06 May 2026
EMA/HMPC/358954/2025
Committee on Herbal Medicinal Products (HMPC)

# Overview of comments received on 'Reflection paper on data recommendations for herbal medicinal products and traditional herbal medicinal products used in children and adolescents' (EMA/HMPC/71333/2023)

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| Discussion in Committee on Herbal Medicinal Products (HMPC) | September 2025<br>November 2025<br>January 2026<br>March 2026 |
| Adoption by HMPC | 06 May 2026 |

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## Organisations and/or individuals that commented on 'Reflection paper on data recommendations for herbal medicinal products and traditional herbal medicinal products used in children and adolescents' (EMA/HMPC/71333/2023) as released for public consultation on 01 June 2025 until 31 August 2025

| Name of organisation or individual |
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| AESGP Association of the European Self-Care Industry |
| GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) |
| Gesellschaft für Phytotherapie e.V. |
| Kooperation Phytopharmaka |
| PETA Science Consortium International e.V. |

# 1. General comments

| Stakeholder | General comment (if any) | Outcome (if applicable) |
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| AESGP Association of the European Self-Care Industry | We appreciate the draft reflection paper on herbal medicinal product (HMPs) for use in children.<br><br>As there is a growing need for HMPs indicated in children, it has become more and more pressing to extend marketing authorizations and registrations. HMPs have a long experience of use on the market in a broad therapeutic range which support pragmatic extrapolation concepts.<br><br>ICH E11A provides a general, flexible framework for pediatric extrapolation, promoting the use of extrapolation when disease, drug pharmacology, and response to treatment are "sufficiently similar" between reference (usually adults) and pediatric populations. It supports leveraging modeling & simulation, real-world data, and expert opinion, and encourages minimizing pediatric exposure to clinical trials where justified.<br>This reflection paper rather limits the application of extrapolation for herbal medicinal products (HMPs), not taking into account that the extrapolation approaches following guideline ICH E11A are not limited to medicinal products with well characterized pharmacokinetics and pharmacodynamics (e.g. p.8-9, lines 287-292) or classical extrapolation approaches.<br>According to the ICH E11A guideline, starting points are the similarity of the disease, the similarity of the drug pharmacology and the similarity of the response to treatment, taking all available evidence into account. If there is evidence for sufficient similarity, no additional data are required, while in case of larger differences and gaps in knowledge, more data are needed (as described in ICH E11A). Accordingly, first all means of extrapolation should be used, and only if these are not sufficient, additional clinical studies may be required. The emphasis should be rather placed on the consistently favorable and well-known efficacy and risk profiles of HMPs.<br><br>In general, the present draft mainly highlights hurdles rather than chances and hence makes extrapolation rather more challenging than highlighting ways forward. | All the received comments on extrapolation relate to similar issues. Therefore, for better clarity, one consolidated answer has been prepared to answer all of them in one place:<br><br>It is agreed that WEU herbal medicinal products are not excluded from the scope of the ICH E11A extrapolation guideline and that the principles described in this guideline are applicable to WEU HMPs, despite the fact that WEU HMPs usually do not provide comprehensive pharmacokinetic and pharmacodynamic data. This is also acknowledged in the ICH guideline which states that when there is lack of correlation between systemic drug exposures/biomarker and therapeutic response, dose-response relationships can rely on a clinical endpoint. The respective parts of the reflection paper have been therefore updated accordingly.<br><br>It is not agreed that requirements for WEU HMPs should be lower compared to non-herbal medicinal products. Currently, the legal requirements for WEU HMPs are identical with the requirements for non-herbal WEU medicinal products.<br><br>It must be underlined that in line with the ICH E11A guideline, extrapolation concerns both efficacy and safety. Therefore, it is not agreed that the main focus of |

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| | It will be important to re-work this draft to enable pragmatic ways forward to meet the need for more pediatric herbal medicinal products and to de facto limit off-label use in children. | extrapolation exercise in WEU HMPs should be on safety only.<br><br>At the same time, in line with the ICH E11A guideline, the use of paediatric extrapolation ensures that the paediatric population only participates in clinical trials when necessary for further scientific understanding of the paediatric use of a medicinal product. First, available published data should be reviewed to confirm the acceptability of WEU status and to identify possible gaps in evidence. If any gaps in evidence are identified, an assessment in line with the ICH E11A guideline should take a place to understand whether it is acceptable to fill these gaps with extrapolation. Only if this is not possible, generation of additional paediatric data should be required. These principles are also described in the ICH E11A guideline; therefore, no additional changes are proposed to the reflection paper.<br><br>It is agreed that HMPs tend to have good safety profiles with wider safety margins, although this is not always the case. This is also acknowledged in the ICH E11A guideline which states that if the safety margin is wide, it may be acceptable to target higher exposures than in adults. As the applicability of this guideline was acknowledged, no additional changes are proposed to the reflection paper.<br><br>It is agreed that evidence from similar/same-class products could be included among alternative supportive data sources. This approach is also supported by the ICH E11A guideline. At the same time, the differences |

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| | | between products need to be reviewed critically in line with the guideline. As the applicability of this guideline was acknowledged, no additional changes are proposed to the reflection paper.<br><br>The proposed approach of conditional approval of adjacent paediatric age groups where generation of data in the adjacent paediatric age group would take place only after granting of conditional approval for the respective age group is not supported. This is because according to the current requirements for conditional marketing authorisation, the product has to fulfil an unmet medical need. However, HMPs are generally not used in indications where significant unmet medical need exists. Second, to grant a conditional marketing authorisation, the benefit-risk balance in the respective age group needs to be positive while according to this proposal, no data would be available in the respective age group for benefit-risk assessment. This way of extrapolation is also not in line with the requirements set by ICH E11A guideline. Third and most importantly, according to the current legal requirements, such a conditional approval does not exist in monograph development.<br><br>As for TU herbal medicinal products, 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 |

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| | | 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. |
| GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | As a leading society in the field we very much appreciate this initiative and the developments of a framework to for establishing of EU herbal monographs focusing on paediatric indication by the HMPC. Clearly safety is a core foundation of this and the scientific data very strongly indicate that specific requirements are needed for use of these products in children\<br><br>We also argue that these (T)HMPs are generally considered to be safe and as such pose a limited risk, esp. if used at the recommended dose levels. Importantly, this needs to be seen in the context of the wider situation as it relates to the use of superficially similar products without medical regulation.<br><br>There is a need for an integrated strategy at an EU level as well as in a systematic assessment of the evidence base, which requires investment in research and development initiatives at an European level.<br>The document in its present form is rather setting the bar for authorizing or registering herbal medicinal products to the same level as for new chemically synthetic products for RX indications like oncology with an unknown or unfavourable safety profile, while herbal medicines in many case have been show to have a therapeutic dose range several hundred fold below doses of toxicological concern, and have been used since decades within the general pharmacovigilance system for drugs.<br><br>At this point the new guideline for pediatric extrapolation comes in. Key principle of the approach given there is, that there is a continuity between products, where the therapeutic profile in adults and pediatric age groups is similar, so that extrapolation is easy, and products, where an extrapolation is more challenging or even impossible. | Please see the consolidated answer above.<br><br>As for the last paragraph, this document is not intended for regulation of supplements but for herbal medicinal products. |

