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Committee on Herbal Medicinal Products

Reflection paper on data recommendations for herbal medicinal products and traditional herbal medicinal products used in children and adolescents

DRAFT

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Table of Contents

1. Introduction

Herbal medicinal products (HMPs) and traditional herbal medicinal products (THMPs) are used in children and adolescents for minor but common problems such as upper respiratory tract infections, gastrointestinal disorders, skin problems, sleep disorders, loss of appetite or urinary tract disorders. A number of European Union (EU) herbal monographs for both traditional use (TU) and well-established use (WEU) have been issued by the Committee on Herbal Medicinal Products (HMPC) that include a paediatric population within the indication(s).

The inclusion of a paediatric population into the indication(s) of an EU herbal monograph with a specified posology of a herbal substance/preparation, the decisions on contraindications and special warnings, etc. have been based on actual documented use of a (T)HMP in the specific paediatric population, supported by published historical and recent bibliographic/expert evidence and/or data from clinical studies conducted with the targeted paediatric population. The HMPC compiled a list summarising the existing indications and any limitations of (T)HMPs use in children, i.e. 'European Union herbal monographs: Overview of recommendations for the uses of herbal medicinal products in the paediatric population' (EMA/HMPC/228356/2012 Rev. 2).

While the herbal legislation for THMPs (Art. 16a Directive 2001/83/EC) does not make any distinction between adults and children, i.e. requirements on TU in the paediatric population and on specific data are the same as for adults, data from clinical studies conducted in paediatric population on herbal medicinal products (Art. 10a of Directive 2001/83/EC) are often very limited. Efforts were made by the HMPC in recent years to promote data generation from paediatric clinical studies and to discuss use of extrapolation.

The HMPC describes in its 'Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population' (EMA/HMPC/833398/2009) three approaches to be followed in order to stimulate research in this field to allow the correct use of HMPs, as follows:

- Identification of herbal substances/herbal preparations for which a therapeutic benefit is expected (HMPC and PDCO should identify appropriate criteria to select them).
- Provision of guidelines and recommendations for developing appropriate paediatric studies for HMPs.
- Promotion of funding to collect more data on monitoring safe use in children and to stimulate further research.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a harmonised E11A guideline on paediatric extrapolation in 2024. The purpose of this guideline is to provide recommendations for, and promote international harmonisation of, the use of paediatric extrapolation to support the development and authorisation of paediatric medicines. This guideline deals with medicinal products with defined pharmacokinetics and pharmacodynamics and does not explicitly mention that it can be considered for the purpose of HMPs containing herbal substances/preparations that are complex mixtures of constituents with different properties.

2. Scope

This reflection paper aims to provide basic recommendations for establishment of EU herbal monographs with a paediatric indication by the HMPC. These recommendations can be applied by analogy by the national competent authority (NCA) when assessing (T)HMP dossiers or by applicants

compiling dossiers of (T)HMPs. Major aspects to be considered are the differences in organ systems maturity and related changes in pharmacological properties of herbal substances/preparations, available efficacy and safety data, suitability of a pharmaceutical form, and legal provisions to be fulfilled for both TU and WEU applications, especially for clinical data.

3. Quality, composition and formulation-related aspects

Quality aspects, i.e. manufacturing process, of (T)HMPs are not addressed in detail in the assessment reports substantiating the establishment of EU herbal monographs. They are however of major importance when evaluating (T)HMP dossiers in marketing authorisation/simplified registration procedures at NCA level. (T)HMPs indicated for children should be age-appropriate ensuring that children in the target age group will have access to medicinal products with a consistent quality and safety with adequate patient adherence. The EMA in its 'Guideline on pharmaceutical development of medicines for paediatric use' (EMA/CHMP/QWP/805880/2012 Rev. 2) addresses age-appropriate aspects with respect to characteristics of active substance, route of administration and dosage form, dosing frequency, excipients, patients' acceptability, packaging as well as user information for medicinal products developed for children. Labelling recommendations related to safety of excipients are published in the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668). All these guidelines are also applicable for (T)HMPs.

