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OVERVIEW OF COMMENTS RECEIVED ON REFLECTION PAPER ON ETHANOL CONTENT IN HERBAL MEDICINAL PRODUCTS[1] AND TRADITIONAL HERBAL MEDICINAL PRODUCTS USED IN CHILDREN (EMA/HMPC/85114/2008)

Table 1: Organisations and/or individuals that commented on the draft Reflection Paper as released for public consultation on 6 November 2008 until March 15th, 2009.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	Kooperation Phytopharmaka, Germany
3	Association of Natural Medicine in Europe (ANME e.V.)
4	German Pharmaceutical Industry Association (BPI)

[1] Throughout the reflection paper, unless otherwise specified, the term "herbal medicinal product" includes "traditional herbal medicinal product".

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Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
BPI	Establishing common standards for the marketing authorization of herbal medicinal products is fully appreciated by the BPI. Therefore, the BPI welcomes the draft of this reflection paper on the ethanol content in herbal medicinal products and traditional herbal medicinal products used in children. The publication of this draft evokes the question whether there is new or any scientific or safety relevant information which could have made it necessary to re-evaluate the safety of herbal medicinal products containing ethanol. Unfortunately, neither the draft reflection paper nor the actual scientific literature offer such data, and the only paper cited in the introduction of the paper is the article of Fiocchi et al (1999) which poses the question whether the ethanol content of certain chemically defined medicinal products used in children is safe from a toxicological point of view. It is widely known, that certain food or products that are given preferably to children of all ages, like apple juice or bananas, do contain almost certainly a significant amount of ethanol. From our point of view, there is no chance to avoid the administration of ethanol to children, and has never been in the human history. Furthermore, it is not yet, at least not in our experience, a common practice to apply childproof closures to every jug, jar or bottle that contains (different quantities of) ethanol designed for human consumption and that are available in nearly every household. But the mentioned containers, filled with the products of breweries, wineries or destilleries do contain much more ethanol than the average Herbal Drug Preparation and are usually consumed in an atmosphere of joy and relaxation – not like drugs that usually smell and/ or taste bad and are only applied if and when there is a need (like a disease) for it. So why should, then, drugs that are in all respects unattractive for the inappropriate consumption (especially by children!) and which benefit is by far larger than the one connected with the intake of bananas or apple juice be treated like life-threatening drugs or dangerous chemicals? Instead, the BPI strongly suggests the introduction of a uniform way of labelling the content of ethanol in all commercial drugs throughout Europe. A role model for this labelling might be the "Guideline on Excipients in the label and package leaflet of medicinal products for human use", where the content of ethanol has to be declared in the package leaflet already. Furthermore, with the German "Arzneimittel-Warnhinweisverordnung (AMWarnV)" the German legislator has established a potent instrument to protect	General comments – no action taken. The specific items are discussed in more detail in the sections below. However, it is acknowledged that across Europe there is no uniform recommendation for safety limits of ethanol intake for children and the reflection paper is aiming at establishing recommendation based on scientific evaluation. In this respect national legistlation is outside the remit of this paper.

	the patients of all ages from the accidental or unintentional intake of ethanol. This and, at a further moment, a comment in the leaflet, comparing the actual intake of ethanol per dose with the intake of ethanol by consuming the above mentioned food or food products, will enable the citizens of Europe to decide competently and independently about the consumption of ethanol-containing medicinal products. (AMWarnV)" the German legislator has established a potent instrument to protect the patients of all ages from the accidental or unintentional intake of ethanol. This and, at a further moment, a comment in the leaflet, comparing the actual intake of ethanol per dose with the intake of ethanol by consuming the above mentioned food or food products, will enable the citizens of Europe to decide competently and independently about the consumption of ethanol-containing medicinal products.	
AESGP	AESGP welcomes, in principle, the preparation of reflection papers which, by providing harmonised assessment criteria, may facilitate mutual recognition in Europe. However, there is no recent scientific data available which put into question the safety of herbal medicinal products authorised or registered so far in Europe which contain ethanol whether they are indicated in adults or in children. This is the case for herbal medicinal products in general, but also for traditional ones, on which this reflection paper is focussed. Thus this draft reflection paper might only be regarded as potentially useful for eventual future products having a less favourable safety profile resulting from an ethanol content which is different from existing products. Already Fiocchi et al. (1999), cited in the introduction of this draft reflection paper, conclude that a toxicological assessment of children-specific drugs could determine safe concentrations for acceptable intakes of ethanol from medications and/or other sources, thus providing research-based parameters on a rationale for the continued use of ethanol in paediatric preparations. However, it has to be pointed out that this article presents data on the use of ethanol in some chemically defined medicines, but does in no way relate to herbal medicinal products. For herbal medicinal products, such a comprehensive toxicological assessment of their use in children has meanwhile been conducted and published (Kelber 2008) (34). This assessment reflects the current state of scientific knowledge on the toxicology of ethanol in children and on the ethanol intake derived from herbal	General comments – no action taken. The specific items are discussed in more detail in the sections below.