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| | First step is accordingly to assess the similarities of the disease, of the drug pharmacology, and the response to treatment.<br><br>First, all existing evidence needs to be assessed and taken into account, and if similarity is proven by this, even no additional data might be needed. So, a general ask for specific types of data (e.g. RCTs) as a precondition for the use in the pediatric age group is not in accordance with the principles of extrapolation layed down in the ICH E11A guideline.<br><br>In case gaps become apparent, these need to be closed in the sense of a risk-based approach.<br><br>It needs to be clearly emphasized that the scope of the guideline ICH E11A is including all medicinal products including those without defined pharmacokinetics, where instead of exposure the dose is the basis of the extrapolation, as we know it also as the approach feasible for our herbal medicinal products.<br><br>This comment provides the general framework and we fully accept the need for such a framework and endorse the strategy of the HMPC for its development herbal medical product including those which are used due to a medical function but which are regulated as supplements. | |
| Gesellschaft für Phytotherapie e.V. | The Society for Phytotherapy is dedicated to improving the accessibility of herbal medicinal products for the therapy of patients and especially for children. While most herbal medicinal products are well accessible for all adult patient groups, we saw in the past two decades an increase of hurdles.<br>On the one hand, the use of many herbal medicinal products in children got restricted as their use in children, despite in many cases widespread, had not been documented according to newly introduced rules, and on the other hand new regulatory requirements made marketing authorization or registration of herbal medicines for children increasingly difficult. This followed the trend towards extended data requirements in children in pharmakotherapy in general, but missed to take into account, that for herbal medicinal products, there have been no signals questioning the long.-standing safe use in children.<br>For reaching the objective of a better availability of herbal medicinal products in children, it is therefore essential to take the long-standing | Please see the consolidated answer above. |

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| | track record of a generally safe use of herbal medicinal products in children into account.<br>A further point is that the paper covers a field, which falls into the framework of pediatric extrapolation. Here it is helpful to take into account, that the guideline ICH E11A gives a framework which eases extrapolation for all types of medicinal products, including herbal medicinal products. | |
| Kooperation Phytopharmaka | Kooperation Phytopharmaka is a scientific society that is committed to strengthening the role of herbal medicinal products in our healthcare system. The members of Kooperation Phytopharmaka deal with specific scientific and medical issues relating to herbal medicinal products. The focus is always on the quality, efficacy and safety of herbal medicinal products and thus the risk-benefit profile for patients.<br><br>We appreciate the draft Reflection Paper, since it elucidates the current state of discussion in the HMPC. It quotes a number of relevant guidelines for the assessment of medicinal products which are, however, in many cases not suitable to address the specific issues of herbal medicinal products. Moreover, the draft focusses on clinical studies, an element more appropriate for prescription medicines. From our point of view this approach is not realistic since it provides little gain in knowledge for the use of established herbal medicinal products in children. Using the ICH E11A approach would therefore be more pragmatic.<br><br>We disagree with the exclusion of the ICH E11A approach in the draft Reflection Paper which – particularly from an ethical aspect – offers an option to "reducing the risks associated with experimental trials" in children and adolescents.<br><br>At the end of the document, an outlook including perspectives for options to handle the complex issue of data generation is missing, Thus, from our point of view, the draft Reflection Paper is in its present form not yet very helpful.<br>On specific issues, we would like to comment as follows: | Please see the consolidated answer above.<br><br>Specifically, regarding the second paragraph, there are no differences in data requirements between prescription and non-prescription herbal medicinal products.<br><br>As for the last comment, we would like to point the scope of this reflection paper: "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." An outlook including perspectives for options to handle the complex issue of data generation is not part of the scope of this reflection paper. |
| PETA Science Consortium International e.V. | PETA Science Consortium International e.V. (the Science Consortium) welcomes the opportunity to comment on this draft guideline. The Science Consortium advances relevant and reliable non-animal testing methods that protect human health and the environment. We are a member of the International Council on Animal Protection in | No action required. |

| Stakeholder | General comment (if any) | Outcome (if applicable) |
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| | Pharmaceutical Programs (ICAPPP), an organisation founded in 2005 to promote the use of non-animal approaches in pharmaceutical testing guidelines worldwide. | |