The presence of toxic herbal compounds and their safe limits, e.g. estragole and pulegone/ menthofuran, or of contaminants, e.g. pyrrolizidine alkaloids (PAs), with respect to specific age groups, body weight, route of administration should be analysed and reduced wherever possible based on recommendations summarised in public statements developed by the HMPC, the European Pharmacopoeia etc. (T)HMPs may contain significant levels of ethanol arising from its use as an extraction solvent in liquid extracts and tinctures or when added as a diluent to liquid herbal preparations. The use of ethanol is necessary for extraction of some active constituents. Depending on its amount, the use of such solvent could be unacceptable in some or all paediatric age subgroups due to its effect on a developing central nervous system. The HMPC summarised aspects to be considered for ethanol content in the (T)HMP used in children in its 'Reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products used in children' (EMA/HMPC/85114/2008) and further safety recommendations on ethanol are available also in the aforementioned excipients guideline. Other possible issues regarding age-inappropriateness can arise from the lack of appropriate formulations for patients unable to suck solid dosage forms such as lozenges.

4. Non-clinical aspects

General requirements for non-clinical data to be submitted in marketing authorisation/simplified registration procedures are summarised in the HMPC´s 'Guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products' (EMEA/HMPC/32116/2005 Rev.1). In general, there are currently no specific provisions for non-clinical data that should be generated for (T)HMP intended for their use in a paediatric population. Documented safe use of a (T)HMP in a specific age group and/or body weight is usually sufficient justification for the absence of non-clinical data.

However, juvenile animal studies could be considered necessary in rare cases, such as when the active constituents of the herbal substance/preparation are associated in the literature with effects on development or target organs that undergo major changes in the clinical age range being targeted.

'ICH guideline S11 on nonclinical safety testing in support of development of paediatric pharmaceuticals' (EMA/CHMP/ICH/616110/2018) recommends approaches for the non-clinical safety evaluation of medicinal products intended for development in paediatric populations and is to be considered for such juvenile animal studies.

5. Clinical aspects

5.1. General considerations

General requirements for clinical data to be submitted in marketing authorisation/simplified registration procedures are summarised in the HMPC´s 'Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 Rev. 1).

The paediatric population spans a wide range of age groups, from neonates to adolescents. Each subgroup is different in terms of organ maturity, therefore pharmacokinetics and pharmacodynamics of active substances can be different and subsequently efficacy and safety. Moreover, there is overlap when considering, e.g. the organ maturity of subgroups. These general principles are applicable also to (T)HMPs.

5.2. Well-established use (WEU)

5.2.1. Data substantiating WEU

The only proof substantiating the indication of an HMP in children and adolescents are published clinical studies of sufficient quality in the relevant age groups, which may be supported by alternative sources of data where justified (see below). Also, the principles laid out in the ICH E11A guideline may be useful when considering whether alternative sources of data, e.g. real-world data (RWD), might in some circumstances help to perform the benefit-risk assessment for an HMP in the paediatric population.

The submitted bibliographical documentation should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature. All documentation, both favourable and unfavourable, must be communicated.

5.2.2. Insufficient levels of WEU evidence

The requirements for the paediatric population are generally the same as for the adult population.

From the current perspective, the 'old' WEU products were often based on limited data (case series, inappropriate clinical studies, etc.) although this evidence was legally sufficient at the time of approval. Therefore, these marketing authorisations should not be simply accepted for the establishment of EU herbal monographs. The data should be carefully reviewed in line with current standards for clinical assessment.

Data from combination products is not sufficient for mono-component products if this is the only evidence to be used, since it is impossible to separate the efficacy of one component from that of another.

5.2.3. Posology

Only doses that have been shown to be effective and safe in clinical data should be used, as only these doses have established efficacy and safety.

5.2.4. Combination of herbal substances/preparations with WEU

For combination HMPs, sufficient clinical study data that substantiates the efficacy of a combination HMP is required, since each individual component may affect the others pharmacodynamic and pharmacokinetic properties.

Evidence from combination products cannot be used to prove WEU of the individual components. If individual components are meant to work on the same organ system, it is not possible to distinguish the effect of each component. Similarly, if one component is removed from a combination product, it may bring into question the efficacy of the combination product as there is no data on the individual contributions from each component.

