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Committee on Herbal Medicinal Products (HMPC)

Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products[1]

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[1] Throughout the document and unless otherwise specified, the term 'herbal medicinal product' includes 'traditional herbal medicinal product'.

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Declaration of the active substance

(1) Question

'How should the drug extract ratio and the extraction solvent be declared for extracts prepared from fresh herbal substances?' *Rev. Nov. 2023*

Answer

The genuine drug extract ratio ($DER_{genuine}$) and the extraction solvent should be declared for extracts.

No matter whether the extract is prepared from a dry or a fresh herbal substance, the quantity of the herbal substance should simply be the quantity used, i.e., including any water naturally contained in the herbal substance.

The quantity of the native extract should be set as the quantity obtained after the extraction process, i.e., including any water and other solvent present in the extract, but without the quantity of any excipient added after the extraction process (excipients used for standardisation or technological reasons).

Due to the natural variability of the herbal substance, the $DER_{genuine}$ will normally be a range, e.g., 3.0-5.5:1. In the case of tinctures, where all of the extraction solvent is maintained in the final extract, the $DER_{genuine}$ will equal the drug extract ratio.

Likewise, the declaration of the extraction solvent should be based on the concentration of the solvent used, without taking any water naturally contained in the herbal substance into account.

Example: An extraction solvent prepared as a mixture of 5,000 kg ethanol 94% m/m plus 1,000 kg purified water means that the declared solvent should be ethanol 78% m/m, irrespective of the water contained in the herbal substance being extracted (approx. 75-90 % of the quantity of a fresh herbal substance).

For further guidance, see *Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products* (EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1).

Testing

(1) Question

A mixed extract is produced by simultaneous extraction of several herbal substances with the same extraction solvent. Is it acceptable to perform an analysis using only one representative analytical marker for stability testing of the herbal medicinal product?

Answer

In principle mixed extracts should fulfil the same requirements as mixtures of single extracts and the individual extracts within the mixture should be quantified. Mixed extracts are produced in a special manufacturing process as a unique extract, but these extracts contain the specific extracts from the different individual herbal substances.

The analytical methods should be selected as prescribed in the *Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products* (EMEA/HMPC/CHMP/CVMP/214869/2006).

(2) Question

'In practice it is sometimes difficult to find suitable analytical markers for quantitative purposes. Can primary metabolites of herbal substances also be used as analytical markers for stability testing in case suitable secondary metabolites are not available? Is this also possible for release testing?'

Answer

The EMA *Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products* (EMEA/HMPC/253629/2007) gives an overview on possibilities and problems with markers. Markers (analytical markers) should ideally be characteristic or specific for the plant/herbal preparation and also stability-indicating at the same time. However, this may not always be fulfilled. Where a marker is unstable in normal conditions of use ("poor analytical tool"), it may not be suitable for determination of an appropriate shelf-life. In some cases, due to low concentrations present or where a chromophore is lacking, potential marker substances may not be readily detectable by the usual chromatographic methods. In many cases marker substances occur in groups of structurally related constituents and a selective separation is difficult (e.g., tannins, proanthocyanidins, saponins, etc.). It is generally assumed that markers should belong to the group of "secondary" plant metabolites such as flavonoids, saponins, terpenes, phenols etc. However, in exceptional cases markers from the group of primary metabolites such as carbohydrates, amino acids/proteins, fats, etc. may be acceptable, if they allow the specific determination of the content of a herbal preparation within a herbal medicinal product (e.g., carbohydrates in linseed, fatty acids in saw palmetto). Such an approach is applicable to both release testing and stability testing.

(3) Question

'Is testing of benzene (class 1 solvent) for herbal preparations necessary?'

Answer

Some solvents used for extraction, purification or during manufacture of a herbal preparation may contain benzene as an impurity. As a consequence, the potential for benzene residues occurring in

herbal preparations and solvents used in their production should be addressed and appropriate controls applied, unless otherwise justified.[2]

Benzene may be an impurity in solvents such as: acetone, ethanol, methanol, isopropanol, toluene, xylene, hexane, cyclohexane and petroleum ether.

