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Committee on Herbal Medicinal Products (HMPC)

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

Table of content

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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?'

Answer

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

The $DER_{genuine}$ is the ratio of the quantity of the herbal substance to the quantity of the resulting native (genuine) extract.

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.

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

Specification & Testing

Specification of the finished product

(1) Question

'Which limits are acceptable for the content of active substances with constituents of known therapeutic activity in the finished product at the time of manufacture and at the end of shelf-life?

Answer

In the guideline on quality of herbal medicinal products (CPMP/QWP/2819/00 Rev. 1) it is stated that for herbal medicinal products with constituents of known therapeutic activity, the variation at the end of shelf-life should not exceed ± 5% of the declared assay value. Furthermore, according to paragraph 2.5 of the guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products (CPMP/QWP/2820/00 Rev. 1) only "in exceptional cases" different acceptance criteria for release versus shelf-life specifications apply. Because the European Pharmacopoeia (Ph. Eur.) allows standardisation for herbal preparations with constituents of known therapeutic activity, the HMPC is of the opinion ± 5% of the declared assay also applies at release.

However, the guideline on specifications: test procedures and acceptance criteria for herbal preparations and herbal medicinal products/traditional herbal medicinal products also states that "The concept of different acceptance criteria for release versus shelf-life specifications applies to herbal medicinal products. This concept can also apply in exceptional cases to herbal substances and herbal preparations, if justified. Examples where this may be applicable include assay and impurity (degradation product) levels. Therefore, if justified and authorised, broader limits may be acceptable. Nevertheless, no general limits can be recommended because the variation depends on the herbal substance used. Setting the limits is a case by case decision. Hence in case of herbal medicinal products with constituents of known therapeutic activity, applicants are advised to ask the regulatory authorities which data are required to justify limits above ± 5% of the declared assay value.

Testing

(1) Question

'What guidance is available on how to take and handle representative samples for analysis?'

Answer

Reference is made to Ph. Eur. 2.8.20 on "Herbal drugs: sampling and sample preparation" (01/2008:20820).

(2) Question

'Is a joint assay of the active substances in a combination product acceptable?'

Answer

Yes, a joint assay would be acceptable if satisfactorily justified in line with the herbal quality guidelines (EMEA/HMPC/CHMP/CVMP/214869/06, CPMP/QWP/2820/00 Rev 1, CPMP/QWP/2819/00 Rev 1).
Example: The group determination of flavonoids from birch leaves and java tea leaves.
In addition, the identity of the individual active substances should be shown by chromatographic procedures (e.g. TLC).

(3) 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 HMP?

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 an 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).

(4) Question

'For the active substance, is it possible to substitute the marker described in the European Pharmacopoeia by an alternative marker?'

Answer

It is possible. The use of the alternative marker should be justified on the basis of sufficient data. Pre-clinical and clinical data should be considered in the justification.

(5) Question

'Can different analytical markers be used for release and stability testing?'

Answer

In principle, the manufacturer should use the same marker for release and stability testing. In exceptional cases different markers can be accepted where justified on the basis of analytical data.

(6) Question

'In practice it is sometimes difficult to find suitable analytical markers for quantitative purposes. Can primary metabolites of herbal drugs 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 (EMA/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.

(7) Question

'What should be taken into account when using non-pharmacopoeial reference standards for herbal substances, herbal preparations and herbal medicinal products (HMPs) / traditional herbal medicinal products (THMPs) (vitamins and mineral excluded)?'

Answer

Reference standards are used for identity and purity testing and for content assignment and they play an essential role when ensuring and demonstrating adequate and consistent quality of herbal substances, herbal preparations and HMPs/THMPs. These reference standards may be a botanical sample of the herbal substance, a sample of the herbal preparation (e.g. extract or tincture) or a chemically defined substance e.g. a constituent with known therapeutic activity, an active marker or an analytical marker etc.

In the European Pharmacopoeia (Ph. Eur.) monographs on herbal substances and herbal preparations, pharmacopoeial reference standards are described for a dedicated purpose and they are only demonstrated to be suitable for the use indicated. Where pharmacopoeial reference standards are available they should be used as primary standards. In cases, where pharmacopoeial reference

standards are not available, non-pharmacopoeial reference standards should be established. Their establishment should follow the guidance given in Ph. Eur. chapter 5.12. “Reference standards”.