5.3. Traditional use (TU)

5.3.1. Data substantiating TU

A TU indication in a specific paediatric age group should, in principle, be granted only if there is evidence for a specific herbal substance/preparation to be used without medical supervision in that age group and for a determined route of administration and dosage form. This approach, therefore, follows the current legislation where efficacy is plausible, and safety established by evidenced long-term use with no unacceptable safety issues. There can be also examples, where an indication cannot be granted in a specific age group (in an EU herbal monograph or in an SmPC of a THMP) despite the availability of a corresponding product (for the THMP) in that age group on the EU market. Such situations can arise, for example, due to conditions requiring medical advice in patients under a certain age.

5.3.2. Traditional herbal medicinal products (THMPs)

If a THMP with a paediatric indication is registered in at least one EU member state, this is sufficient evidence of TU if the requirements for TU are fulfilled (e.g. 30/15 years).

If a medicinal product with a paediatric indication is authorised in at least one EU member state, this could also be considered as sufficient evidence of TU if this product fulfils the TU criteria.

Sufficient information for a proper evaluation of indications, posology, duration of use and safety should be available.

The requirement for the proof of continuous medicinal use over a time-period applies to both scenarios, as without it, the safety and efficacy of this use cannot be established.

5.3.3. Bibliographical/expert evidence

Generally, for bibliographical/expert evidence it can be challenging to meet the requirements of Article 16a of Directive 2001/83/EC, i.e. medicinal use throughout a period of at least 30 years preceding the

date of the application, including at least 15 years within the EU, since it might often include only sporadic literature references which do not guarantee continuous medicinal use.

Hence, there must be a sufficient level of certainty that continuous medicinal use (including description of the herbal preparations, route of administration, posology, age group, etc.) is available, as summarised in the HMPC´s 'Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 Rev. 1).

5.3.4. Clinical studies

Where only data from clinical studies in a specific age group is available, this should not be considered as sufficient level of evidence for TU, as it does not equate to continuous medicinal use outside the controlled clinical study environment.

5.3.5. Posology

If a TU is confirmed, then the dose mentioned in the source data should be selected for the specific age group, as this dose relates to the actual TU. If different doses are mentioned, a dosage range can be recommended for the same age group.

The duration of use is not always well specified in the literature or in 'old' registrations. A THMP is intended and designed to be used without the supervision of a medical practitioner, therefore the duration of use must be as short as possible, taking into consideration the type of indication and safety knowledge about the product.

5.3.6. Combination of herbal substances/preparations with TU

A TU indication for a specific age group should only be granted for a combination product if TU evidence for that combination is available.

Proof of TU requires the gathering of all available evidence of TU for the specific herbal substances/ preparations combination and based on this evidence of use, a TU indication is granted. This approach therefore follows the current legislation where efficacy and safety of combination is established by evidenced long-term use with no unacceptable safety issues.

5.4. Safety

5.4.1. Contraindications

Contraindications in paediatric populations should be based on actual data. Extrapolation of contraindication(s) from other age groups/classes, etc., is acceptable if they are considered plausible. The current 'A guideline on Summary of Product Characteristics (SmPC)' specifies that 'lack of data alone should not lead to a contraindication'. If there are conditions that, from a safety perspective, do not preclude the use of a product, a warning might be included into section 4.4 of the SmPC or in the established EU herbal monograph.

Data for contraindication(s) can come from different (T)HMPs within the same class. It would be unethical to expose the paediatric population to products if it is generally known that a class of products is harmful. Therefore, contraindications may be aligned with other products in the same class (e.g. essential oils and risk of apnoea, cross-sensitivity within one family), or non-herbal products (e.g. as for *Salicis cortex* which includes contraindication from acetylsalicylic acid due to structural similarity), if there is a robust scientific rationale.

Unacceptable toxicities in the paediatric population can include genotoxicity, carcinogenicity, hepatotoxicity, risk of apnoea, spasms (essential oils) or Reye´s syndrome. This list is not exhaustive and other toxicities can be deemed unacceptable specifically for the paediatric population.

5.4.2. Adverse reactions of (T)HMPs

Acceptable adverse reactions that usually do not lead to refusal of a paediatric indication can include minor gastrointestinal disturbances or mild allergic skin reactions.