	medicinal products with paediatric use. After systematic evaluation, it is concluded that the ethanol-related risk of herbal medicinal products is negligible when they are used in the recommended dose. Furthermore, it states that non-intentional intoxications are successfully prevented by the current state of safety measures in medicines. Intensive research in relevant data bases showed that no case of ethanol intoxications after intentional or accidental intake of herbal medicinal products could be found in scientific literature (Kelber et al. 2008). This is also confirmed by recent publications of Schöberl (2008) (35) and Kivistö (2008) (36). Taking due account of the long-standing safe use of ethanol in existing authorised and registered herbal liquid products and the questionable advantages of many alternatives to ethanol in terms of toxicological safety and clinical experience, there are no reasons for a general recommendation that continuous efforts should be made to replace ethanol in herbal liquid preparations intended for paediatric use.	
Kooperation Phytopharmaka	In general, it is remarked with respect to the use of herbal medicinal products containing ethanol, that during the last years, no data changing the risk-benefit evaluation of these preparations have emerged, while at the same time data supporting the established safety of these preparations heve been published. Therefore, while attempts to establish a harmonized view on this theme are highly appreciated, the available data do support neither a changed rating of the toxicological risk of ethanol in herbal medicinal products nor changes in labelling or packaging of products authorized or registered in the European community. So this comment is aimed to provide and analyse scientific data in this field and to propose respective changes of the draft reflection paper. Taken together, there is no cause for safety concerns regarding the safety of existing herbal medicinal products in the EU, and it can be concluded, that even future products resembling the existing products could be safely used also in children. A general conclusion, that continued efforts should be made to have ethanol replaced in herbal liquid preparations intended for paediatric use, is finally not supported, as the ethanol content does typically not relevantly influence the product specific risk benefit analysis in these products	General comments – no action taken. The specific items are discussed in more detail in the sections below.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
1. Introduction Line 3	AESGP	Only a small proportion of the ethanol-containing herbal medicinal products contain high levels of ethanol, as e.g. some valerian preparations with concentrations of up to 66 %. The vast majority has intermediate or low ethanol contents in a range of about 30 % and below. So we propose the following change: In any case, it has to be taken into account that not the absolute ethanol content of the preparation has to be considered in a toxicological assessment, but the amount of ethanol absorbed in a single dose. In existing authorised and registered products, doses recommended for use in children are very low (34). For this reason, a relevant increase of the ethanol content in the blood can be excluded. Furthermore, pharmacokinetic data (34) show that the metabolic inactivation of these amounts of ethanol only takes a few seconds or minutes. Therefore, no toxicologically relevant systemic exposure results from the intake of these herbal medicines. Moreover, the local absorption by the oropharyngeal mucosa is very low, as products are usually diluted in water before use following dosage instructions. This results in ethanol concentrations which are within or below the range of those found in fruit juices. Ethanol has been since early times a component in many foodstuffs and drinks containing sugars, as these sugars are regularly metabolised to ethanol by the intrinsic metabolism or by yeasts present in the environment, so that the metabolism of all omnivore mammalians has adapted to the metabolism of minor amounts of ethanol. Hence, exposure of children to ethanol contained in herbal medicinal products is considerably lower than that of products used as foodstuffs and drinks generally accepted as safe, e.g. fruit juices, bananas, bread or kefir (34,37,38). On the other hand, the use of ethanol in liquid herbal preparations has considerable galenic and pharmacological advantages over many possible alternatives (39). This is not necessarily the case with possible alternatives, so that a replacement without a toxicological advantage would be not justified (39). In addition, already today the ethanol concentrations in existing products like those mentioned above can in most cases be considered as the lowest achievable concentrations taking into account an optimal relation of efficacy and safety. From the toxicological point of view, these would be in all cases acceptable. Therefore, further increasing general attempts to avoid exposure to ethanol are not justified. Based on this, we recommend the proposed change: ***Very few*** *Herbal medicinal products* ~~*frequently*~~ *contain high levels of ethanol arising from the active ingredients where ethanol has been used as the extraction solvent or added as a diluent to liquid herbal preparations*.	

1. Introduction Line 3 Lines 6-7	Kooperation Phytopharmaka AESGP Kooperation Phytopharmaka	Only a small proportion of the ethanol-containing herbal medicinal products contain high levels of ethanol, as e.g. some valerian preparations with concentrations of up to 66 %. The vast majority has intermediate or low ethanol contents in a range of about 30 % and below. So we propose the following change: ***Some*** ~~*H*~~*herbal medicinal products* ~~*frequently*~~ *contain* ~~*high levels of*~~ *ethanol arising from the active ingredients where ethanol has been used as the extraction solvent or added as a diluent to liquid herbal preparations* ***As recommended doses are generally low,*** ~~*E*~~*ethanol* ***from these sources*** *is metabolically* ***in****active*~~*e*~~*ated* ***rapidly and*** *therefore* ***poses no relevant risk to children. Thus*** *formulations with*~~*out*~~ *ethanol* ***contents as those in existing authorised and registered products and taken at the recommended dose(s) can*** ~~*or with the lowest achievable level should*~~ *be* ~~*selected*~~ ***used without any toxicologically relevant*** ~~*to avoid*~~ *systemic exposure* ***even*** *when the target population is children (1,* ***34****).* The conclusion, that ethanol is metabolically active due to the fact that it is arising from the active ingredients, is not convincing. Ethanol is of course metabolized, after having been pharmacologically active, provided doses have been sufficient. But that is established scientific knowledge and needs not to be specially mentioned here. In general, in medicinal preparations a product specific risk-benefit evaluation is necessary. Following the rule stated in line 7, namely that formulations with the lowest achievable level should be selected to avoid systemic exposure, will not necessarily lead to an optimal relation of risk to benefit. Therefore we propose the following changes *Ethanol is* ~~*metabolically active*~~ *therefore to be included into the risk benefit assessment, formulations with the best overall risk-benefit ratio, independent from their* ~~*out*~~ *ethanol* ~~*or with the lowest achievable*~~ *level, should be selected* ~~*to avoid systemic exposure*~~ *when the target population is children* (1).	The HMPC is aware of the issues that are mentioned in the comments. However, any content of ethanol is a matter of concern in pediatric formulations and has to be throughly justified. Partly agreed with the proposed wording and the text has been revised respectively. The provided views on risk assessment are interesting, however they do not coincide very closely with the views of HMPC in all respects. In principle, risk benefit evaluation of medicinal products is to be taken into account whether the product contains ethanol or not. This section outlines general aspects of risk evaluation and ethanol related properties

1. Introduction Lines 6-7	ANME e.V	The draft reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products used in children EMEA/HMPC/84114/2008) addresses the problem of potential alcohol toxicity through medications. As alcohol is metabolically active, the HMPC recommends applying the lowest possible dose of alcohol in children. The ANME clearly supports this approach. However, the ethanol concentration in a medicinal product cannot be assessed without also assessing the dose schemes. A small dose of a preparation with a relatively high percentage of alcohol may provide a lower absolute quantity than a high dose of a preparation with a low percentage of alcohol. E.g., a glass of beer (0.33 l, 5 % of alcohol) provides 13 g of ethanol – this would be a typical reference used by parents when comparing alcohol contents. Typical herbal medicinal products can have much higher alcohol contents, in some cases 50 % and more. However, other than the beer which is entirely consumed with one serving, the herbal medicinal products are multi-dose preparations. A typical dose of 10 drops of an herbal medicinal product containing 50 % ethanol delivers approximately 0.14 g of ethanol, which would lead to a blood alcohol concentration of 0.015 ‰ in a child of 15 kg body weight, or 0.008 ‰ in a child with 30 kg body weight. In any case the blood alcohol levels achieved with such an herbal medicinal product are still below the endogenic blood alcohol level of 0.03 ‰ . With the metabolic clearance capacity the alcohol supplied in the example would be eliminated within 4 and 2 minutes, respectively. For comparison only: A glass of apple juice (200 ml, approximately 0.5 % ethanol) provides approximately 1 g of alcohol leading to a blood alcohol level of 0.11 and 0.055 ‰ in children with 15 and 30 kg body weight, respectively. This quantity is eliminated within 30 and 15 minutes, respectively: *We suggest changing the introductory remark* *“Ethanol is metabolically active therefore, formulations without ethanol or with the lowest achievable level should be selected to avoid systemic exposure when the target population is children”* *Into* *“...to avoid systemic exposure to levels above 0.125 g/l when the target population is children* This change would be consistent with the further argumentation in the draft reflection paper, and still not cause problems even with the comparison of the contribution of typical fooditems such as bananas or fruit juices to the overall ethanol exposure in children	See comments above. Not agreed. Risk benefit evaluation is to be taken into account indepedently from ethanol content. This section outlines general principles of risk evaluation and the specific recommendations are discussed further in the text.