## 2. Specific comments on text

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| **1. Introduction (lines 42-78)** | | | |
| 41 | AESGP Association of the European Self-Care Industry | Comment: The work of HMPC on preparing monographs which include the pediatric population is appreciated, as well as the preparation of the list summarizing existing indications for children EMA/HMPC/228356/2012), and an expansion of this work is encouraged. | No action required. |
| 60-61 | AESGP Association of the European Self-Care Industry | Comment:<br>HMPC refers to efforts made on discussions on use of extrapolation; however no respective reference is available where this guidance/discussion/points of consideration can be accessed and be used as reference or guidance in the preparation of applications.<br><br>Proposed change (if any):<br>A reference should be included; if not available today, a HMPC guidance or similar should be established. | This paper is the reflection of the HMPC discussions. General Guidance on extrapolation is given in ICH E11A.<br><br>The respective part of the reflection paper has been simplified to enhance clarity. |
| 62-71 | AESGP Association of the European Self-Care Industry | Comment:<br>The reflection paper is dated from 2011 and in that paper it is acknowledged that<br>○ HMPs are widely used but have not been adequately studied in all cases<br>○ HMPs have no IP rights remaining and are marketed by several MAH<br>○ HMPs could have therapeutic value for children<br>○ Clinical studies are costly and difficult to recoup if there is no incentive as in the case of HMPs<br><br>Three actions have been proposed in that reflection paper to stimulate research; however, no assessment is included on whether these have led to improvements in the availability of paediatric data for HMPs. | The preparation of this reflection paper was preceded by internal revision of all the data/evidence accepted for pediatric indications. The results of this exercise have been incorporated into the recommendations provided in this reflection paper.<br><br>As for extrapolation, please see the consolidated answer at the beginning of this document.<br><br>The respective part of the reflection paper has been simplified to enhance clarity. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | If not, a critical discussion on why the aims of this reflection paper from 2011 could not be achieved should be done before finalising the current draft reflection paper so that any considerations can be included in this document.<br><br>The currently proposed reflection paper will not support the aims set out in the above reflection paper from 2011 as the main focus is on clinical studies with only limited acceptance for extrapolation or other evidence such as RWE/RWD.<br><br>Proposed change (if any):<br>An overall revision on the data/evidence accepted for a pediatric indication is required to also consider other evidence and substantiation instead of clinical studies only, e.g. a reflection paper on how the ICH E11A guideline could be applied to all herbal medicines (including those for which the pharmacological mode of action and/or pharmacokinetics are now or not fully understood) would be more useful. | |
| 72-78 | AESGP Association of the European Self-Care Industry | Comments: The guideline ICH E11A has a clear scope on pediatric drug development in general, and deals with all types of medicinal products, irrespective of the availability of defined pharmacokinetics and pharmacodynamics. As for some products, like products for local application, biologicals or herbal medicinal products, there might be no meaningful pharmacokinetic data available, in chapter 3.3 explicitly the term "dose/exposure" and not pharmacokinetics is used, so to implicitly cover also e.g. herbal medicinal products. There are also no specific requirements for pharmacological data which could exclude herbal medicinal products.<br>The intention behind the ICH E11A guideline is to provide a toolbox to address extrapolation needs for all types of medicinal products. It is method agnostic, i.e., while | Please see the consolidated answer to extrapolation at the beginning of this document.<br><br>The reflection paper has been updated accordingly. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | describing different approaches for leveraging data for extrapolation, it does not exclude any approach.<br>As is stated in the general considerations of ICH E11A, it is key to take into account that a continuum of similarity/dissimilarity in disease, drug pharmacology, and response to treatment may exist between a reference and target population.<br>Accordingly, the types of data and design of studies proposed in a paediatric extrapolation plan can range from exposure-matching (i.e. by just adapting the dose) to randomized controlled trials (RCTs). So it is crucial to embrace this guideline, which in principle makes it possible to expand the use of medicinal products to children even without generating additional data, provided the disease, the pharmacology and the response to treatment can be considered comparable in adults and children.<br><br>Proposed change (if any):<br>Develop specific guidance on how to apply the extrapolation guideline for all HMPs including combination products. | |
| 72-78 | Gesellschaft für Phytotherapie e.V. | The scope of the new guideline ICH E11A is all medicinal products irrespective of the availability of any pharmakokinetics or pharmacodynamics data.<br><br>Its applicability also to products with a lack of systemic bioavailability and pharmakodynamic data, as e.g. products for external use and other products for which no meaningful PK data can be obtained, is clearly obvious. Already in paragraph 3.3 of the guideline, it is stated that the assessment of similarities and differences of the response to treatment should include an evaluation of data on dose/exposure and response to treatment, i.e. in case that no meaningful exposure resp. PK data can be generated, as e.g. in herbal medicinal products, simply | Please see the consolidated answer to extrapolation at the beginning of this document.<br><br>The reflection paper has been updated accordingly. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | the dose or even the response to treatment can be leveraged for the extrapolation. The conclusion, that the guideline cannot not be considered for herbal medicinal products is therefore explicitly not correct – in contrary, by its openness for the use of any type of scientific evidence for the extrapolation, it is supportive for pediatric extrapolation for all product types.<br>And while for many chemically defined products, meaningful data on biodegradation and metabolism are lacking, for many wide-spread constituents of herbal medicinal products, as flavonoids and essential oils, such data are available. Other phytochemical components, as anthocyanidines and carotenoids, are wide-spread in plants in nutritional use in children, easing an assessment for the purpose of a pediatric extrapolation. | |
| 72 – 78 | Kooperation Phytopharmaka | For gaining data supporting the use of medicinal products paediatric extrapolation is a key factor. The term is defined in the ICH E11(R1) guideline as "an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population."<br><br>Given that herbal medicinal products in many cases have a very broad safe and effective dose range and that experience of a safe use in children might have been already gained, it can be assumed that they are quite well suitable for applying the principles of paediatric extrapolation.<br>Aim of the use of paediatric extrapolation is to ensure "that the pediatric population only participates in clinical trials when necessary to further the scientific understanding of the pediatric use of a medicinal product". So, the first task is to leverage all other options | Please see the consolidated answer to extrapolation at the beginning of this document.<br><br>The reflection paper has been updated accordingly. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | for gaining the evidence needed for supporting the paediatric use of a medicine before considering RCTs. According to ICH E11A, "the use of extrapolation reflects that a continuum of similarity/dissimilarity in disease, drug pharmacology and response to treatment may exist between a reference and target population (…). The degree to which similarity is concluded will depend, in part, on a multidisciplinary assessment of the strength of the evidence, the confidence in the data reviewed, and the remaining gaps in knowledge." | |
| **2. Scope (lines 81-87)** | | | |
| 81 – 84 | Kooperation Phytopharmaka | We welcome the provision of basic recommendations for establishing paediatric indications in EU herbal monographs against the background that due to the lack of accepted data the use of HMP in children and adolescents is today still restricted for a large number of herbal preparations. | No action required. |
| **3. Quality, composition and formulation-related aspects (lines 90-117)** | | | |
| 103 – 107 | Kooperation Phytopharmaka | It is self-evident that toxic compounds and contaminants should be limited. This is already laid down in the respective Public Statements and further documents and is not a specific issue for the use in children. Thus, such general statements are not necessary at this stage. We therefore suggest deletion of lines 103 – 107. | Partially agreed.<br>While the extensive explanation was deleted a short link to existing documents was kept. |
| 107 – 113 | Kooperation Phytopharmaka | Moreover, a general statement on ethanol-containing herbal medicinal products is not necessary at this stage. It has been stated earlier that the ethanol content of many herbal medicinal products is necessary for galenic reasons. Safety data from more than 50,000 children in non-interventional paediatric studies with these products, as well as data from routine clinical use in several million children, showed no evidence that the ethanol content contributed to adverse drug reactions [Kelber et al. 2017]. | Partially agreed.<br>Although ethanol might be needed for some galenic reasons, the usage in children should be avoided as much as possible. Therefore, a short link to the existing documents was kept. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| **4. Non-clinical aspects (lines 120-133)** | | | |
| 120-126 | PETA Science Consortium International e.V. | **Comment:**<br>Neither the reflection paper draft nor the "Guideline Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products - Revision 1 (EMEA/HMPC/32116/2005 Rev.1)" referenced in it mentions the adherence to the 3Rs principle or alignment with EU Directive 2010/63 for the protection of animals used for scientific purposes. We therefore suggest adding wording in this regard to the reflection paper, clearly underlining the EU's commitment to phase out animal tests for chemical safety assessments.<br><br>**Proposed change (if any):**<br>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. However, any data generation strategy must abide by the 3R principle (replace, reduce, refine), ensuring that non-animal methods and approaches (such as in vitro, in silico and in chemico; or a combination thereof) are prioritised and animals are only used as a last resort. 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. | The 3R strategy is addressed in the "Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches" (EMA/CHMP/CVMP/JEG-3Rs/450091/2012) and applies also for (traditional) herbal medicinal products. In order to minimise duplication, it is preferred not to repeat it here.<br><br>No changes to the text have been implemented. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| 127-129 | PETA Science Consortium International e.V. | **Comment:**<br>In line with the EU's commitment to phase out animal tests for chemical safety assessments, any mention of specific animal studies, e.g., juvenile animal studies, should be preceded by a mandate to test without using live animals first. This has the potential to reduce the number of animals used in subsequent tests and replace animal tests entirely by combining data from different models using human tissues, cells, etc.<br><br>**Proposed change (if any):**<br>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, additional non-clinical data generation may be required. Mechanistic information on reproductive and developmental toxicity should be obtained using tiered testing strategies with non-animal methods. Juvenile animal studies may only be used as a last resort, abiding by the rules set out in Directive 2010/63 on the protection of animals used for scientific purposes. | Please see comment above.<br><br>No changes to the text have been implemented. |
| 127 – 129 | Kooperation Phytopharmaka | This paragraph deals with a potential utilisation of juvenile animal studies. As is stated in the guideline ICH E11A, in general, when clinical data are available, data from animal models may be less relevant. As juvenile animal studies are typically not suitable to have an impact on the use in children (the HMPC also states "in rare cases"), we propose deletion of this paragraph. | These principles are already described in the ICH S11 guideline which is referred to in the reflection paper. In order to minimise duplication, it is preferred not to repeat it here.<br>Moreover, since data on reproductive and developmental toxicity is in most cases not available, in such rare cases as described it could be necessary to ask for additional data. This should clearly be outlined.<br><br>No changes to the text have been implemented. |
| **5. Clinical aspects**<br><br>**5.1. General considerations (lines 137-145)** | | | |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| Section 5 | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | There are major quality concerns relating to products not regulated as medicine but as food supplements/botanicals and the extend of adulteration is similar in Europe and North America (see e.g. Orhan et al 2024). This highlights the need to strengthen the medically regulated sector and the planned strategies for the use of (T)HMPs in children and adolescents must ascertain that such products are regulated within a medical framework under the HMPC/EMA<br>Orhan N, Gafner S, Blumenthal M. Estimating the extent of adulteration of the popular herbs black cohosh, echinacea, elder berry, ginkgo, and turmeric - its challenges and limitations. Nat Prod Rep. 2024 Oct 17;41(10):1604-1621. doi: 10.1039/d4np00014e.<br><br>This is a general assessment looking beyond the remits of the EMA/HMPC and we recognise the importance to the approach, but also emphasize that any development in the field of he | No action required. |
| 141 – 145 | Kooperation Phytopharmaka | The draft presents a general statement on differences in pharmacodynamics and pharmacokinetics in different age groups. However, this relates to prescription products in general and has to be considered for (T)HMP very critically, since these products in many cases contain well-known groups of substances for which typically no relevant differences in pharmacodynamics and pharmacokinetics should be expected for age groups from 6 or even 3 years on, compared to adults (e.g., Kearns et al. 2003).<br>Paediatric efficacy can be extrapolated from appropriate and well-controlled studies in adults, usually supplemented by other information obtained in paediatric patients, if the course of the disease and the effects of the medicinal product in adults and paediatric patients are sufficiently similar. A study is not required in every | Organ maturation and its impact on PKPD properties and subsequently on efficacy and safety is equally applicable to (T)HMPs as to non-(T)HMPs. The reference Kearns et al., 2003 also does not differentiate between these two.<br><br>At the same time, it is agreed that maturation of PKPD properties occurs in continuum and that some properties become mature before reaching adulthood (e.g. PK in adolescents) while some mature even after (CNS). This needs to be taken into account in a case-by-case assessment.<br><br>No changes to the text have been implemented.<br><br>Please also see the consolidated answer to extrapolation at the beginning of this document. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | paediatric age group if data from one age group can be extrapolated to another age group. This is particularly beneficial with respect to ethical reasons. | |
| **5.2. Well-established use (WEU) (lines 147-179)** | | | |
| 147-179 | AESGP Association of the European Self-Care Industry | We advocate for alignment with the standards established in ICH 11A, which defines a continuum of similarity/dissimilarity between a reference and a target population in terms of disease, drug pharmacology, and response to treatment. This continuum exists particularly for HMPs, which have a well-known safety profile established after years of use under a very robust pharmacovigilance system.<br>The draft should adopt the continuum model for HMPs as well, looking at the extrapolation to the pediatric population as a case by case assessment each individual HMP. This would contribute to limit running complex clinical trials in this specific population. | Please see the consolidated answer to extrapolation at the beginning of this document. |
| **5.2.1. Data substantiating WEU (lines 148-157)** | | | |
| 5.2.1. Data substantiating WEU | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | It is appreciated that the principles laid out in the ICH E11A guideline are seen as useful when considering whether alternative sources of data, e.g. real-world data (RWD).<br>Indeed circumstances where such sources of evidence are useful are not limited in any extent in the guideline ICH 11A. Also quite some other such sources of evidence are listed in table 1 of that guideline. | Please see the consolidated answer to extrapolation and ICH E11A guideline at the beginning of this document. |