Reference standards should be adequately characterised, they should meet quality standards appropriate for their intended use and they should be an integral part of the manufacturer’s specification.

(8) Question

‘Some monographs for herbal substances in the European Pharmacopoeia do not contain an assay. Is the applicant required to develop an assay for these herbal substances and herbal preparations derived thereof?’

Answer

If a monograph for the herbal substance is given in the European Pharmacopoeia or in another official Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC as amended, the quality of the herbal substance should be specified in accordance to this monograph.

In case the monograph does not include an assay, reference to the monograph only is sufficient, the applicant is not required to develop an assay for the herbal substance.

If no monograph for the herbal substance is given in a Pharmacopoeia, the applicant is required to develop a comprehensive specification including testing of identity, purity and a suitable assay unless otherwise justified.

Specification of herbal preparations derived from herbal substances should include a suitable assay.

In exceptional cases, the assay can be replaced by other tests (e.g. bitterness value, swelling index).

(9) Question

‘Some monographs for herbal preparations in the European Pharmacopoeia do not contain an assay. Is the applicant required to develop an assay for these herbal preparations and the finished products?’

Answer

Applicants are not required to develop a (specific) assay for the herbal preparation if the monograph of the herbal preparation does not include an assay, e.g. Cinnamon, Myrrh, Gentian tinctures. However, because it is a legal requirement that the content of the active substance is determined quantitatively in finished products, an assay is normally needed to calculate the declared content of the active substance in the herbal medicinal product. The selection of appropriate constituents to serve as the basis for the assay will depend on the particular herbal preparation. Guidance on the selection of markers is given in the *Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products* (EMEA/HMPC/253629/2007) (see also question 6 on ‘Testing’ above).

In exceptional cases it may be acceptable to replace the assay by other tests (e.g. bitterness value and swelling index).

Contaminants

Mycotoxins

(1) Question

'What guidance is available on controlling mycotoxins/aflatoxins in herbal substances? Reference is often made to the 'Aflatoxin prohibition ordinance, Federal Law Gazette part I, no33, 25.7.2000 (Aflatoxin-Verordnung)' with limits for aflatoxin B1 NMT 2ppb, sum of aflatoxins B1, B2, G1 + G2 NMT 4 ppb.'

Answer

The Ph. Eur. has included a method of determination of Aflatoxin B1 in herbal drugs and sets limit for herbal drugs, unless otherwise indicated in the monograph, at NMT 2µg/kg (General Chapter 2.8.18, 04/2007). The limit in the General Chapter becomes mandatory when referred to in a General or Individual Monograph, but is considered as generally applicable. The analytical method is validated for devil's claw, ginger and senna pods. Suitability needs to be demonstrated for other herbal drugs.
The Ph. Eur., General Chapter 2.8.18 (4/2007) furthermore states that the Competent Authority may require compliance with a limit for the sum of aflatoxins (B1, B2, G1 and G2) of NMT 4ppb.
The standard set out in the 'Aflatoxin prohibition ordinance, Federal Law Gazette part I, no33, 25.7.2000 (Aflatoxin-Verordnung)' represents the German national requirements.

(2) 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?'

Answer

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 drug 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[2,3]. It is generally recognised that in products with water activity below 0.60, moulds and yeasts do not proliferate.

[2] 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.

Microbiological quality

(1) Question

'The recommendations on limits concerning microbiological quality of herbal products in the Ph. Eur. are for the finished product. What limits should be applied to herbal substances or herbal preparations?'

Answer

The General Chapters 5.1.4 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use' and 5.1.8 'Microbiological quality of herbal medicinal products for oral use' do not include limits for herbal substances or herbal preparations.

Criteria for herbal substances and herbal preparations are currently being discussed within the Ph. Eur. At this stage, it is still under discussion whether general limits for herbal substances and herbal preparations will be set. Meanwhile, acceptance limits proposed by the applicant should be set and justified in relation to the specific herbal substance and subsequent processing. Reduction of the microbial count at level of herbal substance (e.g. geographical origin, appropriate harvest/collection and drying procedures, treatment with water vapour), herbal preparation (processing) and/or herbal medicinal product (boiling water) should be taken into account when setting the limits.