2. Scope	ANME e.V	The scope of this paper is to reflect the need for safety limits for ethanol exposure by oral herbal medicinal products intended for the paediatric population. The given details discuss, however, the toxicity thresholds of ethanol as such, and do neither discuss the absolute contribution of ethanol by single doses of typical herbal medicinal products, nor the toxicity of such single or even repeated doses. Furthermore, we feel that the necessity for regulation should be analyzed before explicit recommendations for regulatory measures are made. If there is no reason for concern, there is also no reason for regulation or harmonization with the argument of safety issues. Although the toxicity of ethanol as such is not questioned (neither is the obviously increasing problem of alcohol addiction in children and adolescents), our impression on reading the reflection paper was that a toxicity issue by the alcohol content of herbal medicinal products was not presented in the reflection paper. The reflection paper remains on the level of the discussion of potential adverse effects on ingestion of the total quantity of alcohol in a medicinal product, but does not discuss the effects of single doses. In fact some preparations contain sufficient alcohol to be a matter of concern if the whole bottle were accidentally ingested by a child. From the toxicological point of view it does, however, not make any difference whether such a form of accidental abuse relates to alcohol as a toxic constituent of the galenical form, or to any other toxicologically relevant constituent. In other words: The question of ethanol toxicity on accidental ingestion of a whole bottle of a given galenical form might be secondary to questions of toxicity by the active constituents. All preparations are clearly labelled with the warning that drug products have to be stored out of the reach of children. The total alcohol content in the bottle and the hypothetical possibility of accidental intoxication should therefore not be defined as the standard case.	No action needed. The paper addressed reflections on risk aspects surrounding the intake of ethanol by paediatric population for regulatory evaluation.
3. Problem statement	AESGP	From our point of view, the ethanol content of a herbal preparation is not of relevance as it is not related to the actual recommended single dose. For this reason, the wording of line 36 citing an AFSSAPS recommendation should be adopted i.e. "*the amount of ethanol in any medicinal product should not produce blood ethanol concentration greater than 0.125 g/L following the administration of only one dose* (31)". However, we suggest leaving out the expression "optional medicinal prescription" as it seems not relevant here. Maximum blood concentrations of ethanol, in smaller children, after intake of the recommended dose of existing herbal medicines, were shown not to be above the range of 0.03 ‰, which is known to correspond to the physiological blood level of ethanol of up to 0.03 ‰ (1). Only with few medicines for older children or adolescents maximum blood levels of up to 0.06 ‰ was shown (1), which is still very clearly below the limit of 0.125 ‰ proposed in this reflection paper. It is the dose that makes the poison, as already known from Paracelsus. *liquid products: This is of potential toxicological concern in children with respect to both short-term and prolonged use of ethanol-containing herbal medicinal products if the*	Disagreed with the proposed wording and with underlying rationale. The suggested sentences are not reflecting on the blood concentration which is referred to in the text. The paper leaves the specific measures to the responsibility of the applicant following the guidance by means of the formulas given in the annex 1.

Line27	Kooperation Phytopharmaka	*recommended doses are not adhered to.* *Line 36 …~~optional medical prescription drugs intended for paediatric use must have a concentration of ethanol less than 5 % and/or~~ or the amount* It is stated, that e.g. ethanol concentrations in excess of 60 % (V/V) are of toxicological concern in children. Of course, primarily not the concentration, but the dose is of concern in the toxicology of internally applied preparations. Therefore we propose: *… liquid products. Th~~is~~e the ethanol contained in a recommended single dose is of toxicological concern ….*	
Line 38	AESGP	insert after …one dose (31).: *But, as maximal blood ethanol concentrations reached after intake of the recommended doses of existing ethanol-containing herbal medicinal products are significantly below that limit, irrespective of the concentration of ethanol they contain (34), these different national labelling practices do not children at risk. They have no practical relevance for authorisation or registration of medicinal products for the paediatric population*.	Not agreed. See comments above.
3. Problem statement Line 44	Kooperation Phytopharmaka AESGP	As is stated in line 57, there is no compelling evidence that children are more vulnerable to the toxic effects of ethanol than adults. Moreover, the metabolism of ethanol in younger children is even faster than in adults. Therefore, an approach related to the resulting blood ethanol concentration (as described in line 37) is more adequate than an approach specifically recognizing children of different age groups: *age groups. But an approach oriented on maximum blood ethanol concentrations ~~Therefore, it~~ is ~~not~~ considered sufficient …* *insert after … different age groups.: However, an approach focussed on the maximum concentration of ethanol in blood resulting from application of a single dose should be considered a sufficient guidance*	No changes are deemed necessary. The single dose approach suggested is scientifically not sound enough, however, the appendix 1 is giving tools for dose evaluation.

