13 September 2011
EMA/HMPC/354690/2011
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on 'Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population' (EMA/HMPC/833398/2009)

Table 1: Organisations and/or individuals that commented on the 'Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population' (EMA/HMPC/833398/2009) as released for public consultation on 18.01.2011 until 15.04.2011

	Organisations and/or individuals
1	MCRN Pharmacy & Pharmacology Clinical Studies Group, UK
2	Dr. Willmar Schwabe GmbH & Co. KG, Germany
3	Royal Pharmaceutical Society , UK
4	Federal Agency For Medicines and Health Products – Unit Homeo-Phyto, Belgium
5	Swissmedic, Swiss Agency for Therapeutic Products, Department of Clinical Review
6	UK Herbal Medicines Advisory Committee
7	Kooperation Phytopharmaka, Germany
8	AESGP- Association of the European Self-Medication Industry
9	BPI - German Pharmaceutical Industry Association
10	GPT- Gesellschaft für Phytotherapy, Germany

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
MCRN	The MCRN Pharmacy and Pharmacology Clinical Study Group agree that the reflection paper is a reasonable review of the current situation with regards to research and information on paediatric uses of herbal medicines. Given that herbal medicines continue to be available to the children of Europe, it is difficult to argue with the conclusions of the reflection paper that further research is needed to establish safety and efficacy in the different paediatric age ranges. However, given that resources may be limited, the group draws attention to the urgent priority to study conventional (allopathic) medicines for children, particularly those older medicines that were supported by the FP7 research programme and focused on the priorities of the Paediatric Committee (PDCO) of the EMA. Since the overall paediatric medicines research capacity is insufficient, it is important that the EC provides funding for research training. The EC should also promote the involvement of ethnic minority practitioners and consumers in policy planning, training and research.	The aim of this paper is to draw attention to the lack of clinical studies on HMPs in children and does not want to interfere with the research on off-label use of medicines, however more evidence is needed in order to make the use of HMPs safer in children. One goal of this paper is to identify which kind of evidence can be achieved at European level. Agreement with this point.
Schwabe	We welcome the draft Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population. We agree with the HMPC that further clinical or cohort studies or epidemiological data are needed to ensure the safe and effective use of well-established use HMPs and THMPs in children.	This paper does not want to give the impression that the lack of paediatric data is a herbal-specific phenomenon, in fact it underlines that the lack of data on off-label use of medicinal products led to the Paediatric Regulation which does not include HMPs.

	We would like, however, to avoid the impression that the lack of paediatric data is a herbal-specific phenomenon. It concerns the majority of well-established use medicines, irrespective as to whether they are synthetic or herbal. There are some herbal medicines with extensive clinical documentation on the use in children that far exceed the documentation available for many synthetic well-established use medicinal products. As far as the proposed approaches of the HMPC are concerned, we suggest the conduct of pragmatic cohort studies as the most appropriate type of trials for the described purpose. An elaborated statement is attached. We would generally not recommend using terms such as “conventional drugs” and “complementary and alternative medicines” which could artificially imply a difference between these two categories which should not exist, especially in relation to well-established use medicinal products. In our opinion, the terms should be replaced by the objective terms “synthetic” and “herbal”. 1 Attachment page 39.	As regards the terminology, it must be taken into account that many drugs are not ‘synthetic’ but biological. For this reason the term” conventional” has been replaced by “other”
RPS	The RPS considers that this Reflection Paper is a good overview of the current position with regard to the current state of research and the information available on the paediatric use of herbal medicines. Both healthcare professionals and patients require good quality evidence on the safety, quality and efficacy of herbal medicines in all age groups, including children. Given the extent of use of herbal medicines across Europe, the RPS supports the view that further research is required to establish the safety, quality and efficacy of herbal medicines in paediatric patients covering various age ranges. Of particular importance will be the effects in children of using herbal medicines in combination with conventional medicines. Children are not just small adults and the way they handle drugs and other compounds is often different to adults, and will change as the child grows and develops. These factors must be taken into account when designing clinical trials, and may affect how paediatric populations are defined.	

	If clinical trials are to be conducted in children it is the RPS's view, there needs to be greater standardisation of the active constituents or ingredients in herbal medicines to address the issue of variability between different manufactures' products. Unless this is achieved, there will be issues around exactly what has caused any positive and negative effects observed in the clinical trials, and may mean results are not applicable beyond the specific herbal product used in the trial. **Research Initiatives** Herbal medicines are being used in the UK and in Europe and there is a clear need for research to be carried out on their use in children. However, while efficacy and toxicity data should be available for all products administered to patients, the RPS believes that research on herbal medicines should only be undertaken where there is a public health imperative for this, for example if a herbal product is being widely used without a good evidence base, and not at the expense of research on conventional pharmaceutical medicines. Herbal medicines are generally obtained by patients outside of the NHS. The RPS has reservations about how randomised controlled trials (RCTs) using herbal medicines in children will be organised, who would sponsor the trials, where the manpower to support the trials will come from, and who would fund the trials. The variable composition of herbal medicines may also make the design of a trial difficult, and there is little or no evidence base to support a suitable dose and treatment regime specifically for children. Therefore, any clinical studies carried out should only use a standardised preparation and preferably one that has been registered under the THMPD**.** The RPS considers that while information obtained from observational and post-	Agreed. The aim of approach 1 is to generate a priority list considering the most used HMPs. The approach 2 will develop which kind of studies are suitable in the specific cases.

	marketing surveillance studies is important, it should be used to support evidence from RCTs and must not be viewed as an alternative.	
	The RPS believes that the creation of a centralised database of all published studies on herbal medicines in children may act as a stimulus for further studies to be carried out. This database may help identify those herbal products that have therapeutic evidence to support their use, as well as encouraging researchers to apply for ethics approval in children, something that is often viewed as an insurmountable obstacle.	This proposal is in principle supported by HMPC.
	Many serious adverse outcomes associated with the use of herbal medicines are the result of herbal medicines being used rather than conventional medicines. This may raise ethical issues in the design of any studies of herbal medicines in children.	This paper expresses concern about the interaction of HMPs with conventional drugs. HMPC is not aware of many serious outcomes of HMPS used rather than conventional ones.
	It is the RPS's view that there should be a mechanism where researchers wishing to carry out clinical studies on herbal medicines in children can obtain guidance directly from the MHRA, possible in a similar way to the "Herbal Forum" which the MHRA holds once a month, where manufacturers of herbal products can ask the MHRA questions about the steps they need to follow in order to register their herbal products.	Approach 2 will deal with this subject.
	Research Funding In the RPS's opinion, any funding that is provided to support studies into the effects of herbal medicines in children must not reduce the level of funding to support studies using conventional medicines in children.	This is not the scope of this paper.
	The RPS considers that it will be unrealistic to expect the manufacturers of herbal products to fund studies that they cannot patent, but has reservations around using financial incentives to the manufacturers of herbal medicines to encourage them carry out clinical trials.	That is why some incentives are necessary.