The most commonly used solvents for the manufacture of herbal preparations are ethanol and water or combinations thereof. Ethanol of chemical origin may contain benzene as an impurity whereas ethanol obtained from fermentation does not normally contain any benzene. Therefore the production process of ethanol used in herbal preparations should be taken into account when considering the need for tests in the specification to control the benzene content and the frequency of testing.

Ethanol, methanol and acetone complying with their European Pharmacopoeia monographs should not exceed 2 ppm of benzene, which is the ICH limit. The content of benzene in solvents used in the manufacture of herbal preparations, which are not covered by monographs in the European Pharmacopoeia, should, preferably, not exceed the ICH limit (2 ppm). Where solvents exceeding the ICH limit are used, potential benzene residues should be identified and quantified.

Where the herbal preparation is a liquid extract or tincture prepared by simple methods without concentration steps using ethanol/water mixtures in accordance with the European Pharmacopoeia, potential benzene residues will not exceed the ICH limit applied to the starting extraction solvents. In such cases, further controls on potential benzene residues are not required.

Where the herbal preparation is a liquid extract or tincture prepared by processes involving more complex processes and concentration steps the potential for benzene residues to exceed the ICH limit of 2 ppm in the resulting preparation needs to be addressed and appropriate controls applied if needed.

Where the herbal preparation is a semi-solid preparation (soft extracts and oleoresins), the extraction solvent(s) and/or other solvents used during purification and manufacture may only be partially removed in the case of some semi-solid preparations. In these cases the potential for benzene residues should be addressed and appropriate controls applied if needed. The limit should not exceed 2 ppm.

Where the herbal preparation is a dry extract, the benzene content would be expected to be reduced during the drying process. However the relative volatility of all solvents used in manufacturing process and of benzene (bp 80.1°C) must be taken into account.

In the case of dry extracts benzene levels should be addressed and appropriate controls applied if needed. The limit should not exceed 2 ppm.

[2] See Annexes to: CPMP/ICH/283/95 Impurities: Guideline for residual solvents (CPMP/QWP/450/03, Rev.1): Annex I: B class 1 solvents present as an impurity.

Contaminants

Mycotoxins

(1) Question

'With regard to the determination of mycotoxins, when is routine testing required and in what circumstances would reduced testing or possibly no testing be acceptable?' *Rev. Nov. 2023*

Answer

In general testing for mycotoxins should be carried out for herbal substances. However, routine testing for mycotoxins is not required for all herbal substances, because only a few herbal substances are at risk of contamination. An appropriate risk assessment should be undertaken, taking account of the plant and the plant part. Routine analysis of mycotoxins should be considered in the case of a herbal substance/plant part at risk such as seed, fruit, root, rhizome. If, in the literature, data are available on mycotoxin formation in the plants, or possible contamination of the herbal substance is known, then testing should be conducted. In addition, as aflatoxins and ochratoxin A are soluble in alcohol, the need for testing of the herbal preparation should also be considered.

For plant/plant parts, not at a particular risk, monitoring would suffice in general and reduced testing (or even omission of testing) may be acceptable if justified. Appropriate harvest/collection, drying and storage procedures reduce the risk for contamination with mycotoxins. For example, drying of the material following harvest as quickly as possible with a homogeneous loss on drying of < 12% (or even < 10%) as control measure reduces the risk. A reduced water activity (Aw) will assist in the prevention of contamination. The water activity requirements for the growth of different Gram-reactive bacteria, bacterial spores, yeasts and moulds are described in the literature[3,4]. It is generally recognised that in products with water activity below 0.60, moulds and yeasts do not proliferate.

[3] Troller et al. Measurement of water activity. In: Compendium of methods for the microbiological examination of foods. American Public Health Association, Washington DC, 1984, pp. 124-134.
[4] USP, chapter <1112> Microbiological attributes of non sterile pharmaceutical products - Application of water activity determination. US Pharmacopoeia Convention, Inc. 31th edition, 2007.