(2) Question

'With regard to microbiological quality, when is routine testing required and in what circumstances would reduced testing or possibly no testing be acceptable?'

Answer

Herbal substance: There may be a need to specify the total aerobic microbial count, the total combined yeast/moulds count and the absence of specific bacteria. The source, collection/harvesting and treatment of the herbal substance should be taken into account when considering the inclusion of other possible pathogens. The acceptance criteria should be justified by the applicant. In general, routine testing is applicable.

Herbal preparation: As a result of analysis of the herbal substance used for production and in view of the production process, testing of microbiological quality may be necessary. The acceptance criteria and frequency of testing should be justified by the applicant e.g. based on the validation of the manufacturing process and of the holding time of the bulk product.

Herbal medicinal product (HMP): There is a need to specify the total aerobic microbial count, the total combined yeast/moulds count and the absence of specific bacteria. The acceptance limits should comply with the Ph. Eur. The frequency of testing should be justified.

For example for solid dosage forms such as tablets, it is advisable to routinely test the HMP unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. Periodic testing may be acceptable if testing is performed at level of the active substance and complies, and if all measures

[3] USP, chapter <1112> Microbiological attributes of non sterile pharmaceutical products-Application of water activity determination. US Pharmacopoeia Convention, Inc. 31th edition, 2007.

are taken to avoid contamination during the manufacture of the drug product. The sampling frequency and time point for testing in the manufacture should be justified by data and experience. With acceptable justification, it may be possible to omit microbial limit testing for solid oral dosage forms. For example for oral liquids, it is advisable to routinely test the HMP unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. Periodic testing may be appropriate. With appropriate justification, it may be possible to omit microbial limit testing for powders intended for reconstitution as oral liquids.
The frequency of testing should be in line with the CHMP guideline on ICH topic Q 6A (CPMP/ICH/367/96), decision tree 8.

(3) Question

'Which frequency of testing of microbiological quality of HMPs is appropriate during stability studies?'

Answer

The testing frequency is set out in the Guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1 corr).The microbiological quality of an herbal medicinal product has to comply with the requirements given in the European Pharmacopoeia.
Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified. As a minimum requirement compliance should be demonstrated at the beginning (batch release) and at the end of a stability studies (accelerated/intermediate/long term conditions).

(4) Question

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

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. Therefore, the testing of the microbiological quality is essential for these studies.

(5) 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.

(6) Question

'Are there data available linking the ethanol concentration of the herbal preparation to the need for microbiological testing? Is there a threshold beyond which no microbiological testing is necessary?'

Answer

Data are available on the bactericidal effects of ethanol as a function of concentration and contact time. Ethanol is bactericidal in aqueous mixtures at concentrations between 60-95% V/V[4,5,6].

The optimum concentration is generally considered to be 70% V/V. Ethanol is however ineffective against bacterial spores and has a poor penetration of organic matter. Reduced (or omission of) microbiological testing of the herbal preparation should be justified.

[4] Rowe et al. Handbook of Pharmaceutical Excipients, 5th edition. American Pharmacists Association and Pharmaceutical Press, London and Chicago, 2006, pp18-20.
[5] Hugo and Russell. Pharmaceutical Biology, 6th edition. Blackwell Science, Oxford, UK. 1998, pp. 208-215.
[6] Wallhauser. Praxis der Sterilisation – Desinfektion-Betriebshygiene . Auflage 5. Thieme, Stuttgart. 1995, pp. 469-473.

Fumigants

(1) Question

'Can aerosols be considered as acceptable formulations for use as fumigants on herbal substances?'

Answer

According to the definition of UN Food and Agriculture Organisation (FAO) and other Regulatory Authorities, aerosols should not be used as fumigants as the particles are deposited on the outer surfaces only and are unable to penetrate materials sufficiently to be effective. Fumigants are chemicals which, at a required temperature and pressure, can exist in the gaseous state in a concentration sufficient to be lethal to a given pest organism. Only gases are able to penetrate into the material being fumigated and spread in all areas and through the small holes and cracks.