	At present the paediatric medicines research capacity is insufficient. If new studies using herbal medicines in children are to be initiated, funding should also be made available for research training to encourage, support and develop new researchers who wish to become involved in paediatric medicines research. All publicly-funded clinical studies must be registered with an appropriate body such as the UK Research Integrity Office.	Agreed. Agreed.
Federal Agency For Medicines and Health Products – Belgium	Although we agree with the need for further investigations when it comes to use of medicines in children in general, we would like to draw the attention to the fact that people are constantly in search of products that help alleviate "common" minor problems and now often chose for herbal (preparations) for the reasons as cited on page 3 paragraph 2 of the Reflection Paper: *"Probably the most important reason for this general popularity is that parents consider them as less dangerous than "conventional" medicinal products because they are "natural", used over hundreds of years and may not be considered as "real drugs"".* When further clinical studies might possibly shed a new light on the appropriate use of (T)HMP in children and indications might become more restrictive or contra-indications might be extended, products not marketed as medicines (e.g. as food supplements) based on the same or comparable herbal (preparations) might still be on the market, bearing no therapeutic indications, no appropriate warnings and might also be combined with standard treatments and consequently interact. Initiatives should be undertaken on that level as well to avoid people using these products in children on the basis of the same Public Health concerns that incited the HMPC to release this reflection paper.	Agreed. The food supplement issue is an important point. Agreed.

	Although the HMPC is only competent for HMP, The Committee should try and raise awareness among all stakeholders including the European Commission of the need to adequately address this issue for the benefit of Public Health on ALL levels. Otherwise the problem will just switch to another distribution channel and will continue to exist. On the other hand, experts in the Belgian Commission for Herbal Medicinal products have, on different occasions, expressed the importance of being able to use (T)HMP in children within the context of e.g. • avoiding resistance to antibiotics by trying to avoid their use by using essential oils first (e.g. via suppositories) • cough relief where the use of herbal preparations could be an alternative to conventional cough suppressants. It was therefore proposed that a more pragmatic approach could be acceptable in order to prove their safe use and efficacy by e.g. • allowing non-interventional studies, risk management programs, proactive pharmacovigilance, … • hereby taking into account the proposed indication and the required level of evidence associated with the used authorization/registration procedure	The pragmatic approach will be considered in approach 2.
Swissmedic	Herbal medicinal products generally are used in unspecific or harmless conditions/indications and show weaker effect-sizes than synthetic medicinal products if they are proved in clinical studies. So herbal medicine products obtain in most cases only minor or medium therapeutic indications or claims. They rarely can be classified as “essential drugs”. Clinical studies in the paediatric population with herbal medicinal products meet therefore particular and in some aspects “higher” ethical requirements than studies with i.e. “essential drugs” as to their lower benefit in comparison with similar risks. Research in children with an herbal product can be labelled as “ethically” if it helps to estimate the safety or to find the right dose for the product in different	Data on safety and on the right dose in different age groups should be necessary for every HMP. Approach 2 will provide recommendations on how to collect data on efficacy.

	age groups, from birth to adolescence. But confirming efficacy of an herbal medicine product would require studies with higher scientific strength. This evokes more ethical implications and questions as to the kind of intervention, the right comparator and definition of endpoints. We would appreciate it if these aspects are considered and discussed more detailed in the reflection paper.	
UK Herbal Medicines Advisory Committee	The Herbal Medicines Advisory Committee advises on the safety, quality and efficacy, in relation to human use, of herbal medicinal products (HMPs) eligible for registration under the simplified traditional use registration procedure established under European Directive 2004/24/EC and also of unlicensed HMPs (unless these are subject to an application for a marketing authorisation, product licence or a homoeopathic certificate of registration). Its comments on the above consultation are as follows. The Committee believes that there is a need to be able to systematically appraise the safety and efficacy of HMPs in children under 18 years of age: however this point is also applicable to many HMPs used for those over 18 years. As such therefore it is highly unlikely that ethical permission would be given for a "classic" pharma approach to conducting a clinical trial of HMPs in children, if a corresponding study has not already been conducted in adults. However there is potential benefit in examining the currently available observational data in order to inform the development of priorities in relation to future potential studies in children. The extent and nature current use of HMPs in children is not well known or quantified. However a number of surveys amongst GPs and other practitioners suggest that up to 10% of children receive HMPs, and other complementary therapies. The risks associated with this use are unknown. An examination of practice in Aberdeen, Scotland concluded that 16% of complementary therapies used by practitioners were for children (many of them infants). This might indicate a need for a formal risk assessment of HMP use in children with a term	Agreement in principle. Nonetheless the “HMPC monographs” paragraph shows that data are often available for adults and not for children and adolescents, The Risk assessment approach will be considered in approach 2.

	of reference that addressed its complementarity with the regulation of HMPs. There are few general data on the uncertainty and variability of the safety and efficacy of HMP in children; there is arguably a need for this to inform public education on the use of HMPs. This type of information would of course fit in with a risk assessment/analysis. Such an analysis would enable assessment of uncertainties and variabilities in dose, exposure and appropriate outcomes in children. No doubt this would also facilitate the appraisal of any claims made regarding the applicability of HMPs in children. Any clinical study would need to consider many of the points made above. Of importance would also be an agreed and transparent approach to the type of evidence that would be acceptable in designing a study and justifying a claim. We support the proposed approaches to the challenge faced by the lack of evidence. However the three approaches outlined in the conclusion to the paper need to be better contextualised by a preliminary "systematic" risk assessment to help to define and prioritise the issues around the use of HMPs In children. Approach 1: The bases for approach 1 are not proposed; these could be addressed better from a more complete idea of current practice, and we believe stimulation of further research on current practice in children (e.g. by identifying funding for such work) would be extremely helpful in this respect. Approach 2: This is clearly important, and appropriate safety endpoints and efficacy outcomes should be easily deduced. The former could come from existing and current considerations for "endpoints" in studies involving children (COMA produced a guideline for infant formula studies, and this initiative has been followed up in the UK, USA and Europe). Approach 3: We support this approach. Clearly however, bids for funding for studies to monitor safe use of HMPs in children should be rigorously reviewed to	This is a general paper and for this reason the approaches are not detailed.

	ensure that they are relevant and well-designed. Professor PA Routledge (Chairman) on behalf of the UK Herbal Medicines Advisory Committee. April 2011. *(We particularly acknowledge the advice of Professor P Aggett, HMAC member and paediatrician)*	
Koop	Herbal medicinal products have been, and are, an important part of the therapeutic options in paediatrics and in self-medication in children in Germany and Europe. For Kooperation Phytopharmaka, as a scientific society in the field of herbal medicinal products, maintaining and improving the availability of herbal medicines for the paediatric population is a central issue. Results of a symposium of our society on that subject have recently been published in the Journal “Zeitschrift für Phytotherapie” (Vol. 31 (1), 2010). Though there is already now a considerable amount of clinical data available for some herbal medicinal products, for many others these data are lacking. This is due to diverse reasons: One of them is the fact that, so that the interest to conduct studies from the point of view of academic science was limited. As also stated in the reflection paper, another even more important reason is the fact that many of the herbal medicinal products used in children cannot effectively be protected by patents, so that also an effective protection of intellectual property rights on studies in children is not possible, even not under the conditions of PUMA. Therefore, for an individual pharmaceutical manufacturer, a return of investment in such studies is not to be expected. Pharmaceutical manufacturers in the field of herbal medicinal products are mostly in a struggle for survival in a highly competitive market, and have to	Agreement with the issue of the lack of patents but for the rest of the comment, the reflection paper states that all medicinal products intended for use in children should be properly assessed.