| 148 – 153 | Kooperation Phytopharmaka | The draft states that "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 …" According to the HMPC Guideline on clinical safety and efficacy, "in general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy". | It is agreed that within the assessment of WEU herbal medicinal products and WEU herbal monographs, all bibliographic documents, including bibliography that is specific to phytotherapy, should be taken into consideration. The following types of documents might be used: controlled clinical trials, other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case- |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | However, in accordance with this HMPC Guideline, not only controlled clinical studies can be used, but "all bibliographic documents, including bibliography that is specific to phytotherapy, should be taken into consideration. The following type of documents might be used: controlled clinical trials, other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case-control-studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience, for example scientific literature and appropriate monographs …". That means that all such documents mentioned in the Guideline can be taken into consideration. Thus, lines 148 – 150 should be re-worded in this sense, by replacing "the only proof substantiating the indication" by the wording "an important proof substantiating the indication."<br><br>This especially, as the above is also taken into account in the guideline E11A, section 3.5. According to this, "expert opinions, including clinical practice guidelines developed by professional organizations, can be used to support the extrapolation concept. Published clinical practice guidelines from professional organizations are considered more informative than unpublished expert opinions. However, published guidelines and expert opinions can vary between regions based on differences in standard of care. Reliance on expert opinion or standard of care without an assessment of the strength of the evidence is generally not sufficient.<br>In summary, the sources and types of data that are described above each have strengths and weaknesses. The confidence in the degree to which the sources and types of data support similarities between the reference and target populations require an assessment of the quantity and quality of data from each source as well as the context in which the data are being evaluated. A | control-studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience, for example scientific literature and appropriate monographs.<br><br>At the same time, several of these data sources come with significant limitations and biases inherent to their data type. Therefore, published clinical studies of sufficient quality in the relevant age groups are considered the most pivotal part of evidence. These may be, however, supported by alternative sources of data described above.<br><br>The text has been reworded, accordingly:<br>"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 (EMA/HMPC/104613/2005 – Rev. 1). 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.<br><br>Please also see the consolidated answer to extrapolation and ICH E11A guideline at the beginning of this document.<br><br>As for the use of RWD, while it is acknowledged that RWD can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose data), they are currently not expected to replace the need for interventional clinical data. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | critical and multidisciplinary assessment of all the relevant data should be conducted to justify the use of the evidence to support the extrapolation concept."<br><br>Moreover, the principle of extrapolation as mentioned in line 150 – 153 consists in extrapolating existing data without demanding new clinical studies. Thus, from our point of view, reference to the E11A principles related to the use of RWD should not apply „in some circumstances" only, but RWD should be considered as the basis for the benefit-risk assessment for herbal medicinal products in the paediatric population.<br>As a consequence, a suitable approach should start with the bibliographic documentation as proof for indication. In case this is not sufficient, RWD should be used to fill potential gaps, and in case this does not lead to satisfying results, the options of the HMPC guideline on clinical efficacy can be applied. This takes into account the ethical aspects by performing clinical trials only if absolutely necessary. | |
| 148-153 | AESGP Association of the European Self-Care Industry | Comment:<br>The aim of pediatric extrapolation is to ensure that the pediatric population only participates in<br>clinical trials when necessary to further the scientific understanding of the pediatric use of a medicinal product. Provided that disease, pharmacology and response to treatment for a specific product can be considered comparable in adults and children, for all herbal medicinal products irrespective of the legal basis extrapolation must be possible without RCTs.<br>RWE can be superior, given that safety is key for extrapolation (ICH E11A, 3.4.1) and controlled clinical studies with their limited number of participants would not add significant evidence for safety in well tolerable products, as are most HMPs. Therefore, RWE needs to be embraced, as far as available. It would even be desirable | Please see the consolidated answer to extrapolation and ICH E11A guideline at the beginning of this document.<br><br>As for the use of RWD/RWE, while it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose data), they are currently not expected to replace the need for interventional clinical data. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | to support the generation of RWE by opening a path for generating RWE under controlled conditions in age groups adjacent to the age groups authorized earlier. | |
| 148-153 | Gesellschaft für Phytotherapie e.V. | ICH 11A subsumes that there is a continuity of approaches:<br>For some products, an extrapolation from adults to children might be even possible without additional data.<br>For other products, RWD might sufficient, or even the optimum to close the gaps between adults and children.<br>In even other products, even additional data from controlled clinical studies might be needed before an extrapolation can be considered.<br>So, extrapolation is a stepwise approach, which starts with available evidence, and with clinical trials only being needed when this, plus potentially RWE are not sufficient to support the extrapolation to the pediatric age group. | Please see the consolidated answer to extrapolation and ICH E11A guideline at the beginning of this document. |
| **5.2.2. Insufficient levels of WEU evidence (lines 159-167)** | | | |
| 5.2.2. Insufficient levels of WEU evidence | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | The statement "The requirements for the paediatric population are generally the same as for the adult population." is not taking the concept of extrapolation into account.<br>The same is the case with the statement that "'old' WEU products were often based on limited data". Extrapolation is exactly working with limited data to establish the use of a product in a pediatric age group, while what is called "current standards for clinical assessment" has been established for high risk RX products with a narrow therapeutic dose range. This needs to be taken into account when reviewing data supporting the pediatric use of HMPs.<br>In general, it is highly concerning and inappropriate that in this paragraphs products which have been authorized or registered on earlier data and plausibility of TU and safety is established by proven long-term use without any | The establishment of WEU herbal monographs involves assessment of mostly safety and efficacy bibliographic data. These data need to meet the standards at the time of the assessment. Therefore, simple availability of WEU products on the EU market is considered insufficient evidence for monograph establishment if data behind these products cannot be reviewed according to the current standards.<br><br>Second, the same standards apply to WEU marketing applications. Per legal basis requirements, these applications should stand on own dossiers of bibliographic data. References to other products are not considered sufficient as in case of e.g. generics.<br><br>It is however agreed that it might be misleading to state that old WEU products were automatically |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | unacceptable risks seem be questioned here as "old" WEU. | based on insufficient data. The paragraph has been therefore reworded accordingly:<br><br>*From the legal basis perspective, both WEU herbal monographs and WEU HMPs should be based on mostly safety and efficacy bibliographic data and not on references to other available WEU HMPs. Therefore, simple availability of marketing authorisations of other 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 data behind these products should be critically reviewed in line with current standards for clinical assessment.*<br><br>For answer to extrapolation, please see the consolidated answer to extrapolation and ICH E11A guideline at the beginning of this document. |
| 159-164 | Gesellschaft für Phytotherapie e.V. | Data are of course always limited, o also here. The question is whether they are sufficient to predict a future safe use in children. What is called here old´WEU products are by no means old for the individual patient but have now been used safely for twenty and more years in the pediactric population, as the pharmacovigilance data records available for this time have been proven. And to the evidence of safety documented by the lack of safety issues in children in many cases RWE data add, which, on top of safety, also document the therapeutic usefulness of these products in the respective target population.<br>Accordingly, based on this convincing evidence, there should even be more trust into such marketing authorizations instead of questioning them based on formal considerations.<br>In addition, there is also the misunderstanding that WEU was meant to be updated anyway. This is not the case: It | The establishment of WEU herbal monographs involves assessment of mostly safety and efficacy bibliographic data. These data need to meet the standards at the time of the assessment. Therefore, simple availability of WEU products on the EU market is considered insufficient evidence for monograph establishment if data behind these products cannot be reviewed according to the current standards.<br><br>Second, the same standards apply to WEU marketing applications. Per legal basis requirements, these applications should stand on own dossiers of bibliographic data. References to other products are not considered sufficient as in case of e.g. generics.<br><br>It is however agreed that it might be misleading to state that old WEU products were automatically based on insufficient data. The paragraph has been therefore reworded accordingly: |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | was meant to maintain products well-established on a historically established ground, i. e because their benefit-risk-relationship had been established already. This should only be questioned in case new data give arousal in particular as to new safety concerns. Thus, there is no need for re-establishing the benefit-risk-relationship ever anew. | *From the legal basis perspective, both WEU herbal monographs and WEU HMPs should be based on mostly safety and efficacy bibliographic data and not on references to other available WEU HMPs. Therefore, simple availability of marketing authorisations of other 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 data behind these products should be critically reviewed in line with current standards for clinical assessment.*<br><br>As for the use of RWD/RWE, while it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose data), they are currently not expected to replace the need for interventional clinical data. |
| 159-164 | AESGP Association of the European Self-Care Industry | Comment:<br>We object that the argument that today's requirements for drug approval can no longer be met by the applications submitted at that time applies to medicinal products. The time on the market is rather a positive element in the context of extrapolation and therefore we are wondering why it is depicted negatively in the RP.<br><br>In addition, the key task of pediatric extrapolation is allowing an expansion to pediatric age groups based on as limited data as possible.<br>Past such approaches, used 15-20 years ago can be a model for future approaches, given that their suitability has been validated in clinical practice since this period of time, given these products have been used since then as medicines within our PV systems, so generating proof for | The establishment of WEU herbal monographs involves assessment of mostly safety and efficacy bibliographic data. These data need to meet the standards at the time of the assessment. Therefore, simple availability of WEU products on the EU market is considered insufficient evidence for monograph establishment if data behind these products cannot be reviewed according to the current standards.<br><br>Second, the same standards apply to WEU marketing applications. Per legal basis requirements, these applications should stand on own dossiers of bibliographic data. References to other products are not considered sufficient as in case of e.g. generics.<br><br>It is however agreed that it might be misleading to state that old WEU products were automatically |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | the validity of these approaches with regards to therapeutic usefulness and safety. | based on insufficient data. The paragraph has been therefore reworded accordingly:<br><br>*From the legal basis perspective, both WEU herbal monographs and WEU HMPs should be based on mostly safety and efficacy bibliographic data and not on references to other available WEU HMPs. Therefore, simple availability of marketing authorisations of other 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 data behind these products should be critically reviewed in line with current standards for clinical assessment.* |
| 160 – 164 | Kooperation Phytopharmaka | The HMPC draft states that marketing authorisations based on studies available for „old" WEU products should not be simply accepted, but carefully reviewed. From our point view, this means a downgrading of studies based on their age which is not appropriate. Such older studies have substantiated the long-term use of efficacious and safe products in children. The extrapolation approach used in these assessments has been validated in the meantime by the safe use of the resp. products in a large number of children under the surveillance of the pharmacovigilance system.<br>There are also chemical medicinal products in the market which are authorized in the paediatric age groups with older or even without clinical studies in children. Thus, solely the age of a study should not be a criterium. We therefore propose to put the focus more on the evidence of the therapeutic usefulness and safety of the products instead of only the regulatory issue of a sole timeframe, particularly against the background that these studies have already proven to be sufficient to substantiate efficacy and safety. | It is agreed that it might be inappropriate to focus on date of approval as the main parameter of data quality instead of data quality itself. The paragraph has been therefore reworded accordingly:<br><br>*From the legal basis perspective, both WEU herbal monographs and WEU HMPs should be based on mostly safety and efficacy bibliographic data and not on references to other available WEU HMPs. Therefore, simple availability of marketing authorisations of other 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 data behind these products should be critically reviewed in line with current standards for clinical assessment.* |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| 162-163 | AESGP Association of the European Self-Care Industry | Comment:<br>The data should be carefully reviewed in line with current standards for clinical assessment<br><br>Proposed change (if any):<br>Where available alternative sources (RWE/RWD, extrapolation) of data can be used to substantiate the indication in case the data available do not meet current standards of clinical assessment. | This information is already included in the section 5.2.1 Data substantiating WEU: "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."<br><br>At the same time, while it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose data), they are currently not expected to replace the need for interventional clinical data. |
| **5.2.3. Posology (lines 169-170)** | | | |
| 169 | AESGP Association of the European Self-Care Industry | Comment:<br>Remove "in clinical data"<br><br>Proposed change (if any):<br>Only doses that have been shown to be effective and safe should be used. | The establishment of WEU herbal monographs and WEU HMPs involves assessment of mostly safety and efficacy bibliographic data. This means that doses to be recommended need to be clinically proven before they can be recommended as efficacious and safe.<br><br>Not endorsed. |
| **5.2.4. Combination of herbal substances/preparations with WE (lines 172-179)** | | | |
| 171-179 | AESGP Association of the European Self-Care Industry | Comment:<br>How to deal with combination products is not related to the pediatric question and therefore out of scope of this paper.<br><br>Proposed change (if any): Remove paragraph. | This proposal is not endorsed as for combination medicinal products foreseen to be used in children the same considerations apply as to all other medicines. |
| 171 – 179 | Kooperation Phytopharmaka | Again, in this chapter, as a first need clinical studies are mentioned, while in a true extrapolation concept, all evidence available needs to be considered, and only | Combination WEU herbal medicinal products are generally designed according to the principle that individual components "work together" to treat one indication. However, if the only available clinical |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | remaining gaps should be closed with resp. studies, where needed.<br><br>In general, in paediatric extrapolation, there are no issues specific to combination products, given that all available information should be taken into account.<br>Also given that the topic of combination products is already covered in specific HMPC documents, this specific chapter on combinations is not needed in this Reflection Paper and should be skipped. | evidence comes from the combination itself, it is not possible to understand how removal of one or more individual components will affect efficacy of the whole herbal medicinal product and vice versa. Therefore, clinical data are needed, and full extrapolation is deemed insufficient.<br>As guidance in this field is obviously needed, the proposal to remove this chapter is not endorsed. |
| 172 | AESGP Association of the European Self-Care Industry | Comment:<br>"Sufficient clinical study data"<br><br>Proposed change (if any):<br>Replace by "sufficient evidence" to enable also the use of other data to substantiate | It is agreed that in some circumstances, published clinical study data may not be the only source of clinical data. However, in this case, it is not agreed that other types of clinical data could provide sufficiently robust evidence due to their inherent limitations.<br><br>Not endorsed. |
