EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Regulatory Q&A on herbal medicinal products

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Question

(R1) Are there any limitations in the number / percentage of excipients in herbal teas?

Answer

The use of excipients in herbal medicinal products is regulated by Directive 2001/83/EC.

Guidance on excipients include:

- the Commission guideline 'Excipients in the label and package leaflet of medicinal products for human use' http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf
- the 'Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product' http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003382.pdf
- the 'Note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products' http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003408.pdf

The pharmaceutical legislation does not provide particulars for excipients' use in traditional herbal medicinal products as the quality aspect of the medicinal product is independent of its traditional use. The legislation does not impose any limitation to the number/percentage of excipients in herbal teas. However, the scientific opinion of the HMPC is that:

- usually no more than 3 excipients should be used in a herbal tea (more than 3 excipients imply technical obstacles in terms of quality testing) and excipients should not represent more than 30% of the total weight
- more than 3 excipients or more than 30% of the total weight in a herbal tea would not raise concerns from a public health viewpoint provided that the marketing authorisation holder/traditional use registration holder can control the quality of the product and that appropriate justification on the need for more than 3 excipients is given by the marketing authorisation holder/traditional use registration holder.

Question

(R2) Are medicinal products containing D-camphor, levomenthol, 1,8-cineol, thymol or rutoside as active substances eligible for traditional use registration?

Answer

Traditional herbal medicinal products exclusively contain as active ingredients herbal substances and/or herbal preparations. Vitamins and minerals with ancillary action may be present. According to Directive 2001/83/EC, herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. Upon clarification by the European Commission it became evident that this list of possible treatments mentioned in Article 1 of the Directive is not exhaustive; moreover no limits regarding the level of

purification or concentration are defined. D-camphor, levomenthol, 1,8-cineol, thymol and rutoside have a long tradition of medicinal use in the EU and are often used in combination with herbal substances/herbal preparations in herbal medicinal products. Taking into account the long-standing use of these ingredients also in combination with herbal substances and/or herbal preparations thereof, the HMPC is of the opinion that these compounds are eligible for traditional use registration, provided that they are of herbal origin, that their quality complies with the respective monograph of the European Pharmacopoeia, where appropriate, and that the medicinal product itself fulfils all requirements for a traditional herbal medicinal product as laid down in Directive 2001/83/EC. The declaration of the particular ingredient in the SmPC should follow the title of the respective monograph of the European Pharmacopoeia or, when absent, of other national Pharmacopoeias or follow other conventional naming references.

Currently, substances of synthetic origin remain unacceptable as active ingredients for traditional herbal medicinal products.

Question

(R3) Are the medicinal products containing propolis eligible for traditional-use registration?

Answer

The HMPC considers that propolis does not meet the legal definition of herbal substances or herbal preparations laid down in Directive 2001/83/EC. The literature classifies propolis as a natural substance of animal origin. As a result of the action of the bees in the course of collection, it is not possible to precisely define the plant part and botanical binomial name as required by the legislation. In addition, it is not clear how the substances collected by the bees are modified.

Therefore, products containing propolis are not eligible for traditional use registration.

Attention should be paid to the possible extension of the scope of the traditional use registration procedure to 'products other than herbal substances with a long tradition of safe use' including 'substances of animal, mineral or metallic origin and micro-organisms' (such as 'honey, royal jelly, propolis, fish oils, minerals, micro-organisms and other substances'). Please see the 'Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products'.

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0584:FIN:en:PDF

Question

(R4) What dosages of vitamins and minerals are acceptable in traditional herbal medicinal products eligible for simplified registration?

Answer

Article 16a(2) of Directive 2001/83/EC states that 'Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins and minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration […] provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s)'.

The pharmaceutical legislation does not impose any limitation to the dosage of vitamins and minerals. However, the scientific opinion of the HMPC is that 'taking into account the pharmacodynamic profile of

typical traditional herbal substances/preparations, dosages of vitamins/minerals that correspond to currently accepted Recommended Daily Allowance (RDA)-values will be considered to be appropriate, unless justified. Dosages of vitamins/minerals that exceed the upper safe limits established by other scientific committees of the EU as applicable will not be acceptable for traditional herbal medicinal products.' as laid in the 'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations'.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003645.pdf

Decisions on eligibility to the national traditional use registration procedure in a Member State are taken on a case-by-case basis by the national competent authority of that Member State. Applicants should therefore contact such authorities for pre-submission dialogue during which the dosage of vitamins and minerals can be addressed.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac0580036d63

Question

(R5) Is reference to "organic farming" acceptable in either the labelling or in the package leaflet of a herbal medicinal product?