	stand the competition by manufacturers of other products such as food supplements on the one hand, and of chemically defined medicines on the other hand. Thus, their possibilities to conduct studies without expected return of investment are limited. Moreover, the conduct of controlled studies in children is difficult. This is especially the case in herbal medicinal products, as many of them have been successfully used in children for decades or even longer, and are, e.g. in Germany, widely accepted by paediatrics and parents, so that there is a wide-spread lack of understanding of the necessity of these studies in potential participants.	
	It seems important to express clearly that the resulting lack of clinical data is in no way specific to herbal medicinal products, but is to the same extent true for the majority of chemically defined products, addressed as “conventional” and as “real drugs” in the reflection paper. It therefore should be highlighted that not only herbal drugs are used in children since a long time on the basis of the personal experience of the prescribing doctors but also a considerable number of "old" chemical-synthetic medicaments is used "off-label" since many decades and no clinical studies have been performed in children.	See answer to Schwabe’s comment. The “conventional” drugs are not reported as “real drugs” by this paper, but by people who generally think that HMPs are “natural” and safer because they are not “real drugs”.
	However, there are already now a considerable number of systematic studies of the use of several herbal medicinal products in the paediatric population, documenting safety and therapeutic benefit. In addition, many herbal medicinal products are known to have a broad therapeutic dose range. This already now allows expressing the opinion that safety problems are comparatively unlikely to be expected, also in children. All in all, however, ways out of the dilemma of a lack of clinical data are urgently	Unfortunately there are not so many studies and this is the reason why this paper has been written.

	needed in order to guarantee availability of well tolerable and accepted herbal medicines of high quality in all suitable indications in the paediatric population also in future, and with respect to the HMPC monographs as the regulatory framework in Europe. A necessary first step is to better integrate clinical data already existing into the assessment of the usefulness of herbal medicinal products in children. Due to the importance of clinical data, the reflection paper of HMPC on the necessity of initiatives to stimulate the conduct of clinical studies in the paediatric population is a highly important part of the activities needed for reaching the goal to maintain and improve the availability of herbal medicinal products for children. Especially the clear emphasis on observational studies and specific post marketing surveillance studies to define the long-term safety of herbal medicines is highly appreciated.	
AESGP	AESGP in principle welcomes the draft Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population. We are aware of the fact that herbal medicinal products and traditional herbal medicinal products are widely used in children but extensive written documentation e.g. clinical or observational studies are often not available e. Hence we agree that there is a need to address this situation and to find appropriate solutions. The priority in any case should be to ensure that there are appropriate incentives for companies performing research on herbal medicines in order to enable them to recoup their investment. In addition, guidance or recommendations for study methodologies in that field should be pragmatic and practical for companies to implement. In terms of terminology, throughout the document we would prefer the use of “chemical” or “synthetic” medicines instead of ‘conventional’ and “herbal” or “phytomedicines” rather than the use of the word ‘natural’. The word “drug” should also be replaced by ‘medicinal product’.	Agreed. For terminology see the above answer to Schwabe’s comment.

BPI	We agree that herbal medicinal products (HMPs) are widely used in the general population and specifically in children even in Germany. It would be highly necessary to improve the current situation described in the reflection paper to ensure that medicinal products including HMPs intended for use in children have been properly assessed in that very patient population.	Agreed.
GPT	The Gesellschaft für Phytotherapy (GPT) welcomes the attempt of HMPC to emphasize the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products (HMPs) in the paediatric population. As in Germany HMPs are in widespread use in children of all age groups, the restrictive requirements of HMPC for granting the use of an HMP in children in the community monographs have been followed with great sorrows. Many herbal medicinal products have been successfully prescribed by paediatricians and recommended by pharmacists to children since old ages, but, as this was widely accepted, no systematic documentation of this use has been conducted. The lack of such data now results in the restrictions mentioned above, as e.g. in the case of fennel tea, which in Germany is widely used in toddlers, even by recommendation of paediatricians, but may be used according to the HMPC monograph in only from an age of 4 years. This gap between practice and documentation is also an effect of the different traditions of use of HMPs in different European countries. It could be overcome by increasingly respecting established medicinal use in different European countries in the paediatric population, as it is documented e.g. in SPCs of established HMPs and in textbooks (Frank, B. 2009) or in surveillances on dosing in children (Kooperation Phytopharmaka 2002). With respect to studies, the special focus of HMPC on observational studies and post marketing surveillance studies is especially welcomed by GPT, as pro- and retrospective observational studies and post marketing surveillance studies, including cohort studies, can document the therapeutic situation better than controlled clinical	Not agreed. See answer to Koop's comment.

	studies. This is especially true in self medication. In addition, observational and cohort studied allow documenting large numbers of patients. However, in the view of the GPT, several points of this reflection paper need improvement and therefore are addressed in specific comments.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 30	RPS	Comment: While a number of references have been provided on the use of HMP's (Herbal Medicinal Product) in the paediatric population, the interpretation of "general popularity" is subjective. It may be worthwhile to provide some specific data on this. Proposed change (if any): It may be worthwhile to provide some specific data on this.	The data are reported in references 1-7.
Line 30-32	Schwabe	„Probably the most important reason for this general popularity is that parents consider them as less dangerous than "conventional" medicinal products because they are "natural", used over hundreds of years and may not be considered as "real drugs". Comment: This statement implies that medicinal products are dangerous in general. Their benefit is not reflected adequately by the statement. Furthermore, historically there are countries with drug-only or	The sentence refers to what generally people think. Proposal of change partially endorsed ("safer" instead of "less dangerous") For the change "conventional" to "other" see the above answer to Schwabe's general comment.

		food-only status, respectively. Proposed change: Probably the most important reason for this general popularity is that parents consider them as generally safer than synthetic medicinal products because they are “natural”, many of them used over hundreds of years and in some member states perceived as safe food products.	
	Koop	Comment: It needs to be emphasized that, at least in Germany, a considerable number of herbal medicinal products is accepted as “conventional” and as “real drugs” by parents and paediatricians, due to their well established efficacy and safety. Thus there are more reasons for the popularity of these products than just a perception as “less dangerous” and “natural”. Proposed change: “... real drugs. *An important reason is also the evidence-based perception in parents and paediatricians, that herbal medicines are effective and safe*.”	Not agreed. Reference 1 reports the important use of HMPs in Germany, but the perception in parents and paediatricians in this country cannot be considered “evidence-based” according to the current scientific guidelines
	AESGP	*“Probably the most important reason for this general popularity is that parents consider them as less dangerous than “conventional” medicinal products because they are “natural”, used over hundreds of years and may not be considered as “real drugs”.”* Comment: This statement is misleading and negative. Medicines are authorised on basis of their positive benefit/risk. Proposed change: “Probably the most important reason for this general popularity is that parents consider them as generally safer than chemical medicinal products because they are “natural”, many of them	Partially agreed (see the above answer to Schwabe’s comment).

		were used over hundreds of years and may be perceived in some member states as “softer treatments”.	
	GPT	Comment: Emphasising only the safe and natural image of HMPs as being no “real drugs” does neglects the fact, that, at least in Germany, but also in several other European countries, many herbal medicines gain their popularity through recommendation or prescription by the paediatricians and have an image as effective and well established drugs. Proposed change (if any): Please add after “... as “real drugs”. But also the recommendation by paediatricians and an image of being effective drugs are important stimuli of the use of herbal medicinal products.”	Not agreed, the paragraph is a generic view of Europe and the addition would not represent the situation among many Member States.
Line 33-35	RPS	Comment: The information provided in this paragraph is rather loose and the reference to “doctor” and “clinician” would appear inappropriate. It seems to suggest that if clinical information on the HMP is available, a “doctor” (assumption the reference is made to those who are licensed to practice conventional medicine) will then be in a position to offer advice on the use of the HMP. The paragraph may lead to the incorrect interpretation of the responsibility on the use of the HMP being placed on a “doctor” as the primary medical practitioner for the community. Proposed change (if any): This paragraph should be revised.	Endorsed. The paragraph has been revised.
	Schwabe	“They can usually be bought without consulting a doctor. Even if consulted, the clinician has documentation on some of the properties of the herbal medicines, but very little clinical information for properly evaluating indications, posology, length of treatment and safety in children.” Comment: There are a few HMPs for which the required data are entirely available. Therefore this statement is too general. Proposed change:	The paragraph has been revised.