3. Problem statement Lines 50-57	Kooperation Phytopharmaka AESGP	The following explanation could be added here: *…toddlers (10). Due to the large amount of breast milk consumed by a toddler, it is thinkable that even very low ethanol concentrations in the breast milk could lead to considerable absolute doses of ethanol. With herbal medicinal products intended for the use in children, very low amounts of the fluid preparations are applied, resulting in ethanol doses far below toxicological relevance. Although …* *insert after … for paediatric use (32). Experience and data accumulated with herbal preparations having a well-established or traditional use on the market should be taken into consideration. Line 55, insert after … age of one year (9). This is plausible due to the fact that from the large volume of breast milk absorbed it follows that even small concentrations of ethanol in the breast milk of alcohol consuming mothers may lead to a considerably high intake of ethanol by the infant, while herbal medicines, even if having higher absolute ethanol concentrations, do not lead to a toxicological relevant ethanol exposition of the breast feeding mother due to the very low doses taken (34).*	Not agreed. The suggestion is not clarifying or bringing any additional value to the text, it may, however, raise the question of the safety referring to the intake of ethanol containing herbal medicinal products by the breast feeding women.
3. Problem statement Line 59	Kooperation Phytopharmaka & AESGP	As stated above and documented e.g. in the review of Kelber et al. (2008), the ethanol dose is decisive for potential toxicological effects, with low doses having not detrimental effects: *… harmful effects of higher doses of ethanol.*	Not agreed. Dose finding studies with peadiatric population have not been done.
3. Problem statement	ANME e.V	The reflection paper refers to typical ethanol concentrations in herbal medicinal products, which may be in excess of 60 % (V/V). The reflection paper further adds that this is of toxicological concern in children with respect to both short-term and prolonged use, especially if several alcohol-containing products are given concomitantly. Usual herbal medicinal products in liquid form contain 30-50 % ethanol (drops), or 3-6 % (juices). Anyhow, it is not the total content which counts, but the ingested dose. Children will not suffer from toxicity of alcohol which is in the bottle instead of on the spoon. Correspondingly, it makes sense to regulate the ingested dose instead of the alcohol concentration in the product. Thus, a limitation of the amount of ethanol to a quantity per dose which will not produce blood concentrations in excess of 0.125 g/l is a feasible solution to the problem, but limitation to less than 5 % in the formulation as in the French suggestion is not. The HMPC supports the idea of limiting ethanol in paediatric preparations by referring to toxicological concerns in babies where alcohol is transmitted by breast-feeding – concerns which according to the presented data were already drawn into doubt. In fact, the situation of babies being intoxicated by breastfeeding is completely unrelated to the question of the safety of herbal medicinal products. In order to produce alcohol contents in breast milk sufficiently high to cause an elevation of blood alcohol levels of toxicological concern in babies the mother herself is unlikely to have achieved this level of drunkenness just by application of herbal	No action needed, see specific comments above and below. The issues are dealt with in the comments throughout the text.

		medicinal products. Even if the mother were drunk and had a blood alcohol concentration of 2 ‰ (and assumed this alcohol concentration will also be present in the breast milk), such a oncentration will not exceed the quantities regularly ingested by normal food – quantities which obviously do not cause problems. A rough calculation will immediately demonstrate the lack of a relation: A typical meal size of a breast-fed baby is 150 ml/kg body weight until the age of 6 months. After six months the total quantity reaches approximately 900 ml per day, but only if the baby is not fed with other food, which has to be expected in an 18 month old toddler. With additional food the quantity of milk is usually 500- 600 ml per day. With the assumption of the mother constantly having an alcohol blood level of 2 ‰ , and the assumption that the same concentration will be found in the breast milk, the baby would be exposed to approximately 1 ml of alcohol per day, usually distributed over 3-5 meals, corresponding to 0.2 - 0.3 ml (0.16 to 0.24 g) of alcohol per meal – which is less than the quantity ingested with one serving of apple juice (see above). Using the method of calculation given in the Annex of the Draft Reflection Paper, the maximum acceptable dose for children of two years of age with a body weight of 12 kg would be 0.9 g per dose – and thus at least three times more than provided by breast milk under conceivable circumstances. In order not to be misunderstood: We do not advocate alcohol consumption by breast-feeding mothers. We simply want to point out that a regular intoxication of breast-fed children through alcohol-consuming mothers would require an accumulation of ethanol in the breast milk. If a joke is allowed in this place: This would give the German wine brand “Liebfraumilch” a completely new meaning. In such a discussion the contribution of regular food must not be forgotten. According to information given by Prof. Keul (University of Freiburg) in an interview published in the internet a number of regular food items contain relatively high quantities of ethanol, among them bread, bananas or fruit juices. These food items are not of toxicological concern, even if ingested by children. Ripe bananas contain up to 6 g of ethanol per kg. Fruit juices contain up to 3 g/l, grape juice even up to 10 g/l. Through the activity of yeast even bread contains 2-4 g/kg. Fermentation by lactic acid (e.g., sour-dough, kefir, sauerkraut) also leads to the formation of ethanol. Keul cites the following typical quantities per serving: - Grape juice: 4 g/l, corresponding to 800 mg/serving’ - Apple juice: 2 g/l, corresponding to 400 mg/serving - Grapefruit: 1 g/kg, corresponding to 200 mg/serving’ - Whey bread: 2 g/kg, corresponding to 100 mg/serving - Rye bread: 3 g/kg, corresponding to 150 mg/serving’ - Kefir: 5 g/kg, corresponding to 1000 mg/serving - Sauerkraut: 5 g/kg, corresponding to 1000 mg/serving’ Such quantities are not causing problems in children. The Nutrition Report of the German Society for Nutrition (Deutsche Gesellschaft für Ernährung, DGE) of 1996 calculated that children in the age of four to 13 years supply approximately 0.2 percent of the total energy intake by alcohol contained in food. In pediatric medicine there is not a single case report or study assuming health damage by the ingestion of regular food, especially food rich in carbohydrates, which is more likely to	