Microbiological quality

(1) Question

'Is it possible to use skip testing for the microbiological quality of herbal medicinal products in specifications for stability studies performed under accelerated/intermediate conditions?' *Rev. Nov. 2023*

Answer

No. The optimal growth temperature of some microorganisms, especially human-pathogenic microorganisms, is in the range of 30°C to 40°C. Particularly in combination with a high relative humidity (e.g., 75 %) these are optimal growth conditions for some microorganisms (see the *Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products* (EMA/HMPC/95714/2013). Therefore, the testing of the microbiological quality is essential for these studies, as a minimum requirement compliance should be demonstrated at the beginning (batch release) and at the end of stability studies.

(2) Question

'Is it possible to replace the testing of the microbiological quality by the testing of the water activity (AW)?'

Answer

Products, brought to market in the EU, must follow the requirements of the European Pharmacopoeia. Therefore, at least at the beginning (batch release) and at the end of a stability study the conformity to the European Pharmacopoeia must be demonstrated. The testing of water activity can give additional information during the stability study, but it cannot replace a necessary microbiological testing.

Elemental impurities

(1) Question

(Traditional) herbal medicinal products are out of the scope of ICH guideline Q3D on elemental impurities. Additionally, the reference to the Ph. Eur. 2.4.8 heavy metals test has been deleted from Ph. Eur. individual monographs. How should (traditional) herbal medicinal products be evaluated with respect to content of elemental impurities? *Rev. Nov. 2023*

Answer

Guideline ICH Q3D on elemental impurities for human medicinal products came into effect in June 2016 for new products and in December 2017 for already authorised products. According to ICH Q3D, control of elemental impurities should be performed by the marketing authorisation holder/registration holder, by an overall risk assessment of the entire product. In general, active substances, excipients, water, packaging materials and equipment should be taken into consideration.

ICH Q3D was implemented in Ph. Eur. 9.3 by the general monograph *Pharmaceutical preparations* and Ph. Eur. 5.20 *Elemental impurities*. The test for heavy metals, Ph. Eur. 2.4.8, was deleted from individual monographs for human use by Ph. Eur. 9.0.

(Traditional) herbal medicinal products are out of the scope of ICH Q3D and Ph. Eur. 5.20, as different provisions on herbal products apply in the various ICH regions, while in the EU, the quality of (traditional) herbal medicinal product should be ensured at the same level as for other medicinal products.

Herbal substances should comply with the limits for heavy metals specified in the Ph. Eur. monograph on herbal drugs (1433). A risk assessment is in general requested by GMP guidelines. However, it is also the marketing authorisation/registration holders' responsibility that the *principles* of risk assessment are applied for controlling the levels of elemental impurities in the products.

This should be fulfilled for (traditional) herbal medicinal products for human use. For herbal medicinal products for veterinary use, further scientific guidance will be elaborated by the EMA.

For new applications, a *summary* of the risk assessment covering the risk evaluation for elemental impurities should be included in the application.

For already authorised/registered products, variation applications should only be submitted in cases where the risk assessment triggers changes in the quality of the product (e.g., change in impurity tests).

Manufacturing

(1) Question

'Is it acceptable to mix batches of 'other' extracts in order to improve the batch-to-batch consistency?'
New Nov. 2023

Answer

Yes, it is acceptable to mix batches which are compliant with the release specification. However, it is not acceptable to use as criterion the content of an analytical marker alone, as this would resemble the manufacture of a quantified extract. Also, chromatographic fingerprints have to be used to justify mixing and to demonstrate the benefit of such a step with regards to the extract in its entirety. Moreover, the natural variability should be considered. It is not acceptable at all to mix batches which do not comply with the release specification in order to achieve a compliant pooled batch.