		They can usually be bought without consulting a doctor. Even if consulted, in many cases the clinician has documentation on some of the properties of the herbal medicines, but very little clinical information for properly evaluating indications, posology, length of treatment and safety in children.	
	Koop	Comment: For a considerable number of herbal medicinal products, there are already now data from systematic studies available documenting their safety and usefulness in clinical practice. By integrating them with individual clinical expertise according to Sackett, this data allows an evidence-based treatment of children already now. Proposed change: "... herbal medicines, but, *despite clinical information in some preparations is good, in others* very little ...".	The paragraph has been revised. As reported in the paper, clinical data are generally lacking for children and therefore it is not possible to "integrate" them with clinical expertise and have an "evidence-based" treatment.
	AESGP	*"They can usually be bought without consulting a doctor. Even if consulted, the clinician has documentation on some of the properties of the herbal medicines, but very little clinical information for properly evaluating indications, posology, length of treatment and safety in children."* Comment: This statement is too general. Proposed change: "They can usually be bought without consulting a doctor. When consulted, clinicians may have documentation on some of the properties of the herbal medicines, but usually lack clinical information for properly evaluating indications, posology, length of treatment and safety in children."	The paragraph has been revised.

	GPT	Comment: The fact, that very little clinical information is available for safe use in children may be true for many HMPs, but there are a considerable number of preparations with established clinical information in children. Proposed change (if any): Please change the sentence, beginning after "..., herbal medicines, but ~~very little~~, while for several preparations there is specific clinical information for properly evaluating indications, posology, length of treatment and safety in children, this is missing in many other preparations, irrespective whether they are herbal preparations or chemically defined preparations."	The paragraph has been revised.
Line 41-43	GPT	Comment: For a considerable number of HMPs there is knowledge, that interactions are not to be expected, and there is also sufficient knowledge about their use in children. Proposed change (if any): " ... the HMPC used, often together with ~~conventional~~ other medicinal products, for chronic diseases ... ". " ... In some HMPs, this may create the possibility of interactions with other ~~This creates the possibility that a HMP may interact with a standard~~ treatments and highlight~~s~~ the need for more information about the use of such therapies."	Endorsed. Not endorsed. It is important to refer to the standard therapy in chronically ill children.
Line 44	Federal Agency For Medicines and Health Products Belgium	Comment: In our opinion it is not the DIR 2004/24/EC that provides a legal basis to facilitate authorization/registration in Europe but it is the DIR 2001/83/EC as amended that does so. Proposed change (if any): Change "DIR 2004/24/EC" to "DIR 2001/83/EC as amended by DIR 2004/24/EC".	Agreed, the text has been revised accordingly.

	AESGP	*"Directive 2004/24/EC aims to harmonise the market for HMPs and provides a legal basis to facilitate their authorisation/registration in Europe".* Comment: the primary goal of the Directive is to harmonise the definition of traditional herbal medicinal products and to facilitate their registration in Europe. Proposed change: *Directive 2004/24/EC primarily aims to harmonise the market for THMPs and provides a legal basis to facilitate their authorisation/registration in Europe".*	The text has been revised.
Line 50	Federal Agency For Medicines and Health Products – Belgium	Comment: It is our view that the 10 years are mandatory so the "usually" must logically be omitted. Proposed change (if any): omit "usually".	Agreed. The paragraph has been revised accordingly.
Lines 52-53	Swissmedic	Comment: the word "efficacy" in the context of Traditional Herbal Medicine Products should be avoided. Proposed change (new text in BIG LETTERS or ~~cancelled)~~: "THMPs…have been proved to be not harmful…and their pharmacological OR THERAPEUTIC effects ~~or efficacy~~ are plausible on the base of long-standing use and experience."	Not agreed. The text comes from the Directive 2004/24/EC
Line 54-60	RPS	Comment: Dosing information in paediatric population does not always relate to "age intervals". Paediatric subsets are sometimes defined according to body weight and body surface area. Proposed change (if any): Make it clear there are several ways a dose for a child can be calculated.	Agreed. The paragraph has been revised accordingly.
Line 60	GPT	Comment: The fact, that the SmPC guideline has not been created for WEU HMPs and THMPs, leads to the consequence	Not endorsed. SmPC guideline has been created for all medicinal products, also HMPs. "Satisfactory efficacy

		that the term plausible efficacy is missing. Proposed change (if any): "... for which satisfactory resp. plausible efficacy and safety have been shown."	and safety" can apply to both WEU and THMPs. In fact in case of the latter 'satisfactory' implies that the plausibility is demonstrated.
Line 61-63	Schwabe	„Very often HMPs for children do not completely satisfy the above criteria. This may result in attempts by manufacturers to sell such products as food supplements, so as to overcome the requirements to demonstrate their quality, safety and adequate labelling." Comment: This statement is not limited to HMPs, but holds true for most synthetic well-established use medicinal products as well. Proposed change: Most well-established use medicinal products (including synthetic drugs) do not completely satisfy the above criteria. This may result in attempts by manufacturers to sell HMPs as food supplements, so as to overcome the requirements to demonstrate their quality, safety and adequate labelling.	Not endorsed, the subject of this paper are HMPs and not all medicinal products.
	AESGP	*"Very often HMPs for children do not completely satisfy the above criteria. This may result in attempts by manufacturers to sell such products as food supplements, so as to overcome the requirements to demonstrate their quality, safety and adequate labelling."* Comment: This is too much of a generalisation. In addition, it is not entirely clear to what the 'above criteria' refer to, if it is to the requirement to have an SmPC, the statement is then incorrect. If it is to the guideline, we would prefer a quote to the guideline as follows: "The specific sub-section 'paediatric population' should always be included and the information given should cover all subsets of the paediatric population, using a	Partly agreed. The paragraph has been revised accordingly.

		combination of the possible situations presented below as appropriate. If the product is indicated in the paediatric population, posology recommendations should be given for each of the relevant subsets. The age limits should reflect the benefit-risk assessment of the available documentation for each subset.". It should be however borne in mind that this is a guideline (hence not binding) and that this is a fairly recent revision. Proposed change: "*HMPs indicated for children may not completely satisfy the recommendations laid out in the SmPC guideline. This may result in attempts by manufacturers to sell such products under other status in order to avoid the very strict pharmaceutical requirements."*	
	GPT	Comment: The statement, that manufacturers overcome the requirements to demonstrate quality, safety and adequate labelling suggests that food supplements are generally not adequately labelled etc. This may be the case in some products not complying to recent requirements, but should not be generalized, especially as several drugs medicinally used in HMPs for children, as e.g. thyme, are also in adequate nutritional use as food. Proposed change (if any): "so as to overcome the requirements to demonstrate their quality, safety and ~~adequate~~ labelling as an HMP."	Agreed.
Line 64-65	RPS	Comment: Proposed change (if any): Suggest the use of the term "conventional medicinal products" to replace "conventional drugs".	The paragraph has been revised.