(2) Question

'How potential fumigants residues should be addressed when the supplier does not give information about actual fumigants used?'

Answer

The herbal substance should be tested for fumigants if no information on fumigants is received from the supplier. It should be noted that fumigation of commodities is often required by quarantine or export/import regulations.

Manufacturing

(1) Question

'Do GMP rules apply to active substances of traditional herbal medicinal products?'

Answer

Under the Article 16g, Articles 40 to 52 apply by analogy to traditional herbal medicinal products. This includes Article 46 (f) of Directive 2001/83/EC which states that the Holder of a manufacturing authorisation shall at least be obliged to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured with the detailed guidelines on GMP for starting materials. Guidance is published in the Guideline "Manufacture of Herbal Medicinal Products" (The Rules Governing Medicinal Products in the European Union; Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use; Annex 7).

(2) Question

'Should details of the geographical origin of the herbal substance always be declared in the dossier?'

Answer

Yes. However, if details on the geographical origin are not sufficient, the potential for residues of pesticides and other contaminants should be fully addressed and where necessary appropriate screening techniques applied. Please refer to Annex 7 of the EU GMP Guide.

Quality of water

(1) Question

'What guidance is available on the quality of water (potable water versus purified water) to be used in preparation of extracts/finished products?'

Answer

Extracts: For the preparation of extracts, water should comply with the Ph. Eur. monograph "Water for preparation of extracts" (2249). If potable water is used, the applicant should provide information on the quality of the water used, and discuss the potential influence of variation in mineral content on the composition of the extract.

Finished products: The use of purified water in the preparation of the finished product is required.

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?’

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.

(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

‘How to proceed, if an analytical marker is stable in the herbal substance (Pharmacopoeia monograph) and in solid dosage forms, but unstable in some liquid dosage forms (e.g. acteoside as analytical marker of ribwort plantain)?’

Answer

The Pharmacopoeial marker for the herbal substance could be replaced by a marker appropriate for the dosage form chosen.

(4) Question

‘Are the following limits acceptable for shelf-life specifications?
Standardised extract: ± 10% of the declared value
Quantified extract: ± 10% of the initial value; wider ranges, if justified
Other extract: ± 10 % of the initial value; wider ranges, if justified’

Answer

For standardised extracts see Question 1.

In the case of a herbal medicinal product containing a herbal substance or herbal preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed ± 5% of the declared assay value, unless justified. In the case of a herbal medicinal

product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown (i.e. quantified and other extracts), a variation in marker content during the proposed shelf-life of ±10% of the initial assay value can be accepted if justified by the applicant [Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00, Rev.1)].

It is agreed that in some cases wider limits may be necessary, but the range should not be widened in general. The range of ±10% should be accepted if justified on the basis of analytical data. Wider ranges can be accepted with adequate justifications. Different ranges for different markers in one active substance or one herbal medicinal product can be accepted.

Combination herbal medicinal products should follow the same principles.

(5) Question

'Can, in the case of herbal medicinal products such as herbal teas or products containing herbal preparations as powders, where constituents with known therapeutic activity are unknown, the minimum content of an analytical marker given in the Ph. Eur. monograph for the herbal substance, be accepted as stability criterion at the end of shelf-life for the finished product?'

Answer

No, because the end of shelf-life specification is linked to the initial value.
However, in exceptional cases (e.g. herbal teas or powders with essential oil), where the decrease in essential oil content of 20% or more is known, it can be accepted as long as the determined value at the end of shelf-life is in line with the Ph. Eur. monograph. The content for the batch release should be calculated on the basis of the stability data and should be higher than the minimum content in the Ph. Eur. monograph.

(6) Question

'What stability data is required if one or more active substances are not detectable in the finished product?'

Answer

The concept for the stability testing should be justified in line with the herbal combination guideline (EMEA/HMPC/CHMP/CVMP/214869/06). Each active substance that can be detected in the finished product should be monitored.

