLT calcium sennosides 80% calculated as a content of sennosides NLT 60%).

Justification: This preparation is not a herbal preparation, because the final calcium sennosides mixture no longer contains the matrix of natural concomitants and therefore meets the criterion of exclusion 1.

Examples for borderline cases

The following example can *a priori* neither be allocated to herbal preparations or pure substances using general inclusion/exclusion criteria without additional information on the manufacturing process

Example 10

Curcuminoids extracted and purified from turmeric: the active substance is not a single chemically defined constituent but a mixture of 3 related constituents in a ratio which can vary within a certain range. Purity 95.0-100.0% curcuminoids calculated as sum of:

Curcumin: 70-80%

Desmethoxycurcumin: 15-25%

Bidesmethoxycurcumin: 2.5-6.5%