Line 68	RPS	Comment: The paragraph indicates that both the THMP's (Traditional Herbal Medicinal Product) and the HMP's are authorised through the well-established medicinal use procedures in the same way. This statement is incorrect as the legislative requirement for the registration of the THMP's is not the same as for herbal medicines that submit full marketing authorisations. Proposed change (if any): This statement should be revised.	The paragraph has been revised.
Line 64-71	Schwabe	„For conventional drugs Regulation(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionized the regulatory environment for paediatric medicines in Europe by ensuring that medicines for children are of high quality, ethically researched and authorized appropriately, without subjecting children to unnecessary trials. However, THMPs and HMPs authorized through the well-established medicinal use procedure are not subject to the requirement set out in this legislation to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing. " Comment: Regulation(EC) No 1901/2006 refers to new full applications only but not to well-established use products, irrespective as to whether they are synthetic or herbal. Proposed change: „For medicinal products authorized through a full marketing authorization procedure, Regulation(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionized the regulatory environment for paediatric medicines in Europe by ensuring that medicines for children are of high quality,	The text has been revised.

		ethically researched and authorized appropriately, without subjecting children to unnecessary trials. However, medicinal products authorized through the well-established medicinal use procedure and THMPs are not subject to the requirement set out in this legislation to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing."	
	AESGP	*"For conventional drugs Regulation(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionized the regulatory environment for paediatric medicines in Europe by ensuring that medicines for children are of high quality, ethically researched and authorised appropriately, without subjecting children to unnecessary trials. However, traditional herbal medicinal products and HMPs authorised through the well-established medicinal use procedure are not subject to the requirement set out in this legislation to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing."* Comment: Regulation(EC) No 1901/2006 refers to new full applications only but not to well-established use products, irrespective of whether they are synthetic or herbal. Proposed change: *(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionized the regulatory environment for paediatric medicines in Europe by ensuring that medicines for children are of high quality, ethically researched and authorised*	The paragraph has been revised accordingly.

		appropriately, without subjecting children to unnecessary trials. However, medicinal products authorised through the well-established procedure and THMPs are exempted to the requirement set out in this legislation to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing."	
Line 72-74	Schwabe	„It is important to note that, despite such lack of data, a considerable number of European children take HMPs along with or without conventional medicines, so it is important that they are also studied in this age group." Comment: This statement is not limited to HMPs, but holds true for most synthetic well-established use medicinal products as well. Proposed change: It is important to note that, despite such lack of data, a considerable number of European children take well-established use medicinal products and THMPs, so it is important that they are also studied in this age group.	Not agreed. This paragraph aims to underline that HMPs (which are very often not studied) can be taken with or without other medicinal products. We agreed that the latter may also be poorly studied, but this is not the subject of this paper.
	AESGP	*"It is important to note that, despite such lack of data, a considerable number of European children take HMPs along with or without conventional medicines, so it is important that they are also studied in this age group."* Comment: The fact that herbal medicines are taken with chemical medicines is irrelevant here. Proposed change: *"It is important to note that, despite such lack of data, a considerable number of European children take HMPs so it is*	Not agreed. It is not irrelevant. This point is very important because HMPs are reported to be taken with other drugs and more information is needed.

		important that they are also studied in this age group."	
	GPT	Comment: When the term "studied" is used here, it is necessary to keep in mind, that also observational studies etc. meet these requirements, as is stated on page 5, line 1.	Agreed.
Line 75-79	Schwabe	"One of the most important aims of the Paediatric Regulation is to reduce the very frequent off-label use of Synthetic drugs in children, but the situation of HMPs is similar to the off-label use: they are commonly used but have not been adequately studied, they have been on the market for many years via multiple licence-holders, they have no protected intellectual property rights and yet they may be of therapeutic value to children. Moreover performing proper research without any incentives is very costly." Comment: This statement is not limited to HMPs, but holds true for most synthetic well-established use medicinal products as well. Proper research is always costly. What is missing are incentives such as data protection, which is particularly important due to the longer return of investment period in limited age groups. Proposed change: One of the most important aims of the Paediatric Regulation is to reduce the very frequent off-label use of drugs in children, but the situation of many well-established use medicinal products and THMPs is similar to the off-label use: they are commonly used but have not been adequately studied, they have been on the market for many years via multiple licence holders, they have no protected intellectual property rights and yet they may be of therapeutic value to children. Moreover performing proper research is very costly and incentives (e.g. data protection) are missing.	Partially agreed. The paragraph has been revised accordingly.

	AESGP	*"One of the most important aims of the Paediatric Regulation is to reduce the very frequent off-label use of drugs in children, but the situation of HMPs is similar to the off-label use: they are commonly used but have not been adequately studied, they have been on the market for many years via multiple licence-holders, they have no protected intellectual property rights and yet they may be of therapeutic value to children. Moreover performing proper research without any incentives is very costly."* Comment: Proper research is always costly. What is missing are incentives such as data protection, which is particularly important due to the longer return of investment period in limited age groups. It should also be noted as well that studies performed years ago may not be retained as not meeting 'today's quality standards'. Proposed change: *"One of the most important aims of the Paediatric Regulation is to reduce the very frequent off-label use of drugs in children, but the situation of HMPs is similar to the off-label use: they are commonly used but may not have been adequately studied, they have been on the market for many years via multiple licence-holders, they have no protected intellectual property rights and yet they may be of therapeutic value to children. Moreover performing proper research without any incentives is very costly and difficult to recoup if there is no incentives (e.g. protection of the data)."*	Agreed. The paragraph has been revised accordingly.
	GPT	Comment: In this paragraph it is suggested, that HMPs are generally not adequately studied. This is of course not true; therefore the sentence should be more precise.	Agreed.

		Proposed change (if any): "...they are commonly used but many of them have not been adequately studied, ...".	
Line 80-82	Schwabe	"Taking into account the differences between conventional drugs and HMPs it would be useful to improve the situation to ensure medicinal products intended for use in children have been properly assessed in that patient population." Comment: This statement holds true for all medicinal products and is not limited to HMPs and THMPs. Proposed change: It would be useful to improve the situation to ensure medicinal products (including HMPs and THMPs) intended for use in children have been properly assessed in that patient population.	Not agreed because the priorities of research on drugs for the treatment of important diseases must be taken into account.
	RPS	Comment: Proposed change (if any): Suggest replacing "to ensure medicinal products intended for" with "to ensure herbal medicinal products intended for".	The text has been revised.
	AESGP	*"Taking into account the differences between conventional drugs and HMPs it would be useful to improve the situation to ensure medicinal products intended for use in children have been properly assessed in that patient population."* Comment: The 1st part of the sentence is not really relevant here. Proposed change: *"It would be useful to improve the situation to ensure medicinal products intended for use in children have been properly assessed in that patient population."*	Not agreed; see answer to the Schwabe's comment.