		contain ethanol. In addition to such considerations it has to be kept in mind that the human organism itself produces ethanol and maintains a regular blood level of approximately 0.03 ‰ . Toxicologically relevant consequences of ethanol intake can only be expected when the physiological capacity of ethanol clearance is distinctly exceeded. This is, however, not normally the case with the ingestion of regular doses of herbal medicinal products, as was already explained in the introduction. Another example shall underline this fact: Typical cough syrup preparations contain 5-6 percent of alcohol. A typical daily dose is approximately 6 ml for babies in single doses of 1 ml, which leads to an intake of approximately 40 mg of ethanol per day. Applying the method of calculation presented in the Annex of the Draft Reflection Paper, a single dose of the preparation will increase the blood alcohol level by 0.008 ‰ . Ethanol clearance in babies reaches 0.06 to 0.09 ‰ per hour. The hourly clearance rate is thus approximately 10 times higher than the dose ingested with the medication. The clearance capacities would not even be exceeded if the total daily dose were accidentally applied. Thus, if symptoms of deficient psychomotor development are found in babies where the mother is under constant influence of alcohol, the reason for such deviations should rather be sought in the neglect of the child than in the alcohol transmitted through breast milk. Regardless of these considerations, the example of drunken breastfeeding mothers is clearly unrelated to the question of safety of application of herbal medicinal products, and should therefore not be used as an argument for a need for regulatory activity.	
4. Discussion	Kooperation Phytopharmaka	It has to be considered, that data on physiological blood ethanol concentrations show that levels of up to 0.03 ‰ are still in this range. As can be calculated (Kelber et al. 2008), maximum blood levels after intake of recommended doses of herbal medicines are not above this value. Moreover, adverse effects of these ethanol doses have not been described, so that we propose the following changes: *… arising with blood ethanol concentrations in the range of 0.01 – 1 g/L (6). With herbal medicinal products in doses recommended for children, maximum blood ethanol concentrations are not above 0.03 ‰ , which is still in the range of physiological blood ethanol concentrations, and adverse effects caused by the ethanol content of the products have nor yet been described (Kelber et al. 2008).* *With alcoholic beverages consumed by children, the situation is other. It should ~~also~~ kept in mind that trauma is one of the major causes leading children to hospitalisation. Ethanol use is linked to a 3- to 7-fold increased risk of trauma. In adults, blood ethanol concentrations in the range of 0.15-0.3 g/L (0.15 – 0.3 ‰) have been reported to impair tasks that require a high degree of attention and motor coordination (18, 19, 20*). *In contrast, ~~T~~he paediatric use of herbal medicinal products containing ethanol ~~should~~ does not lead to blood ethanol concentrations affecting attention and motor coordination.*	No changes are deemed necessary. Disagreed with the underlying rationale presented. This is a guidance document for herbal medicinal products, which are medicinal products defined by the Community Legistlation. Medicinal products have precise indications and dose recommendations including the duration of use. The food items are under other regulatory bodies. The estimates for food items given are not exact and standardised.

Lines 80-84	AESGP	This section talks about the general aspects of misuse of ethanol and seems at odd with the overall scope of the paper. There is no link to the intake of liquid herbal medicinal products through which relatively low amounts of ethanol are absorbed, taking into consideration the low daily doses of the preparations. It is evident that a significant risk is linked to the consumption of ethanol-containing beverages e.g. during pregnancy or lactation or in case of excessive drinking of large amounts, but this same risk does not apply here. Herbal medicinal products used at the recommended doses would lead to amount of ethanol in the blood which bear no comparison with the facts cited here. As stated above, this is confirmed by recent intensive searches in relevant databases which did put into light cases of ethanol intoxications caused by administration of herbal medicinal products (34, 41). *80 insert after: … in the range of 0.01 – 1 g/L (6), which reach levels significantly above maximum blood levels achieved with usual ethanolic liquid herbal preparations. The latter are not higher than 0.03 ‰ , which is still within the range of physiological blood ethanol levels.* *81 insert after: … children to hospitalisation. Ethanol ~~use~~ in high doses is linke* *84insert after: … 20), which cannot be achieved by the therapeutic use of doses of existing herbal medicinal products containing ethanol recommended for children. The paediatric use of herbal medicinal products containing ethanol should not lead to blood ethanol concentrations affecting attention and motor coordination*	Moreover, eating habits and recommendations may differ from one country to another, especially when small children are concerned. However, if the food intake of ethanol is of concern it will be another risk evaluation process and may together with ethanol intake of herbal medicinal product give rise to blood ethanol content at risk levels.
4. Discussion Lines 87-88	Kooperation Phytopharmaka	A risk evaluation with relevance to the uses of herbal medicinal products containing ethanol primarily needs to take into account the maximum values reached with these preparations, the ethanol intake from other sources (food and beverages claimed suitable for children), and the physiological ethanol levels. Ethanol doses applied with repeated doses of herbal medicinal products containing ethanol are in the range or below those ingested with commonly used foodstuffs and beverages (e.g. apple juice or bananas, see Kelber et al. 2008). Therefore effects of long term exposure to higher doses of ethanol are of no relevance. The same applies to the fetal ethanol syndrome, which is caused not by ethanol intake of children, but by chronic maternal ethanol intake in doses several orders of magnitude higher than those achieved with recommended doses of herbal medicines. Therefore we propose the following changes: *Risk evaluation of chronic toxicity of ethanol in children should be associated not only with routine use of herbal medical products containing ethanol, but also the ethanol intake with the normal nutrition, and also the physiological blood levels of ethanol reported in the literature. ~~The effect of long-term exposure to ethanol has never been studied in a paediatric population. Studies and observations on FAS (foetal alcohol syndrome) and FAE (foetal alcohol effects) children, however, give direct evidence of the grave deleterious effects of chronic ethanol exposure, for example, on neurological and cognitive developmental processes (21, 22).~~* *insert: Risk evaluation of chronic toxicity of ethanol in children should be associated with the*	No changes are deemed necessary. Disagreed with the underlying rationale presented. See comments above