Quality of water

(1) Question

'For the manufacture of herbal extracts, water complying with the Ph. Eur. monograph 2249 (water for preparation of extracts) may be used. In the case of liquid extracts, this water would be part of the herbal medicinal product. In contrast, Ph. Eur. requires for the preparation of medicines the use of purified water. Is it therefore required to use for the manufacture of liquid extracts purified water?'
New Nov. 2023

Answer

No. The extraction solvent is integral part of the herbal substance and not considered as an excipient. Therefore, it is acceptable to use *water for preparation of extracts* (Ph. Eur. monograph 2249) in the manufacture of liquid extracts, which are used as such in herbal medicinal products.

Stability

(1) Question

'A medicinal product is manufactured by an interrelated production process comprising the production of the active substance and the production of the finished product. Example: The active substance is a powdered herbal substance in hard capsules. The maximum time frame between powdering and production of the finished medicinal product is three months. Are stability studies necessary for both the active substance and the finished product?' *Rev. Nov. 2023*

Answer

In the case of an interrelated production process such as that described above, the stability testing has only to be performed on the herbal medicinal product. However, justification is needed for the choice of the packaging material, transportation and storage conditions for the active substance.

(2) Question

'A herbal tea consists of a mixture of cut herbal substances packaged in a multi-dose bag. Are comprehensive stability studies necessary for both the active substances and the finished product?'

Answer

Provided that comparable packaging material is used, the stability tests on the active substances are not necessary if each of the active substances can be determined by an appropriate assay method in the finished product throughout the shelf life.

Alternatively, in special cases, where stability data for each active substance in the finished dosage form exist and interactions between the active substances are unlikely, the stability tests for the finished product can be replaced by the stability data for the single active substances.

(3) Question

'Is it possible to make reference to stability data obtained from comparable herbal preparations (from the same herbal substance) when both active substances are covered by the same Ph. Eur. monograph?'

Answer

As most Ph. Eur. monographs for herbal preparations cover different extraction solvents and DERs and, in addition, the excipients and packaging materials are not part of the monograph, it is necessary to establish stability data for each individual active substance. In very exceptional cases, it may be possible to make reference to a closely related preparation provided satisfactory justification is given.

(4) Question

'Where it is evident from former stability studies on laboratory/pilot batches that the finished product is unstable under accelerated and/or intermediate conditions are further studies still required under such conditions?' *Rev. Nov. 2023*

Answer

In the case of herbal medicinal products, in situations where former stability studies are available, demonstrating that the finished product is unstable under accelerated and/or intermediate conditions, it may be acceptable in such cases to justify the omission of further stability studies under accelerated/intermediate conditions.

(5) Question

'Are stability overages for herbal active substances acceptable?'

Answer

In general, as the whole herbal substance/preparation is considered as the active substance, stability overages would not be acceptable. However, stability overages would be acceptable for standardised extracts if justified.

Essential oils as active substances

(1) Question

Many essential oils are produced by farmers or small manufacturers. In some countries essential oils are not classified as "active pharmaceutical substances" and in other countries it is difficult to control the GMP status during the first production step. Is it acceptable that the production process is in line with local regulations and not with GACP principles and EU GMP?

Answer

No, it is stated in Directive 2011/62/EU and in detail for herbal medicinal products in the GMP Guideline, Annex 7, that all active substances should be produced in line with EU regulations. However, early production steps could follow the GACP principles if the last steps were in line with GMP. Similar standards can be accepted if justified (including risk assessment). Where the active substance is produced in non-EU countries, compliance with written confirmation according to the provisions of the Directive 2011/62/EU is required.

(2) Question

Is it permissible to blend essential oil sub-batches which are not in line with the chromatographic profile of the relevant Ph. Eur. monograph?

Answer

Sub-batches may be blended or further processed to be brought in line with the chromatographic profile of the relevant Ph. Eur. monograph. In some cases the Pharmacopoeial limits are based on blended and/or processed essential oils, therefore it is sometimes necessary to extend the limits for primary batches. In these cases; appropriate fixed limits should be justified on the basis of sufficient batch data and the plant material used for distillation should be adequately controlled. These limits should be approved by the competent authority.