Line 84-85	Schwabe	„The aim of this document is to highlight the lack of studies on the majority of herbal medicinal products in children and the need for initiatives to stimulate the conduct of clinical studies with HMPs properly designed for children.“ Comment: On the ground of legally acquired marketing authorizations and registrations and the well documented long-standing use of well-established use medicinal products and THMPs the design of clinical studies must be tailored in a way that the effects of the products concerned are investigated with respect to scientific questions in the context of their every-day use. Please refer to the attached statement. Proposed change: The aim of this document is to highlight the lack of studies on the majority of herbal medicinal products in children and the need for initiatives to stimulate the conduct of clinical studies with HMPs properly designed for children and thereby taking into account their established use in long-standing practice based on legally acquired marketing authorizations or registrations.	Not endorsed. The purpose of the paper must be more general.
	RPS	Comment: Consistency should be maintained throughout the paper. Proposed change (if any): Suggest the use of the term “herbal medicinal product” to replace “herbal medicine”. Comment: Proposed change (if any): Suggest replacing “studies” with “clinical studies”.	Agreed.
	AESGP	*“The aim of this document is to highlight the lack of studies on the majority of herbal medicinal products in children and the need for initiatives to stimulate the conduct of clinical studies with HMPs properly designed for children.”*	In this paper the term “clinical studies” include clinical trials, observational and post marketing studies.

		Comment: We suggest not only to focus on the conduct of clinical studies as main purpose of the reflection paper, but to find a more general wording. In addition, the well-established long term use of these products (and the fact that they are subject to pharmacovigilance requirements as any medicine) should be reflected here. Proposed change: "The aim of this document is to highlight the lack of studies on the majority of herbal medicinal products in children and the need for initiatives to stimulate the collection of data on the use of herbal medicinal products in children including clinical and observational studies with herbal medicinal products, taking into account their established use in long-standing practice."	
	GPT	Comment: Already in the purpose it should be clear that in the scope of the paper are not only clinical studies in the narrow sense of this term, but also other study types like observational studies. Proposed change (if any): "... to stimulate the conduct of clinical **and observational** studies with HMPs ...".	See answer to AESGP's comment.
Line 87	RPS	Comment: The sub-heading of "importance of sound evidence" does not reflect well on the content of the sub-section. Proposed change (if any): "Types of clinical studies" may be a more appropriate sub-heading.	Not agreed. The point is the hierarchy of the evidence (sound evidence) the first three paragraphs are not about clinical studies but on the types of evidence.
Line 87-110	BPI	Comment: One major problem is the evidence level of trials accepted for submission under Article 45 and 46 of Regulation (EC) No. 1901/2006. Many trials performed with THMPs and HMPs are not designed as randomised controlled trials but as	They will be examined when they will be accessible and taken into account if they are of good quality.

		non interventional trials, summarised as observational studies. This design needs to be accepted for post marketing surveillance, as well.	
Line 88-90	Schwabe	"It is now well accepted that to find the most appropriate treatment for a patient it is necessary to integrate the best evidence available to the clinician with the wishes of the patient. This is important for conventional, complementary and alternative medicines (34-35)." Comment: This statement holds true for all medicinal products and is not limited to HMPs and THMPs. Proposed change: It is now well accepted that to find the most appropriate treatment for a patient it is necessary to integrate the best evidence available to the clinician with the wishes of the patient. This is important for all types of medicines (34-35), including HMPs and THMPs.	Endorsed. It is considered editorial only.
Line 97-106	Schwabe	"Considering experts' opinions, lack of agreement between them has often been reported (38) raising difficulties for the clinician who has to make a decision on the best treatment for the patient. Regarding the need for information based on evidence, it is difficult to find good quality studies especially in children (39-40) even though many herbal preparations are standardized and can be adequately studied (41). For this reason, tools to design good trials for HMPs have been proposed by the CONSORT (Consolidated Standards of Reporting Trials) group (42). However, rigorous research is not limited to randomized clinical trials, which also have disadvantages such as costs (both of time and of money) and sometimes ethical problems (43) as well as the risk of incorrect conclusions due to badly designed studies (44)."	The text has been deleted.

		Comment: In our opinion, this section contains a number of sentences which are of limited value. Not only standardized but also quantified and „other“ extracts can be adequately studied. Proposed change: We propose to shorten the section to the following: „Rigorous research is, however, not limited to randomized clinical trials, which also have disadvantages such as costs (both of time and of money) and sometimes ethical problems (43) as well as the risk of incorrect conclusions due to badly designed studies (44).“	Not agreed. The sentences explain better what is meant by rigorous research.
	AESGP	“Considering experts’ opinions, lack of agreement between them has often been reported (38) raising difficulties for the clinician who has to make a decision on the best treatment for the patient. Regarding the need for information based on evidence, it is difficult to find good quality studies especially in children (39-40) even though many herbal preparations are standardized and can be adequately studied.” Comment: We do not agree with the statement “even though many herbal preparations are standardized and can be adequately studied.” Only few herbal preparations are standardised in the strict sense of the definition of the European Pharmacopoeia. Standardisation of an extract is not necessarily a precondition for the conduct of a clinical study. This should not mean that this should be a criterion o achieve comparability of studies performed with different types of extracts. Proposal:	Agreed. The text has been deleted.

		"Considering experts' opinions, lack of agreement between them has often been reported (38) raising difficulties for the clinician who has to make a decision on the best treatment for the patient. Regarding the need for information based on evidence, it is difficult to find good quality studies especially in children (39-40) *"For this reason, tools to design good trials for HMPs have been proposed by the CONSORT (Consolidated Standards of Reporting Trials) group (42). However, rigorous research is not limited to randomized clinical trials, which also have disadvantages such as costs (both of time and of money) and sometimes ethical problems (43) as well as the risk of incorrect conclusions due to badly designed studies (44)."* We fully agree with the statement that rigorous research is not limited to randomized clinical trials. From our point of view, observational studies (see comment for 5th paragraph) as well as documented experiences should be taken into consideration as well. Furthermore, we regard a clear differentiation between traditionally used herbal medicinal products and well-established medicinal used products as necessary, because clinical studies are not required for the proof of efficacy of traditional herbal medicinal products. In this context we would like to mention the enormous diversity of herbal products in the European Union, e.g. identical or almost identical products are marketed in different Member States of the European Union with different indications, posologies and declarations as well as traditional or well-established use products, depending on the countries where marketing authorisations or THMP-registrations have been applied for.	The variable situation concerning indications, posology etc in different countries is the proof that more data are required to achieve harmonisation.

Line 99	GPT	Comment: There is a very considerable number of good quality studies in children, which have been reported to the national competent authorities in 2008 according to directive (EG) Nr. 1901/2006 and should be accessible to the EMA. Proposed change (if any): " ... Regarding the need for information based on evidence, despite there is a considerable number of good quality studies in children with HMPs, it may be difficult to find good quality studies especially in children... ".	These data will be examined when they will be accessible and taken into account if they are of good quality.
Line 100	GPT	Comment: The term standardized seems to have been used here in an unspecific way. A small number of extracts used in children is standardized in the sense of PhEur, others are other resp. characterized extracts with the same level of quality as in standardized extracts. All extracts with a registration or marketing authorization within the EU can be supposed to have a sufficient quality for being tested in clinical studies. Proposed change (if any): " ...even though all herbal preparations having a registration or marketing authorization within the EU are standardized resp. characterized and can be adequately studied ... ".	The text has been deleted.
Line 107-110	Koop	Comment: Kooperation Phytopharmaka would like to underline the statement that observational studies, including cohort studies, as well as specific post marketing surveillance studies, are most useful for defining the key issue of a paediatric use of medicinal products, which is safety. This statement of HMPC is of special importance, as it gives the signal that such studies will find increased regulatory acceptance by the HMPC and also by national regulatory authorities.	Agreed for safety studies.