	AESGP	*routine use of herbal medical products containing ethanol and should consider the fact, that the blood ethanol concentrations achieved with routine use of herbal medicinal products is within, near or even below the range of physiological blood ethanol concentrations of up to 0.03 ‰ as well as the fact that such concentrations are also achieved by everyday exposure to food and beverages, as e.g. to fruit juices and kefir (34). The effect of long-term exposure to ethanol in concentration significantly above the physiological one has never been studied in a paediatric population, but is not considered specifically relevant for herbal medicines, as they do not induce elevated blood levels and are applied only during a short and therapeutically necessary period of time. Studies and observations on FAS (foetal alcohol syndrome) and FAE (foetal alcohol effects) children, however, give direct evidence of the grave deleterious effect of chronic ethanol exposure to doses, which by far exceed those achieved with herbal medicines (34), for example, on neurological and cognitive developmental processes (21, 22).*	
4. Discussion	ANME e.V	The most important argument in the discussion of the deleterious effects of alcohol intake by children is that "the paediatric use of herbal medicinal products containing ethanol should not lead to blood ethanol concentrations affecting attention and motor coordination." We are fully in support of this requirement. However, we are missing data from the discussion demonstrating a risk emerging from the application of herbal medicinal products containing alcohol. The data cited in the Draft Reflection Paper doubtlessly allows concluding that infants and the unborn need to be protected from toxic quantities of ethanol. The data cited does, however, not discuss whether such quantities can reasonably be expected to be reached by the application of herbal medicinal products (abuse notwithstanding). The application of, e.g., an herbal cough preparation for the duration of the disease (which will rarely exceed two weeks) cannot be considered a chronic exposure with a risk of addiction. A presentation of concerns emanating from the use of herbal medicinal products should be the given in order to argue for the requirement of regulatory restrictions. The discussion of alcohol toxicity with quantities by far exceeding the contribution of herbal medicinal products, even of food, cannot replace a real discussion of the facts. If there are none – as is obviously the case since the facts would otherwise have been presented – this lack of facts should at least be clearly mentioned.	No action needed. The section is stating general clinical data and goals. The provided views on risk assessment of ethanol intake by peadiatric population are interesting, however they do not coincide very closely with the views of HMPC which focus on broader approach in risk assessment process.
4. Discussion Lines 94-95	Kooperation Phytopharmaka	Development of dependence is not known from ethanol doses in the range of those applied with the normal nutrition and with herbal preparations. Given the low doses of ethanol applied with these preparations, even the data on adolescent alcohol use disorders cited, are of no relevance for a risk extrapolation for herbal medicines: *Chronic exposure to ethanol in relevant doses may lead to dependence the mechanism of which is poorly understood and may also be related to genetic factors (23), There are no studies on the addictive property of ethanol with paediatric population, however, adolescent alcohol use disorders with consequences have been documented (24, 25). The ethanol exposure resulting from the intake of herbal medicines is by far below doses having such consequences.*	Not agreed. Although suggestions are acknowledged there are no data which consider the proposed statements warranted. Thus, the proposed wordings are not seen clarifying or bringing any additional value to the text.

	AESGP	*Chronic exposure to ethanol may lead to dependence, the mechanism of which is poorly understood and may also be related to genetic factors (23), but is resulting from clearly pharmacologically active ethanol doses, which are significantly exceeding those achieved by using herbal medicines at the recommended doses. There are no studies on the addictive property of ethanol with paediatric population, however, adolescent alcohol use disorders with consequences have been documented (24, 25). However, these have never been shown for doses as low as those provoked by the intake of herbal medicines at the recommended doses*	
5. Conclusion	AESGP	A general warning from combining ethanol-containing preparations does not seem appropriate, as blood ethanol levels achieved with usual preparations as described in (34) are low and additionally are metabolised within a few minutes, so that even combining them is unlikely to lead to blood levels above the proposed limit of 0,125 ‰ . A general contraindication for children below 2 years of age should be deleted as there are no data demonstrating that an adequately dosed ethanolic preparation, which should be diluted before application, is generally questionable from a toxicological point of view for children below 2 years of age. It is not justified to exclude children from the use of effective and safe existing herbal medicinal products. Accumulation is impossible as soon as the dose interval exceeds the elimination time. As elimination times do in most cases not exceed few seconds or minutes, and are almost always to be expected to be far below about 30 min (34), usual dose intervals are by far above these times, so that a dose interval may be omitted. Therefore the respective sentence should be deleted Alternatives to ethanol, e.g. propylenglycol or glycerol, are much less well-documented from a toxicological point of view than ethanol, which is a component of natural foodstuffs and beverages generally accepted as safe (39). Furthermore, in many cases additional excipients, also with less good toxicological data, are necessary for preparing ethanol-free fluid preparations. Therefore, a general recommendation to replace ethanol does not seem to be justified (39, 40). Moreover, it would be more helpful to improve the regulatory conditions for reducing the ethanol content in herbal preparations, as this entail putting together a new marketing authorisation/registration. In addition, this would lead to preparations not covered by traditions and therefore outside of the scope of traditional use. In the published literature, there are lots of reports on intoxications of children with alcoholic beverages, but no such reports for herbal medicinal products. Up to now, the existing protective measures (including the use of droppers) are apparently sufficient. However, in case childproof closures are taken into consideration, they should only be used for bigger	Partly agreed and the text has been revised. This paper was reviewed by the PDCO which took a strict position of ethanol intake by children below 2 years of age. However, there are no clinical studies on the ethanol exposure in children. The study design for such a study would – among other things- raise ethical concerns which reflects the complexity of the matter. Many questions can thus only be answered in general terms. HMPC is not aware of any specific guidance giving safe blood levels of ethanol in children without interaction potential. Therefore, the interaction potential is seen clinically relevant as well as the goal for finding

		packages. Interactions are likely to occur with the use of alcoholic beverages, but not with the low amount of ethanol in the above-mentioned herbal preparations. Furthermore, this paragraph does not seem to herbal medicinal products. We propose removing this section.	alternatives to ethanol.
5. Conclusion Lines 102-104	AESGP Kooperation Phytopharmaka	***Data from clinical experience or observational studies do not support the theoretical concerns that small amounts of ethanol ingested via ethanol-containing herbal preparations might have negative side-effects in children.*** *It is* ***therefore*** ~~*unrealistic*~~ ***not necessary*** *to* ***conduct*** ~~*expect*~~ *studies* ***with the aim to establish*** ~~*where*~~ *safety thresholds in herbal medicinal products intended for paediatric use*~~*are directly demonstrated*~~*.* ***There exists a significant number of studies in children of all ages conducted with herbal medicinal products containing ethanol. These studies, mainly of non-interventional design, clearly demonstrate the complete lack of any side effects attributable to the ethanol content of these preparations.*** ~~*It is unrealistic to expect*~~ ***From these*** *studies****,*** ~~*where*~~ *safety thresholds for ethanol content in herbal medicinal products intended for paediatric use* ***can well be deducted***~~*are directly demonstrated*~~*. The evaluation must* ***include these*** ~~*stand on other*~~ *bases.* ***In addition, t***~~*T*~~*he following aspects should be considered*	Not Agreed The clinical studies on the ethanol exposure in children have not been done. See comments above.
Line 106	Kooperation Phytopharmaka AESGP	As ethanol doses not leading to toxicologically relevant local or systemic levels are safe, a minimisation below these levels has no benefit for the patient. The same is the case with a general age limit of 2 years, which is not supported by the information given in line 57-58 of the draft reflection paper and the data presented in the review of Kelber et al. (2008). Therefore we propose the following changes: *Ethanol administration to children should be minimised to toxicologically safe levels and the benefit/risk -ratio should be judged keeping in mind the target population.* ~~*All herbal medicinal products containing ethanol, in neonates and infants below 2 years are contraindicated.*~~ *Ethanol administration to children should be minimised* ***to a toxicologically acceptable level not leading to a relevant increase of blood ethanol levels above physiological levels e.g. in the range of 0.03 ‰ .***~~*, and the benefit/risk ratio should be judged keeping in mind the target population.*~~ *A* ***general contraindication for a****ll herbal medicinal products containing ethanol in neonates and infants below* ~~*2 years are contraindicated*~~ ***a certain age, do not seem appropriate under these conditions.***	Partly agreed and the text has been revised. This paper was reviewed by the PDCO which took a strict position of ethanol intake by children below 2 years of age.