Answer

Article 62 of Directive 2001/83/EC states that 'the outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for the patient, to the exclusion of any element of a promotional nature'.

Having regard to the position adopted by the Pharmaceutical Committee in March 2000 on this matter, the HMPC is of the opinion that "accreditation logos", like the "Kosher" and "Halal" or the "organic farming" logo are not acceptable as they cannot not be considered as "health information" and as the risk of an inflation of additional items on the packaging requires a restrictive interpretation of the provisions of Article 62.

However, in some Member States certain expressions, including symbols and pictograms have become established for expressing certain items of information. These items are outlined in the Annex to the Commission 'Guideline on the packaging information of medicinal products for human use authorised by the Community' and they should appear in the so-called 'blue box'. For further information, please refer to the Commission guideline.

http://ec.europa.eu/health/files/eudralex/vol-2/c/bluebox_02_2008_en.pdf

Question

(R6) What kinds of safety data are required for applications according to Article 16a of Directive 2001/83/EC in case of Ayurvedic preparations?

Answer

Article 16c(1)(d) of Directive 2001/83/EC states that 'a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product'.

The legislation does not include any specific provisions for Ayurvedic medicinal products. Ayurvedic medicinal products have to comply with the same requirements as any traditional herbal medicinal

products.

Attention should be paid to statements on several traditional forms of medicine, including Ayurveda, in the 'Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products'.

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0584:FIN:en:PDF

Question

(R7) How can I relate my product to a EU herbal monograph where herbal preparations are listed and have 'well established medicinal use' indications?

Answer

Where the EU herbal monograph refers to 'well established medicinal use', herbal preparations with a specific posology will be stated. The specific herbal preparation listed will have been shown to be effective in published clinical studies for the stated indication. The applicant therefore will need to demonstrate that the proposed product contains a herbal preparation which is 'similar' to the preparation listed in the monograph. To demonstrate comparability the applicant would need to address the following:

- equivalent strength and posology of the intended product*
- the same or similar route of administration
- same plant species
- same plant part
- same extraction solvent with an identical strength
- same or comparable DER**
- same physical state

***Where the herbal ingredient is a standardised preparation or is quantified with respect to active markers then this should be taken into consideration when justifying the 'equivalent strength' of the product. The Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC (EMEA/HMPC/CHMP/CVMP/287539/2005) should be taken into account.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003272.pdf

**A certain flexibility may be possible with respect to DER as often the published references do not include the full details of the DER.

Where possible, data comparing the proposed product with the product cited in the bibliographic references would be important supporting evidence.

Although the concept of bioequivalence possibly could be considered applicable for certain herbal medicinal products, the general principles outlined in the CHMP guideline are not applicable to the majority of herbal medicinal products, as the active constituents are generally less well defined than for chemical entities. However, in the case of herbal preparations where the constituents responsible for therapeutic activity are known, it may be feasible to apply the principles set out in the guidance on

bioequivalence on a case by base basis. (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** Guideline on the Investigation of Bioequivalence). In some such cases the concept of 'biowaiver' may be applicable.

Depending on the product other biopharmaceutical aspects may also need to be considered. For example, in the case of solid oral dosage forms a comparison of solubility and dissolution characteristics may be appropriate particularly where there are active constituents with known therapeutic activity or active markers.

In the case of locally acting products the existing guidance should be taken into account on a case by case basis (CPMP/EWP/239/95 Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents).

For products containing herbal preparations claimed to be similar to one stated in the monograph, the comparability may require bridging studies to address issues relating to non-clinical toxicology and clinical safety/efficacy. In cases where comparability cannot be demonstrated satisfactorily, a full non-clinical and clinical data package may be required.

Question

(R8) How can I relate my product to an EU herbal monograph where herbal preparations are listed with 'traditional medicinal use' indications?