		This regulatory acceptance can be the most vigorous incentive for motivating manufacturers to conduct or support such studies in the paediatric population.	
	AESGP	We agree with both statements of this paragraph and consider observational studies as well as post-marketing surveying studies (for demonstrating safety) useful tools. However, the results of the studies which are performed with a defined preparation can normally only be utilized for these specific products. This would result in performing numerous studies with similar slightly different preparations. For this reason a pragmatic procedure in order to avoid redundant work and unnecessary studies is required, especially because relevant national authorities may come to different opinions regarding the need and the scope of additional data to be provided.	This comment will be considered in approach 2.
	GPT	Comment: The appreciation of observational studies and especially of post marketing surveillance studies as most useful tools for defining long term safety is very important, as these study types have been proven to be useful for supporting paediatric use also in several HMPC monographs. This has been emphasized also by Knoess and Alban (2009).	Agreed.
Line 111	RPS	Comment: The sub-heading of “state of the art of HMPC monographs” seems somewhat elaborate in relation to the information provided. Proposed change (if any): Delete this sub-heading.	Partially endorsed. The sub-heading has been modified.
Line 128-137	BPI	Comment: THMPs and HMPs authorised through the well-established medicinal use procedure are not subject to the requirement of the Regulation (EC) No. 1901/2006 to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing. On the other hand, in	They will be examined when they will be accessible and taken into account if they are of good quality.

		accordance with Article 45 and 46 of Regulation (EC) No. 1901/2006, all paediatric studies involving an authorised medicinal product had to be submitted by 26 January 2008, even if they had been concluded before the Regulation entered into force.	
Line 134-135	Koop	Comment: It will be of key importance that identification of herbal substances/herbal preparations, for which a therapeutic benefit is expected, is based on a survey on the therapeutic reality in the member states. The existing therapeutic use, may it be well established or traditional, best depicts the expectations of a therapeutic benefit in paediatricians and parents, and thus will be the best evidence for identification of this benefit. Merely theoretical considerations and criteria are likely not to lead to equally relevant results. Proposed change: "*... criteria to select them, with therapeutic reality in the member states being a key criterion.*"	This will be discussed when the approach will be put into practice.
	GPT	Comment: The identification of herbal substances/ preparations for which a therapeutic benefit is expected should not be conducted by theoretical considerations, but by a systematic check, which preparations have been used traditionally in children of the different European countries. Proposed change (if any): " ... (HMPC and PDCO should identify appropriate criteria to select them**,** considering the long traditional resp. well established medicinal use of these preparations in the different European countries)" .	This will be discussed when the approach will be put into practice.

Line 136-137	Schwabe	"2. Provision of guidelines and recommendations for developing appropriate paediatric studies for herbal medicinal products." Comment: One of the few issues specific to herbal clinical trials is the question of transferability of the results of clinical studies with a specific herbal preparation to other preparations made from the same plant. Proposed change: We propose to add the following sentence: "The transferability of the results of clinical studies with a specific herbal preparation to other preparations made from the same plant has to be adequately assessed on a case-by case basis."	This will be discussed when the approach will be put into practice.
Line 138-139	BPI	Comment: Concerning the monitoring of safe use, BPI stipulates the integration of the activities for HMPs into the existing EU-System of Pharmacovigilance.	Agreed.
	GPT	Comment: Promotion of funding is an important issue. Actually funding is almost only possible by companies, and other support is lacking. In case that public funding will be possible, a tight cooperation with experienced experts, also from scientific societies like the Gesellschaft für Phytotherapie, is recommended.	This will be discussed when the approach will be put into practice.
Line 127-141	AESGP	Bearing in mind that many of the finalised HMPC Community herbal monographs include a recommendation not to use the product in children and/or adolescents under 12 or 18 years, we agree with the statements that there is a need for initiatives to specifically stimulate research in this field. However, from our point of view research should not be limited to clinical and observational studies, but also take into consideration documented experiences of physicians and practitioners specialised in paediatrics, according to	The proposal will be discussed when the approaches will be put into practice.

		EMEA/HMPC/104613/2005. We would like to comment on the proposed approaches as follows: 4.1. Identification of herbal substances/herbal preparations for which a therapeutic benefit is expected From our point of view the first step should consist in a broad collection of data on preparations that have been used in children. The assessment of the therapeutic benefit should follow as a second step in order to avoid an early restriction of collected data. Furthermore from a pragmatic point of view the identification of herbal substances and herbal preparations could start with dose covered by Community herbal monographs. According to Articles 45 and 46 of Regulation 1901/2006, many companies have submitted data on clinical studies already performed in the past to their national competent authorities. These lists may provide a useful basis of existing data as soon as all Member States have submitted their collected data. As a side note, industry should also be consulted on the selection criteria. 4.2. Provision of guidelines and recommendations Such guidance documents would be useful to provide pragmatic recommendations for all parties involved in the conduct of clinical and observational studies taking into account the specific characteristics of herbal medicines. In view of the high acceptance and appreciation of many HMP	Generally in the monographs HMPs are not CONTROINDICATED in children as it can be easily seen in the tables of the annex of the reflection paper, but are NOT INDICATED for lack of data.

		by pediatricians and parents it is essential to avoid wherever possible in HMPC monographs the stipulation of absolute contraindications such as "children under 18 years of age" or "children under 12 years of age" in order to enable the future performance of observational studies as they are rightfully recommended in the reflection paper. Where no specific serious risk to certain age groups has been demonstrated or is a least reasonably expected, absolute contraindications would be imbalanced in detracting valuable products from pediatricians and parents hands without providing a safer alternative. 4.3. Promotion of funding We highly appreciate the option of public funding to collect more data on monitoring the save use in children and to promote further research. Other incentives should be sought of as well to enable single companies that invest in research to recoup the investment. In terms of incentives, a strong signal should be given by Member States themselves i.e. when a community monograph mentions the possibility to use the plant preparation in a defined age group, Member State should not restrict the corresponding registration to use in adults only. Last, industry would be prepared to get actively involved in any further concrete developments of this initiative (e.g. selection of priority criteria, development of guidelines, etc.).	
Line 140-141	Koop	Comment: Kooperation Phytopharmaka is prepared to continue the discussion, evaluation and publication of experiences with studies on the use of HMPs in the paediatric population, as well	The proposal will be considered when the approaches will be put into practice.

		as searching options for developing and supporting new approaches for data collection on the paediatric use of herbal medicinal products.	
	GPT	Comment: Stakeholders have already submitted studies in the paediatric population to the competent authorities, many of which are based on experience in these patients. EMA should have access to these data. Experience is also documented in an issue of Zeitschrift für Phytotherapie presenting the results of a symposium on paedriatric use of HMPs in children (ZPT 2010, issue 31, articles in German).	Studies under Art. 45 will be examined when they will be accessible and taken into account if they are of good quality.
Annex, table 1	GPT	Comment: It will be helpful, if not only numbers of indications, but also the lists of the respective indications are available.	The list is too long (20 pages) to be added to this document. The data can be checked in the monographs.
	Schwabe	Attachment to Comment on Draft Reflection Paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population. We agree with the Reflection paper that children and juveniles are a patient group needing special protection. For this reason, legislators in the USA and the European Union created a legal framework that gives adequate consideration to the supply of medicinal products to this patient population. The core of this framework is Regulation No. 1901/2006/EC (1). A careful evaluation is necessary, in particular against the background of drug research in children and juveniles: On the one hand, clinical trials are related to risks, but on the other hand, it is precisely the lack of clinical trials in this patient group that may lead to the inappropriate use of any medicinal product i.e. not only herbal ones, at an inadequate dosage. Various designs, especially of epidemiological investigations as controlled cohort studies, can be suited in particular for this very sensitive patient	Partially agreed. Even if RCTs are considered the best type of studies to demonstrate efficacy, in case of HMPs a more pragmatic approach as the one proposed by the comment will be discussed when approach 2 will be put into practice.

