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Reflection paper on data recommendations for herbal medicinal products and traditional herbal medicinal products used in paediatric patients

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1. Introduction

Herbal medicinal products (HMPs) and traditional herbal medicinal products (THMPs) are used in paediatric patients 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 age range within the indication(s).

The inclusion of a paediatric population age range 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 paediatrics, 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 (Article 16a of Directive 2001/83/EC) does not make any distinction between adults and paediatric patients, i.e. requirements for TU in the paediatric population and on specific data are the same as for adults, data from clinical studies conducted in paediatric population on HMPs (Articles 8(3) and 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 already 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) the need for initiatives to specifically stimulate research in this field to allow the correct use of HMPs in the paediatric population. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a harmonised 'ICH E11A Guideline on paediatric extrapolation' (EMA/CHMP/ICH/205218/2022) 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.

2. Scope

This reflection paper by the HMPC aims to provide basic recommendations for establishment of EU herbal monographs with a paediatric indication. These recommendations can be applied by the national competent authorities (NCAs), by analogy, 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 paediatric patients should be age-appropriate ensuring that patients in the target age group will have access to medicinal products with a consistent quality and safety with adequate patient adherence. The European Medicines Agency (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 paediatric patients. 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. Furthermore, specific guidance documents of the HMPC exist, which were developed for paediatric patients (e.g. 'Reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products used in children', EMA/HMPC/85114/2008) or which are also applicable to paediatric patients (e.g. public statements on various toxic herbal compounds such as pyrrolizidine alkaloids (EMA/HMPC/893108/2011 Rev. 1), estragole (EMA/HMPC/137212/2005 Rev. 1 Corr. 1) and pulegone/menthofuran (EMA/HMPC/138386/2005 Rev. 1).

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 and therefore pharmacokinetics and

pharmacodynamics (PK-PD) 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 most important proof substantiating the indication of an HMP in paediatric patients are published clinical studies of sufficient quality in the relevant age groups, which may be supported by alternative sources of data where justified ('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)). Also, the principles laid out in the 'ICH E11A Guideline on paediatric extrapolation' (EMA/CHMP/ICH/205218/2022) 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, considering 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 legal basis perspective, both WEU herbal monographs and WEU HMPs should be based mostly on bibliographic data covering all aspects of the safety and efficacy. Therefore, simple availability of marketing authorisations of WEU HMPs should not be accepted as sufficient level of evidence for the establishment of EU herbal monographs or approval of new WEU HMPs. On the contrary, the available scientific literature behind these products should be critically reviewed in line with current standards for clinical assessment.

Data generated to support combination products is not considered sufficient for mono-component products, if this is the only evidence to be used, since it is expected to be 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 published 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 published clinical study data that substantiates the efficacy of a combination HMP is required, since each individual component may affect the others PK-PD properties.

Evidence from individual components cannot be used to prove WEU of combination products. 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 a summary of product characteristics (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, 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.

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 TU requirements of Article 16a of Directive 2001/83/EC, 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 all 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 safety and plausible efficacy 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 may be included into section 4.4 of the SmPC (and corresponding section of the package leaflet) or in the established EU herbal monograph.

Data supporting contraindication(s) can be derived from different (T)HMPs within the same class. It would be unethical to expose the paediatric population to medicinal 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 a robust scientific rationale is available.

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 the acceptance of TU for an herbal substance/preparation is that they are not harmful under the specified conditions of use. The assessment of safe use is often challenging for THMPs, for example due to some exemptions from the provisions of pharmacovigilance legislation that apply to them, e.g. absence of requirement to submit a summary of the pharmacovigilance system, risk management plan, and periodic safety update reports (PSURs) unless specifically 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, for example, to operate a pharmacovigilance system, to submit a summary of the pharmacovigilance system, risk management plan, or PSURs if requested by NCA or if imposed as a condition of marketing authorisation, to make an entry to the '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.

Underreporting of adverse events can occur also in (T)HMPs field. This together with specificities of THMPs described above, need to be considered during the assessment process as 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 ensured 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. In principle, resorting to extrapolation is also acceptable to fill gaps in the available evidence for the respective age groups. This, however, refers to scenarios where published clinical data are not sufficiently robust on their own, and not to those where new clinical data need to be generated.

The ICH in their E11A guideline on paediatric extrapolation provides reflections on the extrapolation concept and promotes the use of quantitative methods to support the assessment of 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, PD similarity, target organ maturation, relevance of pharmaceutical target, comparability of PK exposure, etc. The principles described in this guideline are considered applicable to WEU HMPs.

At the same time, HMPs have their specificities, namely there is generally an incomplete understanding of how HMPs act pharmacologically as well as absence of comprehensive PK data. This data gap restricts the approaches available to support paediatric indications, allowing for methods like paediatric dose-response analysis but limiting others, such as PK-PD or exposure-response analyses.

5.5.2. Extrapolation in TU

Proof of TU requires the gathering of all available evidence for the specific herbal substance/ preparation and the indication is granted based on this evidence of use. Such an approach ensures that plausibility of TU and safety is established by proven long-term use without any unacceptable reported issues. This means that extrapolation of TU, to age groups which are not explicitly mentioned in TU evidence, is not generally acceptable.

In specific instances, e.g. adolescent population, it may be more difficult to draw a conclusion as use in adolescent may not have been explicitly mentioned in the posology. 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, e.g. it can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan in case of WEU HMPs. It is also important to recognise that this data may come with significant limitations with regards to their quality (e.g. lack of granularity, lack of fit-for-purpose data) and therefore would not replace the need for interventional clinical data. For example, it can be difficult to collect data that sufficiently covers the preceding 30 years. The use of data from different source groups may improve the overall data reliability. The collected data should be sufficiently robust with emphasis placed on collecting information such as the size of the exposed population, age, symptoms/diagnosis, type of product, dose, outcome of treatment, tolerability and duration of use. Prospective collection of RWD could be considered where feasible, and the relevant aspects of such collection should be ideally discussed in advance with regulators.

6. References

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5. Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
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