Line 109 AESGP	Kooperation Phytopharmaka	Blood ethanol concentrations reached by doses recommended for children are far below toxicological relevance and elimination takes place within seconds or minutes (Kelber et al. 2008), so that even the concomitant use of more than one preparation is unlikely to cause a risk. Therefore this warning is not necessary: ~~The concomitant use of other medicinal products that contain ethanol should be avoided.~~ *The concomitant use of other medicinal products that contain ethanol should ~~be avoided~~* ***not result in a dose exceeding a blood ethanol content of 0.125 g/L****,* ***which is unlikely to be achieved even by combining two or three herbal medicinal preparations actually available in the market.***	Not agreed. See comments given (p. 16).
5. Conclusion Lines 110-111	Kooperation Phytopharmaka AESGP	As mentioned above, the elimination of the ethanol doses applied with the recommended doses of herbal medicines is so quick, that even a dose interval of some seconds or minutes would be sufficient (Kelber et al. 2008). As it can be expected, that dose intervals in clinical practice are not below these short intervals, the definition of a minimal dose interval is not necessary. As the safety of herbal medicines is not relevantly influenced by their ethanol content, there is also no scientific base for a special limitation of the overall duration of treatment: *As is true in all medicines, ~~T~~he dose interval should be kept as long as possible, ~~however it should be at least 4 hours to avoid accumulation. T~~and the whole treatment period should be as short as possible.* ***Since the maximum dose achieved in practice is far below the maximum blood ethanol content of 0.125 g/L*** *, the dose interval* ***is not of relevance but*** *should* ***nevertheless*** *be kept as long as ~~possible~~* ***necessary from a therapeutic point of view.~~,~~*** *~~however it should be at least 4 hours to avoid accumulation.~~ The whole treatment period should,* ***as for all medicines,*** *be as short as possible*	Not agreed. This paper was reviewed by the PDCO which took a strict position of duration of use..
5. Conclusion Lines 112-114	Kooperation Phytopharmaka AESGP	Replacement of liquid preparations containing ethanol by changed liquid preparations with other constituents or excipients or by solid preparations may have diverse consequences for efficacy and safety of these preparations. E.g., for propylenglycol, which has been used for replacing ethanol in liquid preparations for children, toxicological data are by fare less complete than in ethanol, and tolerability is obviously less favourable. Therefore a balanced risk-benefit evaluation should precede such a replacement, which then can be a chance for the development of a new preparations especially dedicated to pediatric populations and in accordance to actual pediatric recommendations and guidelines. We propose the following change of the text: *Appropriateness and safety of alternatives to ethanol should be considered and ~~continued~~ efforts ~~should be made~~ to have ethanol replaced in herbal liquid preparations intended for paediatric use should be based on a preparation-specific risk-benefit evaluation.*	No changes are deemed necessary. Disagreed with the underlying rationale presented. See comments given p 16.

		Appropriateness and safety of alternatives to ethanol should be considered ***in general, but as the ethanol-related risk of herbal medicines currently authorised or registered in the EU is negligible in children (34)****, ~~and~~ continued efforts ~~should be made~~ to have ethanol replaced in herbal liquid preparations intended for paediatric use* ***would not contribute to a relevant increase of the benefit/risk ratio of these preparations***.	
Lines 115-118	AESGP	*Harmful impairment of psychomotor functions can already occur when blood ethanol concentration is above 0.125 g/L. Therefore, the recommendation is that a 0.125 g/L blood ethanol concentration should not be exceeded following a single dose of herbal medicinal product containing ethanol (see Annex 1).* ***This limit is unlikely to be achieved by herbal medications already authorised or registered in the EU (34), or by new preparations with similar ethanol concentrations and therapeutic doses***	No changes are deemed necessary, see previous comments
Lines 119-120	Kooperation Phytopharmaka	There are actually no data pointing to a risk of intoxications in children due to accidental ingestion of large amounts of herbal medicines containing ethanol, despite many millions of packages have been distributed throughout Europe during the last years. This allows the conclusion, that actual protective measures are sufficiently efficient. By far most herbal liquid preparations containing ethanol are packed in bottles covered by droppers, which inhibit the access of children to toxicologically relevant amounts of the preparations. In addition, the unpleasant taste may also make voluntary intake of overdoses by children unattractive. The introduction of smaller package sizes or additional child proof closures therefore seems not to contribute to an increased patient or consumer safety; respective proposals should be deleted: ~~*Consideration should be given to herbal medicinal products containing more than 30 g of ethanol being packed in small volumes with childproof closures (26).*~~	Not agreed. The recommendation is seen relevant. In the reference (26) this approach is clearly appreciated
	AESGP	*Consideration should be given to herbal medicinal products containing more than 30 g of ethanol being packed in small volumes or with childproof closures (26). Droppers are part of these type of closures, as they hinder children from drinking toxicologically relevant amounts directly from the bottles within a relevant period of time (34).*	
5. Conclusion Lines 123-128	Kooperation Phytopharmaka	Preconditions for interactions are relevant effects on absorption, distribution, elimination or the pharmacological or toxicological effects of substances. Such effects are not to be expected from ethanol doses applied with recommended doses of herbal medicinal products, which are in the same range as ethanol intake with usual foodstuffs or beverages claimed to be ethanol free. We propose the following textual changes: *Interactions for herbal combinations or concomitant medications likely to be used in paediatric population ~~should~~ need not to be taken into account, as ethanol doses are below relevant levels. Only significantly higher ~~E~~ethanol doses may enhance the absorption and pharmacological effect of some drugs, such as sedatives, and affect the elimination of others by inducing and/or inhibiting the cytochrome P450-dependent elimination pathways (27, 28).*	Not Agreed. The interaction potential is a relevant issue to remind, see comments p 16.