One of the conditions for acceptance of TU for an herbal substance/preparation is that they are not harmful under the specified conditions. The assessment of safe use is often a challenge for THMPs, for example, due to some exemptions from the provisions of pharmacovigilance legislation that apply to them, e.g. no need to submit a summary of the pharmacovigilance system, risk management plan, and periodic safety update reports (PSURs) unless requested.

As per Article 16g(1) of Directive 2001/83/EC, the pharmacovigilance obligations provided in Articles 101 to 108b of Directive 2001/83/EC shall apply, by analogy, to THMPs registered further to a simplified registration procedure (TU registration) based on Article 16a of Directive 2001/83/EC. However, holders of registrations for THMPs referred to in Article 16a of Directive 2001/83/EC shall not be required to submit PSURs, except when one of the cases provided for in Article 107b(3)(a) or (b) of Directive 2001/83/EC is applicable, i.e. unless laid down as a condition in the marketing authorisation or requested by a competent authority.

For HMPs authorised according to Article 10a of Directive 2001/83/EC, the pharmacovigilance provisions provided in Articles 101 to 108b of Directive 2001/83/EC apply, as for any other medicinal product authorised on the basis of Article 10a of Directive 2001/83/EC, e.g. to operate a pharmacovigilance system, to submit a summary of the pharmacovigilance system, risk management plan, or PSURs if requested by NCA or if laid down as a condition of marketing authorisation, to make an entry to the so-called 'Article 57 database'. The 'Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations IV: Paediatric population' (EMA/572054/2016), is also relevant for safety assessment.

Also, due to pharmacovigilance specificities, such as underreporting and specificities of THMPs described above, the absence of reported adverse reactions does not necessarily mean that the product is associated with no adverse reactions.

5.5. Extrapolation

5.5.1. Extrapolation in WEU

It must be made sure that the requirements for WEU (e.g. scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety) are fulfilled in the respective age group. This concerns, for example, age groups where clinical study data is not sufficiently robust on their own, rather than age groups where no data are available.

The ICH in their guideline E11A on paediatric extrapolation provides reflections about the extrapolation concept and promotes the use of quantitative methods to help assess the relevance of existing information in one or more source populations to one or more target populations, in respect of the disease, the drug pharmacology and clinical response to treatment. The degree of extrapolation of efficacy depends on the indication and other factors like disease similarity, pharmacodynamic similarity, target organ maturation, relevance of pharmaceutical target, comparability of

pharmacokinetic exposure, etc. This guideline deals with medicinal products with defined pharmacokinetics and pharmacodynamics.

Notably, HMPs have their specificities that may render extrapolation according to the principles described in the ICH E11A guideline an impossibility. Even if comparability of disease between adults and the paediatric population can be supported for some conditions, there is generally an incomplete understanding of how HMPs act pharmacologically and an absence of comprehensive pharmacokinetic data. In the absence of these data, the extrapolation based on pharmacological principles is not possible and clinical data will be needed to support the paediatric indication.

5.5.2. Extrapolation in TU

Proof of TU requires the gathering of all available evidence for the specific herbal substance/ preparation and based on this evidence of use, the indication is granted. Such an approach ensures that plausibility of TU and safety is established by proven long-term use without any unacceptable reported issues while no actual hard clinical data are available. This means that extrapolation of TU, to age groups which are not explicitly mentioned in TU evidence, is not generally acceptable.

In specific instances, like the adolescent population, it can be more difficult to draw a conclusion. In the past, adolescents were treated as adults and sometimes were not mentioned explicitly in the indication. If such a case is identified, a robust scientific rationale supporting the TU indication in adolescents should be available.

5.6. Real-world data (RWD)

In specific cases, RWD can be supportive during the assessment process. Collection of data from different source groups may improve the reliability of the data. The collected data should be sufficiently robust. The focus should be placed on collecting information on size of exposed population, age, symptoms/diagnosis, type of product, dose, outcome of treatment, tolerability and duration of use. It is also important to understand that these data may come with significant limitations with regards to their quality and may only be supportive. For example, it can be difficult to collect data that sufficiently cover the last 30 years. A prospective collection of RWD could be considered when possible and aspects of this collection should be ideally discussed in advance with regulators.

6. References

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6. Public statement on the use of herbal medicinal products containing pulegone and menthofuran (EMA/HMPC/138386/2005 Rev. 1)

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