| 172-179 | Gesellschaft für Phytotherapie e.V. | Based on the wealth of non-clinical, and sometimes also clinical evidence, it has been proven possible to well extrapolate efficacy and safety both when combining products as when reducing the number of constituents of combination products.<br><br>There are many use cases from the past, e.g. documented in the regulatory data bases, which have proven the feasibility of such changes.<br>In an evidence-based approach, it is not justified to ignore this valuable experience. | Combination WEU HMPs are generally designed according to the principle that individual components "work together" to treat one indication. However, if the only available clinical evidence comes from the combination itself, it is not possible to understand how removal of one or more individual components will affect efficacy of the whole HMP and vice versa. Therefore, clinical data are needed.<br><br>Not endorsed. |
| **5.3. Traditional use (TU) (lines 181-228)**<br><br>**5.3.2. Traditional herbal medicinal products (THMPs) (lines 192-199)** | | | |
| 191-199 | Gesellschaft für Phytotherapie e.V. | A harmonization based on these principles is desirable, Therefore all member states should accept these criteria, also to harmonize accessibility of THMPs for children. | No action required. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| 192 – 199 | Kooperation Phytopharmaka | The two scenarios presented here seem rather unrealistic. It is unlikely that there are any registered or approved products in one Member State with paediatric indications for which an HMPC monograph with a corresponding paediatric indication has not yet been issued.<br><br>For products without a paediatric indication, it might be difficult to prove the traditional evidence and to meet the requirements in lines 196-199 since a specific paediatric use might not be mentioned in the bibliographic literature and/or many of "older" products were on the market without age restrictions, so that paediatric use was indistinguishable part of the traditional use.<br><br>A further problem arises from the fact that data for a traditional paediatric use could not be generated retrospectively, since newly collected data alone cannot provide evidence of a traditional use. This is also not possible from a purely regulatory perspective.<br>Here, it is necessary to apply a pragmatic approach here and to accept a plausibility of paediatric use as sufficient proof for a paediatric tradition. Subsequently collected data in children should be accepted as proof for traditional use without leading to a new marketing authorisation. | TU implies evidence of continuous use (including description of the herbal preparations, route of administration, posology, age group, etc.) to establish the safe use of a product. As it is explained in the chapter 5.3.3, it can be challenging to meet the requirements of Article<br>202 16a of Directive 2001/83/EC. If the data of continuous use is absent, the indication is not possible, as the safety cannot be guaranteed. This is addressed in the chapters 5.5.2.and 5.6. |
| **5.3.3. Bibliographical/expert evidence (lines 201-209)** | | | |
| 201-209 | Gesellschaft für Phytotherapie e.V. | A harmonization based on these principles is desirable, Therefore all member states should accept these criteria, also to harmonize accessibility of THMPs for children. | No action required. |
| **5.3.4. Clinical studies (lines 211-213)** | | | |
| 210-213 | Gesellschaft für Phytotherapie e.V. | The concept of pediatric extrapolation is explicitly built on extrapolating data from an age group, where evidence has been generated, to other age groups, which are similar, so that the medicine can be used there, too. | In TU, the focus lies in proving evidence of safe use over specified timeframe contrary to WEU where the focus lies in showing efficacy and safety via published clinical data. This means that in absence of evidence of TU in a specific age group, it is not |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | Therefore, starting from available data from clinical trials for one age group could be the ground to take action for e.g. observational studies or other real-world data for safety in neighbouring age groups that are reasonably similar. | possible to "create" TU by extrapolating data from age groups where evidence of TU is available.<br><br>The proposal is not endorsed. |
| **5.3.5. Posology (lines 215-221)** | | | |
| 215-221 | Gesellschaft für Phytotherapie e.V. | Furthermore, the duration of use must be adequate to treat the disease or symptoms efficiently. | This information is already included in the following part: "... ... therefore the duration of use must be as short as possible, taking into consideration the type of indication."<br>No further action necessary. |
| **5.3.6. Combination of herbal substances/preparations with TU (lines 223-228)** | | | |
| 223-228 | Gesellschaft für Phytotherapie e.V. | Whether a pediatric medicine is a combination or not, does not make a difference with regard to its use un children. So, this paragraph can be skipped.<br>Of course, in the ICH guideline E11A, it is clearly stated that also evidence on similar products should be taken into account in the extrapolation. This would also apply to herbal medicinal products, with similar constituents, irrespective whether these are mono products or combinations. | The proposal for deletion of the paragraph on combinations is not endorsed. This is because this paragraph is considered relevant as for combination medicinal products foreseen to be used in children the same considerations apply as to all other medicines.<br><br>As for extrapolation in TU, the focus lies in proving evidence of safe use over specified timeframe contrary to WEU where the focus lies in showing efficacy and safety via published clinical data. This means that in absence of evidence of TU in a specific age group, it is not possible to "create" TU by extrapolating data from age groups where evidence of TU is available.<br><br>The proposals are not endorsed. |
| **5.4. Safety**<br><br>**5.4.1. Contraindications (lines 231-245)** | | | |
| 231 – 232 | Kooperation Phytopharmaka | The HMPC draft seems to only accept extrapolation in the context of safety issues. Extrapolation, however, should | Please see the consolidated answer to extrapolation at the beginning of this document. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | also be possible with regard to efficacy/therapeutic indications. | |
| 231-242 | Gesellschaft für Phytotherapie e.V. | These considerations are not specific to children. The question is whether this is plausible in a pediatric setting.<br><br>The term of alignment is not appropriate here, more clearly stated, because here an extrapolation of data from one product to a different product is necessary.<br>Given the differences in the toxicity and the different dose dependency of putative adverse reactions, such alignment needs to be done with care and based on specific evidence grounded on extrapolation of existing data.<br>Only if there is evidence that there is a reasonable assumption that transferability is possible, this must be taken into account. | It is agreed that alignment should not be done automatically but only if there is sufficient scientific evidence and rationale to do so.<br><br>The current text already contains this rationale: "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."<br><br>Therefore, no further changes are proposed. |
| 239 – 242 | Kooperation Phytopharmaka | The HMPC draft states that contraindications may be aligned with other products in the same class. This suggests, that in this case some kind of uncritical "extrapolation" is possible. From our point of view, it is important that such alignment can be made in exceptional cases only, i.e. in the rare cases where a scientific rationale exists. We propose to add in line 242: "if there is a robust scientific rationale and this is justified for the individual product" | It is agreed that alignment should not be done automatically but only if there is sufficient scientific evidence and rationale for an individual product/preparation to do so.<br><br>The current text already contains this rationale: "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."<br><br>Therefore, no further changes are proposed. |
| **5.4.2. Adverse reactions of (T)HMPs (lines 247-271)** | | | |
| 5.4.2 Adverse reactions | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and | Of course, safety is paramount, and we fully endorse this. However, this needs to be seen in the wider context of such product incl. the current off-label use of (T)HMPs. These are widely employed in children esp. for many of the minor self-limiting conditions (like respiratory | The wording was endorsed. No further changes to the text were proposed. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | Natural Product Research) | conditions) (Hensel et al. 2024, Planta Med 2024; 90: 416–425). Therefore, it is essential that the barriers for (T)HMPs do not push such products out of the EU-markets.<br>Here, too, additional investment and an EU-wide level into research enabling a more informed risk-assessment is essential. | It is agreed that also safety data from off-label use (if available) can provide supportive evidence on safety of (T)HMP. |
| 247-253 | Gesellschaft für Phytotherapie e.V. | From our point of view, this is misleading as it turns around cause and result: Due to the documented long-standing use for at least thirty years, it is clear that their safety is accepted to an extent that leads to the named exceptions for PSURs and RMPs. To turn that around makes the legislation obsolete. | One of the requirements for THMPs is that the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use on the basis of long-standing use and experience. In practice, this involves assessment of mostly safety bibliographic data. Due to some exemptions from the provisions of pharmacovigilance legislation described also here, however, this assessment may become more challenging. Therefore, it is crucial to highlight these limitations so that they can be taken into account during the assessment process. At the same time, this does not mean that they have to necessarily block the assessment. |
| 254-260 | Gesellschaft für Phytotherapie e.V. | "By analogy" article IX of Dir. 2001/83 as amended applies in full. | Article 9 in the directive 2001/83 states the following:<br><br>In addition to the requirements set out in Articles 8 and 10(1), an application for authorisation to market a radionuclide generator shall also contain the following information and particulars: — a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation, — qualitative and quantitative particulars of the eluate or the sublimate. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | | No action proposed. |
| 269-271 | Gesellschaft für Phytotherapie e.V. | Underreporting is described here as a specificity for THMPs – however, there is no proof or evidence. Unfounded assumptions are be out of scope of a science-based reflection paper. | The current text states the following:<br>"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."<br>It does not state that underreporting is unique to THMPs. On the contrary, underreporting of adverse events is a phenomenon widely described in scientific literature, common for all types of medicinal products.<br>It does however state that underreporting of adverse events together with exemptions from the provisions of pharmacovigilance legislation that apply to THMPs need to be kept in mind when assessing safety data of THMPs.<br>To avoid future confusion, it is proposed to reword this paragraph more clearly:<br>"Underreporting of adverse events can occur also in (T)HMPs field. This, together with specificities of THMPs described above, needs to be taken into account during the assessment process as the absence of reported adverse reactions does not necessarily mean that the product is associated with no adverse reactions." |
| 269 – 271 | Kooperation Phytopharmaka | This is a general statement about a potential "underreporting" which has nothing to do with the subject of the draft Reflection Paper. Adverse drug reaction reporting is part of the overall regulatory framework and not specific to the use of herbal medicinal products in children. | It is agreed that underreporting is not an issue specific to (T)HMPs in children. At the same time, underreporting needs to be taken into account during the assessment process due to its potential impact on safety dataset. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | On the contrary: Most herbal medicinal products show a lower frequency in adverse drug reactions based on their benefit-risk assessment as compared to many medicinal products of chemical origin. The pharmacovigilance provisions of the European legal framework including PSUR, literature search etc. are in general also applicable to herbal medicinal products which is already described in detail in chapter 5.4.2 of the draft. | At the same, it is agreed to reword this paragraph more clearly:<br>"Underreporting of adverse events can occur also in (T)HMPs field. This, together with specificities of THMPs described above, needs to be taken into account 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**<br><br>**5.5.1. Extrapolation in WEU (lines 274-292)** | | | |
| 5.5.1. Extrapolation in WEU | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | The guideline E11A deals with medicinal products with defined pharmacokinetics and pharmacodynamics does not mean that it does not cover all other medicinal products and opens ways for the assessment of all other types of evidence. And the statement that there is generally an incomplete understanding of how HMPs act pharmacologically is – in scientific terms – not fundamentally different from chemically defined medicines, which have been on the market for longer periods. Nevertheless, a medicinal use in children has been successfully established for these products.<br>Herbal medicinal products are used for minor self-limiting conditions, like cough and cold and functional GI diseases. This is based on an excellent safety record of these products and the pharmacological action of the products used are similar in children and in adults. | Please see the consolidated answer to extrapolation at the beginning of this document. |
| 279-286 | Gesellschaft für Phytotherapie e.V. | The concept of pediatric extrapolation is explicitly built on extrapolating data from an age group, where evidence has been generated, to other age groups, which are similar. The aim is that the medicine can be used there, too, without unnecessary clinical studies in these vulnerable age groups. This applies also to WEU products. | Please see the consolidated answer to extrapolation at the beginning of this document. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | The guideline E11A does not only deal with products with defined PK or PD data; it is meant for all medicinal products without exemption. Therefore, other data than PK/PD data are taken into account explicitly. | |
| 279 - 286 | Kooperation Phytopharmaka | It is not the intention of the guideline ICH E11A to deal exclusively with medicinal products with defined pharmacokinetics and pharmacodynamics. While in this guideline of course detailed guidance is given on the use of pharmacokinetics and pharmacodynamics data, in case that available, the guideline is not defining requirements on the availability of specific data or on the use of specific tools for extrapolation.<br><br>Further on, it is not specific to herbal medicinal products that there is an incomplete understanding of how they act pharmacologically and that comprehensive pharmacokinetic<br>data are absent. This is to different extents also the case of many chemically defined products, where also by far not all metabolites and their actions are known. For certain chemically defined product groups, like topically applied products, even no meaningful pharmacokinetic data can be generated at all. To take this, and the properties of complex active substances like herbal medicinal products into account, in section 3.5 of the guideline ICH E11A the term "dose/exposure" is used, to make clear, that in case that exposure data are not available, the dose is the basis for extrapolation. | Please see the consolidated answer to extrapolation at the beginning of this document. |
| 279-292 | AESGP Association of the European Self-Care Industry | Comment:<br>Extrapolation is the transfer of one age group to another – this tool needs to be accepted here, too. | Please see the consolidated answer to extrapolation at the beginning of this document. |
| 287-292 | Gesellschaft für Phytotherapie e.V. | A complete understanding of how they act pharmacologically and comprehensive pharmacokinetic data are not available or even needed for chemically defined products either. | Please see the consolidated answer to extrapolation at the beginning of this document. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | While the availability of such data is helpful to ease extrapolation in high-risk pharmaceuticals like e.g. oncological drugs, they are not generally available and also not required. This applies also to herbal medicinal products, as already mentioned above.<br><br>The guideline E11A is explicitly aiming for making the generation of new clinical data obsolete as far as possible, by guiding applicants and authorities to a more efficient extrapolation of existing scientific evidence of diverse types.<br>A general ask for specific clinical data is therefore not necessary and also not in accordance with E11A. | |
| 288-292 | AESGP Association of the European Self-Care Industry | Comment:<br>In line 60 the HMPC refers to discussions on the use of extrapolation for herbal medicinal products. In this paragraph however it seems that in the majority of cases extrapolation is considered not possible. Instead of this general statement it would be more useful for applicants to receive guidance on how the ICH guidance 11A which also has herbal medicinal products in scope, can be used given specific characteristics of HMPs.<br><br>Proposed change (if any):<br>Revise paragraph and provide guidance on what could be possible or how the extrapolation approach could be adapted to HMPs. | Please see the consolidated answer to extrapolation at the beginning of this document. |
| 290 - 292 | Kooperation Phytopharmaka | The collection of product-specific PK/PD data for use as surrogate parameters as the only tool for determining a safe dose in children is not feasible. Therefore, providing PK/PD data should not be made mandatory in paediatric research. Well-established medicinal products are characterized by long-standing use with typically a broad therapeutic range and only few side effects. Based on existing similarities, available and sufficient data from adults (> 18 years) could be extrapolated to an adjacent | Please see the consolidated answer to extrapolation at the beginning of this document.<br><br>As for the use of RWD/RWE, while it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose |

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| | | age group (e.g., 16–18 years) and a specific "Conditional Approval" granted with the condition to establish further data by performing a non-interventional study (NIS). If sufficient evidence is established for the younger age group these data can be extrapolated to a third age group (e.g., 14–16 years), and so on. Based on such a well-documented NIS, an iterative extrapolation from the age group for which the product is already authorised, and a consecutive extension of these age groups (age staggered approach) should be scientifically justifiable. A "conditional approval" followed by an iterative NIS-based process may serve as a sequential deescalation of age groups in the labelling of established medicinal products over time. In addition, the extrapolation of Real World Data (e.g. electronic health records, health claim databases, regulatory and scientific monographs, periodic safety update reports, scientific literature or reference books) on well-established medicines can be an acceptable alternative to the PK/PD based extrapolation [Kraft 2017].<br>It needs to be considered that for many herbal medicinal products detailed knowledge on pharmacology is available. And even if not, most HMPs contain a large number of phytochemical compounds for which PD and PK data are available, so allowing plausible conclusions on the action of the HMP. | data), they are currently not expected to replace the need for interventional clinical data. |
| **5.5.2. Extrapolation in TU (lines 294-302)** | | | |
| 5.5.2. Extrapolation in TU | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | In the guideline E11A, also evidence Including but not limited to systematic reviews, scoping reviews, or meta-analyses, relevant published literature can be used for extrapolation. TU is based on such evidence. Accordingly, also an extrapolation of TU based on such evidence should be possible. | In TU, the pivotal requirement lies in proving evidence of safe use over specified timeframe. This means that in absence of evidence of TU in a specific age group, it is not possible to "create" TU by extrapolating data from age groups where evidence of TU is available to age group where no evidence of TU is available. |