		group for demonstrating the traditional and established use of traditionally registered or WEU-approved phytopharmaceuticals. An essential point of this Regulation No. 1901/2006/EC is the legislator's intention to set up rules for the development of human medicinal products allowing to meet specific therapeutic needs in the paediatric population. It is also stipulated to avoid conducting unnecessary clinical or other trials in children and juveniles (1). The concept of safeguarding this very sensitive population is taken into account in a twofold manner: by promoting adequate research and simultaneously preventing inadequate research. Corresponding committees for the assessment of relevant research projects have also been created in view of this concept. This complies with the Guideline on the Assessment of Clinical Safety and Efficacy in the Preparation of Community Herbal Monographs for Well-Established and of Community Herbal Monographs (2) which states with respect to well-established use (WEU): "In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy." It must be stressed that, for the proof of WEU, no randomized placebo-controlled double-blind study is required, but phase-IV or epidemiological studies of good quality. Apart from that, the other provisions for proving WEU have to be respected in accordance with the Community code relating to medicinal products for humans (3) which stipulates that no clinical trials are necessary if it is possible to demonstrate a well-established use for at least ten years with recognized efficacy and an acceptable level of safety. No clinical trials must be submitted for the registration of traditional herbal medicines in accordance with the Directive 2004/24/EC, since here a plausible efficacy is	

		accepted on the basis of a traditional use throughout at least 30 years including at least 15 years within the Community with proven safety and adequate quality (4). In a general manner and in consideration of this population deserving special protection, it must be discussed to which extent what type of studies can corroborate this plausibility, regardless of the registration under day-to-day conditions. Since the 1940ies and throughout the past century, scientific progress and the improvements involved made randomized controlled clinical trials a prevalent standard procedure for demonstrating the use of a new medicinal product with respect to its specific efficacy (5, 6). These studies are conceived in such a way that the effect of unspecific parameters is separated and selected off. For this purpose, it is necessary to conduct the trial in a very restricted and specific patient population (7). For compensating the lack of transferability of data to individual patients whose characteristics do not comply with the selection criteria chosen, procedures for individual testing were developed. For dosage optimizations, in particular in the treatment of children and juveniles where the optimal dose is either unknown or not researched for all age groups, these procedures can lead to improved usage safety especially in the off-label area. Apart from phase I to III clinical trials with experimental design needed for obtaining the approval of new medicinal products, a series of methods have emerged and become accepted, in particular in epidemiological research, which document the issue of supply and use of approved and available medicines under daily-life conditions. It is characteristic for these studies to observe the application of a treatment without intervening in this treatment chosen by the physician or pharmacist in	

		agreement with the patient, as would be the case in randomized controlled studies. Besides cross-sectional and case-control studies, cohort studies have to be mentioned here in particular. Whereas cross-sectional studies look at a time section of a treatment and can thus provide no information on the course of the application of a medicinal product, case-control studies have a retrospective design. In contrast with this, cohort studies can be controlled and prospective. They all have in common selection and observation in the case of exposure to a medicinal product; they differ with respect to the time relation of exposure and outcome (8, 9). Thus, in a prospective and controlled cohort study, patients and health-care professionals can agree upon one of several accepted therapeutic strategies, individually adjusted to the patient, such as medicinal, surgical, physical or complex interventions, or they can chose to watch and wait. After a defined observational period and symptom monitoring in the therapeutic groups observed in parallel, these strategies can be evaluated comparatively and with characterisation of the single treatment options. Cohort studies can be conducted openly without randomization and without control. Historical control can be applied and treatment assignment can take place according to the patient's preference, medical prescription or recommendation, or the recommendation of another health-care professional, e.g. a pharmacist. Finally, the assignment can be made by cluster, i.e. centre-based, according to the centre's usual accepted treatment. For evaluating the question as to what type of design is most appropriate, it is decisive to consider the study purpose (9). In particular, it could be shown repeatedly and over several studies that epidemiological observational studies generate	

		results which are comparable with those of randomized controlled studies (10, 11, 12, 13). The limitations of randomized and especially placebo-controlled studies have been discussed extensively in the scientific literature. The limits of transferability to the treatment of individual patients basically result from the strong restrictions due to narrow selection criteria. These criteria characterize part of the patients included as untypical, whereas other patients, for whom the investigated medicinal product is intended for daily life use, are excluded because of the selection criteria and the selection process (5, 9, 14, 15, 16). It has been pointed early to the problems induced by highly experimental designs in therapeutic studies with respect to their generalizability. Schwartz and Lellouch therefore coined the term of the explanatory therapeutical trial, against which they set the pragmatic therapeutical trial, more suitable for daily use (17). With a view to the applicability to routine medical care necessary in the everyday context and taking into consideration relevant aspects for the patient in the practical care-seeking situation, it is required to give up placebo control and patient blinding in order to optimize unspecific aspects instead of separating them off (18). If randomization as an additional experimental factor is abandoned too, the passage from pragmatic clinical trials to controlled cohort studies, which are conceived in such a way as to reflect daily-life reality in clinical practice, becomes fluent. The disadvantages of pragmatic cohort studies described in the literature can be limited through suited mathematical procedures developed in the meantime, blinded observers or assessors of outcome parameters and setting up of centre clusters (19, 20, 21). Since for herbals too, there are no sufficient data from	

		systematic investigations in children and juveniles with respect to effect, dosage, galenical form and application safety in this special population, it is recommendable that further studies acknowledging this concrete purpose are being carried out. The use of most herbal medicines in adults, children and juveniles is in most cases founded on decades of documentation. Therefore, their traditional application as described in Directive 2004/24/EC or even their established use according to Directive 2004/27/EC is often appropriate in all age groups, and this is frequently proven by a corresponding regulatory status. Against this background of a large and long reality of application, standard designs of explanatory trials do not meet the requirements for the use of herbal medicines, and in particular in children and juveniles as a patient population deserving special protection. Depending on the regulatory status, comparative cohort studies, e.g. with blinded observers, or pragmatic clinical studies conceived to reproduce application reality, are the method of choice for demonstrating a sustained positive risk-benefit ratio of established herbal medicines under conditions of everyday life in children and juveniles. Dr. Stephan Köhler, Head of Clinical Research, Dr. Willmar Schwabe GmbH & Co. KG **References** 1 European Parliament and Council on Medicinal Products for Paediatric Use (2006) Regulation of (EC) No 1901/2006 of the European parliament and of the Council on Medicinal Products for Paediatric Use 2 Guideline on the Assessment of Clinical Safety and Efficacy in the Preparation of Community Herbal Monographs for Well-Established and of Community Herbal Monographs (2006); Doc. Ref. EMEA/HMPC/104613/2005	

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