Answer

Where the EU herbal monograph refers to **'traditional medicinal use'**, specific herbal preparations with a specific posology will be stated. The specific herbal preparations have been included in the monograph because they have been shown to fulfil the criteria and have a documented traditional use. The applicant will need to demonstrate that the proposed product contains a herbal preparation which 'corresponds' to the preparation listed in the monograph.

When an application concerns a herbal preparation not mentioned in a monograph, a reference to the monograph could still be possible under certain conditions. Greater flexibility in the choice of preparation may be acceptable in view of the fact that the product is not based on proven efficacy but on medicinal traditional usage. For example, where a monograph lists a range of alcoholic extracts e.g. passion flower 25%, 45%, 70% it may be acceptable to propose a product based on any extract falling within the range of 25 – 70%. Likewise, the DER for many traditional extracts is often not fully documented and therefore it may be appropriate to adopt a pragmatic approach where e.g. a range of DERs is already accepted within the monograph.

In all cases, however, the same plants/plant parts would be required.

The posology for the herbal substance in the proposed product should correspond to that stated in the monograph.

Where a monograph refers to a liquid extract a corresponding dry extract would normally be acceptable.

If the extract solvent and/or concentration is/are different from those given in the monograph, comparability has to be demonstrated by using appropriate analytical data, for example chromatographic profile(s) and marker(s) content.

In absence of a traditional use monograph, reference may also be applicable to a corresponding traditional herbal medicinal product on the EU market.

Question

(R9) Are herbal medicinal products which fulfil the medicinal use requirement of 30 years in a Member State which acceded recently to the EU eligible for the simplified registration procedure (or traditional-use registration)?

Answer

Yes. Section 3.4 ("Procedure for traditional herbal medicinal products (traditional-use registration)") of the Notice to Applicants Volume 2A Chapter 1 (Revision 5 - July 2015, http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf - hereinafter "NtA Volume 2A Chapter 1"), states:

"*According to Article 16c(1)(c) of Directive 2001/83/EC bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Union. Medicinal use which has taken place on the territory of a new Member State is to be taken into account for the purpose of application of Article 16c(1)(c) even if it has partly or fully occurred before the accession of that State to the European Union.*"

Therefore, the period of 15 years (or more) of medicinal use (which is supported by relevant bibliographical or expert evidence) of a herbal medicinal product, or a corresponding product, in a Member State should be taken into account for the purpose of traditional-use registration as a fulfilment of the condition of at least 15 years of medicinal use within the Union, irrespective of whether this use has taken place either fully or partially before that Member State's accession to the EU . Moreover, the medicinal use requirement of at least 30 years shall be considered met if the herbal medicinal product has been in medicinal use for at least 30 years in that Member State only, irrespective of the date of accession of that Member State to the European Union.

Question

(R10) Are herbal medicinal products with medicinal use in Iceland, Liechtenstein and Norway (i.e. EEA EFTA States) throughout a period of at least 30 years eligible for the simplified registration procedure?

Answer

Yes. According to Article 16c(1)(c) of Directive 2001/83/EC, "*bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years*" within the Union shall accompany the application for traditional-use registration.

As stated in Section 2 of the NtA Volume 2A Chapter 1, Norway, Iceland and Liechtenstein have, through the EEA agreement, adopted "*the complete Union acquis on medicinal products and are consequently parties to the Union procedures. Where in this chapter reference is made to Member States of the Union this should be read to include Norway, Iceland and Liechtenstein*".

Therefore, for the purpose of Article 16c(1)(c) of Directive 2001/83/EC, the Union shall be understood as including all countries of the EEA (including EEA EFTA States). The medicinal use which has taken place on the territory of the EEA States should be taken into account for the purpose of traditional-use registration, irrespective of when they joined the EEA. Moreover, the medicinal use requirement of at least 30 years shall be considered met if the herbal medicinal product has been in medicinal use for at least 30 years in an EEA EFTA State (or more EEA EFTA States) only.

Question

(R11) Are medicinal products, which have been extensively used for 10 years in a Member State before its accession to the EU, eligible to demonstrate their "well-established use" according to Article 10a of Directive 2001/83/EC?