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| | | | Not endorsed. |
| 297 – 298 | Kooperation Phytopharmaka | The draft mentions that extrapolation of TU to age groups not explicitly mentioned in TU evidence is not acceptable. From our point of view, in case evidence for TU without age limitation is available in adults, the use in children should also accepted to be plausible as long as there are no concerns related to safety. | If no age restriction in the indication and no explicit paediatric posology is available, it is very difficult to draw a conclusion on appropriateness of TU in specific paediatric population. In absence of this information, it is not possible to judge whether TU is plausible. No further change has been therefore implemented. |
| **5.6. Real-world data (RWD) (lines 304-311)** | | | |
| 5.6 Big Data and general | GA Gesellschaft für Arzneipflanzen- und Naturstoffforschung e.V. (Society for Medicinal Plant and Natural Product Research) | Real world data are a crucial new way to understand the safety and general benefits of (T)HMPs and we will endorse this strategy and also call for systematic investment by the relevant agencies.<br>The HMPC needs to facilitate such approaches, for example via approaching the relevant stakeholders to develop an integrated and EU-wide funding initiative.<br>More generally, In Europe there is very limited investment in research on HMPs which puts the community at a disadvantage, for example, most notably compared to ASEAN countries, the PRC and the other major Asian markets. | No changes to the text of the reflection paper proposed. |
| 303-311 | AESGP Association of the European Self-Care Industry | Comment:<br>The value of RWE/RWD is increasingly recognized and accepted by authorities and this should also be reflected in this guidance document. Furthermore, guidance on the specific aspects of the collection and use of RWE/RWD for HMPs and/or non-prescription products should be considered. In this context, it should also be noted that data collection in these age groups in CTs is significantly more difficult. This is evidenced not least by the figures from the pediatric studies conducted after the enactment of pediatric legislation. It is more important to accept that the collection of prospective RWD can play a crucial role | While it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations (e.g. lack of granularity, lack of fit-for-purpose data), they are currently not expected to replace the need for interventional clinical data.<br><br>The guidance on the specific aspects of the collection and use of RWE/RWD is out of the scope of this reflection paper. Moreover, these principles are also not considered to be specific to herbal medicinal |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | here and that the derived RWE substantiate an extension of the indication to pediatric age groups. | products and the currently available guidance documents can be used in this regard. |
| 303 - 311 | Kooperation Phytopharmaka | The consideration of RWD in the analysis of the usage of herbal medicinal products in different populations is mentioned only very limited in this draft. This is contrary to the huge effort of EMA to include RWD into the regulatory assessment of medicinal products, especially with the support by the DARWIN project. The EMA approach clearly states that RWD can be very beneficial in analysing the use, safety and effectiveness of medicinal products and can support regulatory decision-making. Therefore, we do not understand why this draft states that "Real World Data are considered to have significant limitations with regard to their quality and may only be supportive". Indeed, RWD can be heterogenous, but this does not necessarily lead to the conclusion that RWD quality is generally low. We would be interested in knowing what exactly the HMPC understands by "limitations with regard to their quality" and what the term "supportive" means.<br><br>Additionally, in the publication by Hölzle et al 2024 an accurate description of herbal substances and preparations in herbal medicinal products is recommended, to ensure comparability and high quality of RWD.<br><br>Several international symposia discussed the challenges and opportunities to use RWD with respect to children and adolescents in the last years. The results have been published in scientific journals. At the latest symposium in July 2024 in Krakow the was an extensive discussion with experts from academia, paediatricians, regulatory authorities (also HMPC representatives) and industry. The participants summarized that there is a widespread and routine use of herbal medicinal products in children and adolescents, but many herbal medicines for children are | While it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations, they are currently not expected to replace the need for interventional clinical data. These limitations include e.g. lack of granularity, lack of fit-for-purpose data or even absence of herbal RWD/RWE as such.<br><br>The text in the reflection paper has been updated accordingly. |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| | | prescribed off-label due to the lack of paediatric approvals, particularly in preschool-aged populations, which often results in dosages being individually adjusted based on adult data. This situation is further complicated by the fact that existing data sources on herbal medicinal products frequently lack complete and standardized information on plant species, preparations, or dosages, making it difficult to generate robust evidence. While randomized controlled trials (RCTs) could address these knowledge gaps, they are costly, time-consuming, and ethically challenging in paediatric settings, which highlights the potential of RWD as a scalable and more feasible alternative. By drawing on information from electronic health records, registries, or pharmacy data—such as those derived from DARWIN /HMPC Pelargonium root projects—RWD can provide valuable insights into the safety, efficacy, and usage patterns of herbal medicinal products in children. Consequently, RWD is increasingly recognized as a valuable complement to RCTs, offering economic, practical, and ethical advantages. However, its successful application depends on close interdisciplinary collaboration between scientists, industry, healthcare practitioners, and regulatory authorities. To fully realize this potential, the symposiums' participants have proposed concrete next steps, including the implementation of further pilot studies, the systematic integration of herbal medicinal product data into electronic health records, and the establishment of harmonized framework guidelines for RWD collection and analysis [Symma et al. 2025].<br><br>Therefore, we encourage HMPC to advocate for greater consideration of RWD in the future assessment of herbal medicinal products. | |