	AESGP	*In addition, higher doses of ethanol may, in the presence of, e.g., some antibacterials, cause a disulfiram-like reaction (29, 30)* *Interactions for herbal combinations or concomitant medications likely to be used in paediatric population should be taken into account**, in case a relevant increase of the blood ethanol level is expected during therapeutic application. This is not the case with herbal preparations actually authorised or registered in the EU (34)**. Ethanol may **dose-dependently** enhance the absorption and pharmacological effect of some drugs, such as sedatives, and affect the elimination of others by inducing and/or inhibiting the cytochrome P450-dependent elimination pathways (27, 28). In addition, ethanol may, in the presence of, e.g., some antibacterials, cause a **dose-dependent** disulfiram-like reaction (29, 30)**.**	
5. Conclusion	ANME e.V	The conclusions drawn from the previously presented data are not really conclusions, but partly call for regulatory action for which no justification has been provided. E.g., the claim that ethanol administration to children should be minimized is undisputed. The same applies to the call for benefit-risk-assessments with the target population in mind. The latter needs no regulation, as it is already part of the process of herbal medicinal product registration. Stating all herbal medicinal products containing ethanol as generally contraindicated for infants below two years of age can, however, not be derived from the presented data. This is not a conclusion, but a political question, especially as the risk-benefit assessment mentioned in the same paragraph would simply be overruled without even looking at the facts. And the fact are that corresponding preparations are applied in babies below the age of two years, without any problem to be expected from the recommended dose schemes. Corresponding data from observational studies is published (e.g., {Schmidt, 2008 54236 /id}). We support that the combined intake of several medicinal products containing alcohol should be avoided, that the dose interval be kept as long as possible and the total duration of intake as short as possible. Reducing the intake of medicinal products to the lowest possible exposure is self-saying and not restricted to herbal medicinal products. A general spacing by 4 hours is, however not necessary in every case, as the spacing in time would depend on the single dose of ethanol and the metabolic clearance capacities, not on the fact that there is ethanol in the drug product. As presented in the introduction, the elimination of ethanol from a single dose of a cough drop preparation with 50 % ethanol requires 2-4 minutes in children with 15-30 kg body weight. A general spacing of intake of 4 hours based on hypothetical concerns is therefore not justified. The spacing of dosing must rather be defined by the clinical and pharmacodynamic effects. The development of safe alternatives of ethanol in paediatric formulations cannot be expected to be a quick process. Mankind has always had experience	No action needed. The issues dealt with in the comments throughout the text.

		with exposure to ethanol (not always good experience, though), and no replacement can be expected to be as welldocumented in terms of safety and toxicity. As yet unknown hazards with replacements such as sugar alcohols may be expected to be detected only after years of accumulated experience. n alternative appearing to be safe as judged by toxicological research is not necessarily free of risks. Although it is necessary and important to develop safe alternatives to ethanol, there is no guarantee that the replacements will really be safer than ethanol applied in dose schemes known to be of no concern. The Draft Reflection Paper expects harmful impairment of psychomotor functions in excess of 0.125 g/l of ethanol in the blood. As already outlined, such concentrations are not likely to be reached with the recommended dose schemes of usual herbal medicinal products. Still, the formulation of such a threshold is considered helpful for the risk-benefit assessment, as it would provide a reference value. We are therefore fully in support of the definition of the upper limit of 0.125 g/l blood alcohol upon single doses of paediatric medicinal products (not restricted to herbal medicinal products).	

References Line 131 ff	Kooperation Phytopharmaka AESGP	Please add the following reference: Kelber O, Gaedcke F, Steinhoff B, Winterhoff H. (2008) Ethanol in Herbal Medicinal Products for Children. Pharm Ind 70:1124-1127 [34] Kelber O, Gaedcke F, Steinhoff B, Winterhoff H. Ethanol in Herbal Medicinal Products for Children. Pharm Ind 2008 (9);1124-1127. [35] Schöberl S, Nickel P, Schmutzer G, Siekmeyer W, Kiess W. Alkoholintoxikation bei Kindern und Jugendlichen. Eine retrospektive Analyse von 173 an einer Universitätsklinik betreuten Patienten. Klin Pädiatr (Online Publication). 2008. DOI 10.1055/s-2007-984367. [36] Kivistö JE, Arvola T, Parkkari J, Mattila VM. Paediatric poisoning treated in one Finnish main university hospital between 2002 and 2006. Acta Paediatr 2008; 96:790-794. [37] Gnann A. Alkohol in Therapeutika – eine kritische Prüfung. Naturheilpraxis 2008 (12):1623-1624. [38] Laven A, Kern M. Alkoholische Tropfen für Kinder? Argumente für Ihre Beratung. PTA heute 2008 (21):42-43. [39] Brand N. Alkohol in Arzneimitteln. Pflanzliche Liquida im Wandel – Sind die klassischen ethanolhaltigen Fluidextrakte und Tinkturen in Gefahr? Dtsch Apoth Ztg 1996;136:251-258. [40] Kauert G. Sind ethanolhaltige Phytophamakazubereitungen in der Pädiatrie toxikologisch bedenklich? In: Loew D, Rietbrock N, editors. Phytopharmaka IV. Darmstadt: Steinkopff, 1998:95-100. [41] Kiesewetter S. Ethanolmetabolismus bei Kindern: Alkoholtoleranz und Gefahren. Pharm Ztg 1996;141:2195-2204. Schmidt, M. (2008). Fixe Kombination aus Thymiankraut- und Primelwurzel-Flüssigextrakt bei Husten. Eine nichtinterventionelle Studie mit Bronchicum Elixir bei Säuglingen. Z. Phytother. 29 (1): 7-14.	No changes are deemed necessary. These references are acknowledged. However, there are no new scientific sound data presented in the proposed references. Kelber et al (2008) is an overview of Ethanol in Herbal Medicinal Products for Children by Industrial point of view and the comments given above take into account aspects as presented in the reference.

Annex	Kooperation Phytopharmaka & AESGP	As herbal preparations are safely used also in children below 6 years of age, please add data for these age groups also to table 1.	Not agreed. The table is a general guidance. Lower age groups should be considered on case by case basis, if necessary