Answer

Yes. As mentioned in Section 5.4 of the NtA Volume 2A Chapter 1, according to Article 10a of Directive 2001/83/EC as amended, it is possible to replace results of the pre-clinical tests and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in **well-established medicinal use within the Union** for at least ten years, with recognised efficacy and an acceptable level of safety. In this regard, specific rules for the demonstration of well-established medicinal use, as outlined in Annex I of Directive 2001/83/EC, shall apply.

Section 5.4 of NtA Volume 2A Chapter 1 also states that "*extensive medicinal use (well-established use) which has taken place on the territory of a new Member State is to be taken into account for the purpose of application of Article 10a even if it has partly or fully occurred before the accession of that State*".

Question

(R12) Are medicinal products, which have been extensively used for 10 years in an EEA EFTA State eligible for demonstration of well-established use according to Article 10a of Directive 2001/83/EC?

Answer

Yes, it can be envisaged. However, the criteria to be taken into account for the demonstration of a well-established medicinal use under Annex I of Directive 2001/83/EC refer also to the quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods.

In this regard, the presence of the medicinal product on the market in e.g. Liechtenstein only (due to the size of its population) might be unlikely to suffice on its own to demonstrate extensive medicinal use for the purpose of Article 10a of Directive 2001/83/EC.

Question

(R13) Can the data which formed the basis for the granting of a Swiss marketing authorisation be eligible for demonstration of well-established use according to Article 10a of Directive 2001/83/EC?

Answer

Section 2 of the NtA Volume 2A Chapter 1 states that "in application of a bilateral agreement between Switzerland and Liechtenstein, a Swiss marketing authorisation is automatically effective in Liechtenstein. This recognition has no effects outside the customs union between Switzerland and Liechtenstein. Consequently, a marketing authorisation granted by the Swiss authorities and recognised by Liechtenstein, while Switzerland does not apply the EU pharmaceutical acquis, cannot be

considered as a marketing authorisation granted in accordance with the pharmaceutical acquis for the purpose of EU legislation and in particular cannot be considered as a starting point for the purposes of data exclusivity/market protection in the EU".

For the purpose of demonstrating well-established use, Section 5.4 of NtA Volume 2a Chapter 1 states that "evidence must be supplied to demonstrate that a constituent has been extensively used for the 10-year period, although "medicinal use" does not exclusively mean "use as an authorised medicinal product, so that proof of medicinal use may be submitted even in the absence of a marketing authorisation.

The data of the Swiss marketing authorisation can be provided as supportive data for the purpose of demonstrating well-established use according to Article 10a of Directive 2001/83/EC, but "this cannot replace the need to demonstrate extensive use for that 10 year period. Where relevant, the prevalence of the condition/disease should be taken into account when demonstrating such extensive use", as per Section 5.4 of NtA Volume 2a Chapter 1. In any case, systematic and well-documented use needs to be proven, taking into account the time and the extent of use in the EEA, among other criteria.

Question

(R14) Is a European Union monograph equivalent to a summary of product characteristics (SmPC)?

Answer

No. The **summary of product characteristics (SmPC)** sets out the agreed position of **the medicinal product** as distilled during the course of the assessment process in a national, decentralised, mutual recognition or centralised application procedure. The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.

A **European Union monograph or 'Monograph'** is the result of the HMPC evaluation of safety and efficacy data relevant to **a herbal substance and/or its preparations**, used as active substances for (traditional) herbal medicinal products. Monographs are published together with supporting documents, including the assessment report containing reviews of all available data relevant for the medicinal use of the herbal substance and /or its preparations.
Within an application procedure, additional data may be provided by the applicant to the National Competent Authority to complement the documentation which has been assessed during the preparation of the monograph. For example, for a finished (traditional) herbal medicinal product within a specific application, additional information could be submitted e.g. on local tolerance for a semisolid preparation for cutaneous use. Therefore, the monograph as such cannot be considered equivalent to a SmPC of a finished medicinal product, but it forms the basis for the required individual medicinal product information such as the SmPC and the package leaflet (PL). Furthermore, the wording in the SmPC and the PL should be in line with the current versions of the product-information templates and respective guidance.