| Line number(s) of the relevant text | Stakeholder | Comment and rationale; proposed changes | Outcome |
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| 304-311 | Gesellschaft für Phytotherapie e.V. | This view on RWD is from our perspective too critical, as it does not include the manifold advantages of RWD. In general, the draft only briefly addresses Real-World Data (RWD), despite EMA's strong emphasis on its value through initiatives such as DARWIN. While RWD can be heterogeneous, this does not mean it is generally of low quality. We therefore question the draft's statement that RWD "may only be supportive" and ask what limitations are specifically meant by this. Recent symposia, including the 2024 Krakow meeting with HMPC participation, highlighted that herbal medicinal products are widely used in children, often off-label due to a lack of paediatric approvals. Given the general aim of reducing RCTs in this population, RWD offers a feasible alternative to generate evidence on use, safety, and effectiveness. However, robust data require accurate description of herbal substances and standardized collection methods, as emphasized by Hölzle et al. (2024) and Symma et al. (2025).<br>Additionally, there is a continuity between cases, where an extrapolation is possible without additional data and other cases, where an extrapolation is not possible and therefore clinical trials are needed to support the extrapolation.<br>In between, there are cases, where RWE is well sufficient or even superior to clinical trials to support the extrapolation.<br>It would help to give RWD greater consideration in this paper, as it is a major source of children's data. | While it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations, they are currently not expected to replace the need for interventional clinical data. These limitations include e.g. lack of granularity, lack of fit-for-purpose data or even absence of herbal RWD/RWE as such.<br><br>The text in the reflection paper has been updated accordingly. |
| In addition | | | |
| New paragraph „Perspectives" | Kooperation Phytopharmaka | Real-world evidence (RWE) may be a valuable source of information on efficacy and safety in children. The recent focus on the potential of RWE for regulatory approval and use may provide an urgently needed solution. The interest in RWE stems from the limitations associated | While it is acknowledged that RWD/RWE can help to inform and support the paediatric extrapolation concept and the paediatric extrapolation plan, due to their inherent limitations, they are currently not expected to replace the need for interventional |

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| | | with randomised controlled trials and the growing opportunities to obtain real-world data from a range of sources. Real World Data (RWD) are related to the health status of patients and/or the delivery of therapeutic measures including drug therapy, which are routinely collected from a variety of sources outside clinical trials. Since herbal medicinal products were rarely approved for children in the past, it is rather difficult to collect RWD in this age group. Nevertheless, due to their good tolerance and wide therapeutic margin herbal medicinal products (HMPs) were used in children to a large extent. In this situation data including electronic health records, health claim databases, regulatory and scientific monographs, periodic safety update reports, scientific literature or reference books should be used for paediatric extrapolation. In addition, similarities of the underlying disease, drug pharmacology and response to treatment should be considered. Since most HMPs contain a large number of phytochemical compounds for which PD and PK data are available, plausible conclusions on the effects of HMPs and their extrapolation for children are also available. All this data should be used for the extrapolation of the use for children without the need to perform controlled clinical studies. | clinical data. These limitations include e.g. lack of granularity, lack of fit-for-purpose data or even absence of herbal RWD/RWE as such.<br><br>The text in the reflection paper has been updated accordingly. |

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