(7) Question

'The high instability of acylated glycosides is known. More stable constituents, as hydrolysed glycosides are formed during storage of finished products containing cut/powdered herbal substances or other herbal preparations. Is it acceptable to quantify the herbal substance or herbal preparation on the basis of the combined acylated and hydrolysed glycosides?'

Answer

This should be decided case by case on the basis of the analytical data and taking full account of the implications for efficacy and safety. A suitable stability-indicating method should be used to determine the glycosides and their degradation products unless otherwise fully justified.

(8) Question

'Are stability tests on the basis of one pilot scale batch of the finished product for an application for marketing authorisation/registration and only one production batch for post-approval studies sufficient?'

Answer

No. The requirements in the guidelines should be followed.

(9) Question

'The 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 Rev.2) states that in herbal medicinal products primarily toxicologically relevant impurities/degradation products should be addressed. In which cases degradation products should be analysed and limited in the case of HMP?'

Answer

It is a case by case decision and should be based on the toxicological assessment of the specific herbal ingredients. An example is the determination of aglycones arising from hydroxyanthracene glycosides containing herbal substances or preparations.

(10) 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.

(11) Question

'Is the accelerated (40°C, 75% RH) and intermediate testing (30°C, 65% RH) of active substances (herbal preparations) which are not intended for storage at higher temperatures required?'

Answer

The accelerated and intermediate testing is a part of the overall control strategy. However, some exceptions have been made for herbal preparations and are set out in the 'Guideline on stability testing: stability testing of existing active substances and related finished products' (CPMP/QWP/122/02, Rev. 1).

(12) 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?'

Answer

For herbal drugs/herbal drug preparations (in accordance with the Guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1 corr) testing at the accelerated storage condition and/or at the intermediate storage condition may be omitted if justified by the applicant and if the storage condition (e.g. below 25° C) is clearly stated on the label. In the case of HMPs, 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.

(13) Question

'Is one type of chromatographic fingerprint sufficient for stability testing of the finished product?'

Answer

Yes, in most cases. If more than one group of constituents is known to contribute to the activity of the active substance, the fingerprints should cover all the groups.

(14) 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.

(15) Question

'Which space of time is considered acceptable for the start of stability studies with herbal substances/herbal preparations/herbal medicinal products?'

Answer

In general, up to 3 months after the manufacturing date is considered acceptable for the starting point of stability studies. However, 3 months after the manufacturing date is not acceptable, in case extensive degradation occurs during the first three months.

(16) Question

'Can data from the accelerated or intermediate storage conditions be used to evaluate the effect of short-term transport conditions exceeding the labelled storage condition (e.g. during shipment)?'

Answer

Yes, this is possible based upon a product-specific risk analysis.

(17) Question

'Is blister and container tightness a criterion for the stability of an HMP?'

Answer

Blister tightness is normally tested as an IPC-step (in-process control) and is conducted on randomly selected samples. Theoretically, blister tightness could change during stability testing, especially at higher temperature/humidity and potentially lead to a higher water uptake. As long as the water uptake is within the specified values additional blister tightness testing should not be required. If the water uptake is out of specification, blister tightness should be investigated.

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 acceptable for wild growing plants to be collected and processed by people with limited botanical/scientific education, and for GACP rules to be applied only to further production steps carried out in larger, more developed manufacturing sites?

Answer

The GACP rules apply to collection and processing of wild growing plants. The collectors should be trained and controlled by a local supervisor with a higher botanical/scientific education.

(3) Question

In many cases the distillation of oil from fresh plant material is performed in the fields. In these situations the water used for distillations could originate from wells or directly from a local river. This means water testing is not performed on a routine basis and appropriate specifications or a link to national regulations for potable water are absent. What are the quality criteria for water used for steam distillation?

Answer

In principle the water should be in line with the Ph. Eur. monograph “water for extraction”. An appropriate control of the water steam – which is in primary contact with the medicinal plant - with derived specifications for input water is required. Specifications can be based on the limits applied to drinking water and a database evaluation of historical data following a risk-based approach. Testing should also include parameters that represent a potential risk regarding contamination of the water because of former agricultural or other uses of the area. The frequency of the testing should be established following GMP guidelines. The specification should be approved by the Competent Authority.

(4) 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.