European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT REFLECTION PAPER FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	European Federation of Pharmaceutical Industry Associations (EFPIA)	Belgium
2	Les Enterprises du Medicament (Leem)	France
3	Neonatal and Paediatric Pharmacists Group (NPPG)	United Kingdom
4	Fertin Pharma A/S	Denmark
5	Alpha MOS	France
6	Siri Wang / Ingrid Gronlie	Norway
7	Joseph Standing, Centre for Paediatric Pharmacy Research	United Kingdom
8	Michael Rasburn	United Kingdom
9	European Pharmaceutical Aerosol Group (EPAG)	Belgium
10	Afssaps	France
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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
The text seems in places to be a general treatise of paediatric drug treatment which would be most appropriate for a clinical audience. We believe the text should be reviewed to focus on points to consider when MA applicants (essentially pharmaceutical companies) develop products for application in paediatric therapy.
Consistency in device terminology with the draft EMEA guidance (EMEA/CHMP/QWP/49313/2005 corr. London 16 February 2005). Proposal: There is continued reference to spacers and no reference to holding chambers or valved holding chambers (e.g. see section 2.7.3 page 19). It is necessary to differentiate between such devices which have different applications
• We welcome the Reflection Document, which draws the attention to the paediatric patients' needs and the challenges that the development of paediatric formulations may present. As a guidance for the development of specific paediatric formulations, the Reflection Document has its limitation in terms of completeness of information necessary for a specific development project and capturing new research results. The Reflection Document contains useful information, but it does not provide guidance on the essential requirements for paediatric formulations from a regulatory perspective. Therefore the document is not suitable as a guideline, since it does not focus on requirements for authorisation. • Our members have a widely divergent view on what changes might be made in order to improve the reflection paper. However, given the consensus view that the paper should not form the basis of a guideline, we believe providing detailed comment is not useful. • Answers to the specific questions are provided, in as much as member companies could understand the requests. Our members are opposed to the encouragement or support of off-label use for liability reasons. • If CHMP is intending to continue developing a Note for Guidance, then we request involvement at the stage of drafting the revised concept paper or draft guideline • We are not yet convinced of the value of developing a specific guideline on requirements for paediatric dosage forms. We believe that, for all practical purposes, no different quality and safety requirements apply for dosage forms used in adults or in children. However, there are different technical challenges associated with the development of medicinal products for administration to children. These technical challenges sometimes can prove insurmountable. Practical and realistic guidance to industry on strategies for the development of suitable dosage forms in this small and sensitive population could be welcome if it aids obtaining fast registration, thereby addressing patients' needs more quickly. With this element in mind, we would be interested in discussing with the CHMP whether a guideline on requirements which must be met to achieve approval of paediatric formulations would be of value, and what options there are should technical obstacles appear insurmountable. *Comment: as stated in the background, the reflection document is intended to provide information. It is not intended as a guideline on the essential requirements for paediatric formulations from a regulatory perspective. However, elements of the reflection paper may be incorporated into CHMP/QWP Guidelines on pharmaceutical development. This would of course follow the normal transparent route, i.e. any draft concept papers or guidelines would be published for consultation.*

We welcome the reflection document which draws attention to the paediatric patients needs and gives information on the development of pharmaceutical forms. However, the pharmaceutical industry would like to have more flexibility of choice concerning the type of galenic form to be used. This is because these forms are dependent on the specific drug characteristics, and have to be justified case-by-case as well as validated through their respective indication. At the same time, we do not consider that “off-label use” has a legitimate place in this document, for the obvious reason of shared responsibility between “manipulators” and the pharmaceutical company. We would rather encourage the inclusion of useful paediatric information in the SPC of drugs for adults in cases where a large experience is known, as well as where sufficient data has been given to the authorities. For these reasons, Annex 1 should be deleted, especially if this reflection document is to be transformed into a guideline.
In general, it is our feeling that the content of the Reflection Paper is very good and that it provides indeed useful information and guidance for formulating medicines for children.
I thought it covered all the main issues and it is encouraging to see the EMEA tackling these issues
It would be useful if some of the 'should' statements were mandatory, e.g.. stability testing of preparations when dispersed or mixed in a limited range of common foods or drinks/liquids
I welcome the return to the view that the taste of medicines is of great importance for children. Most children, particularly when ill, have difficulty in swallowing unfamiliar things, beit foods or medicines. That is why the provision of attractively flavoured medicines is vital. Liquid formulations, when well formulated, offer the best chance of getting medication - at the parental level - into the poorly child. There was a strong move some years ago to replace sucrose and similar nutritive sweeteners in paediatric medicines. It was a species of "political correctness" in that the aim of the sucrose - to disguise the sometimes truly disgusting taste of certain medicines (paracetamol comes to mind; also the various penicillins and cephalosporins) - was ignored in a grand sweep of preventing Caries. Whilst this latter does matter for the chronic patient, short-term it was not important. I wonder how many courses of treatment were abandoned over that period of time. Certainly I, for one, remember the gagging and expulsion of doses by my own children. And when I tasted that which they were expected to swallow; I knew why. The latter stages of the Reflections paper contains a most useful section on a "Taste Panel" of children. I applaud it. Those who continue to think inside the confining box should be encouraged to compare the flavour of Calpol as made in the 1970's with the generic Paracetamol Elixir for children of about that time. In my time in industry, I was involved in the production of both. It is vital for the young patient that their very great sensitivity to disgusting tastes is recognised and addressed.
A recent systematic literature review shows that highly cited journals permit inadequate formulation information in paediatric drug trials that they publish, impairing their validity and reliability. It is important for the investigators to provide full formulation information in all paediatric clinical trial reports. In it’s absence there is no way of assessing the bioavailability of a given dose. (3) Standing JF, Khaki ZF, Wong IC. Poor formulation information in published pediatric drug trials. Pediatrics. 2005 Oct;116(4):e559-62.
SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
"Background and objective", point 4, first indent:	"authorised dosage forms": at this stage, the forms are not still authorised. Propose to use "acceptable dosage forms " instead	Disagree. Text describes the aim: to have dosage forms specifically authorised for the use in the paediatric population available.
last indent	Unnecessary for the understanding of the scope. Delete "to summarise available information on paediatric formulations, and to use examples of authorised paediatric products"	Disagree. Text provides background information on the document.
1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1	I couldn't see any mention of newly licensed medicines – a statement to the effect that the EMEA will expect paediatric formulation is developed for all new medicines licensed for children would be welcome. This could be backed up by discussion of why licensed medicines are preferable to unlicensed specials etc.	Paragraph on the impact of the paediatric regulation on drug development has been added to the background section.
	Chapter 1 talks about developmental pharmacology and the potential for altered drug handling. However, it doesn't discuss the clinical significance of this (e.g. decreased protein binding is probably insignificant in many cases, other metabolic pathways can sometimes compensate meaning metabolism is usually unaffected, and catastrophic in other e.g. grey baby/cpl). Should there also be a discussion of the inappropriateness of calculating doses by mg/kg (Anderson et al 1997 Clin. Pharmacokinet. 33 (5) 313-27?)	Section 1.4 includes a general "disclaimer". As the focus of this document is on providing information on formulation development aspects, a discussion of potential clinical significance of e.g. different metabolic pathways is not deemed necessary. The comment on a potential discussion of the inappropriateness of calculating doses by mg/kg is taken note of. However, it is felt as being outside the scope of this document.
1.2	1.2: The age definitions guideline is based on the ICH document; we agree that the 2-12 years group should be sub-divided into the younger age group and older age group. There is a lack of research in this area,	The age definition provided in 1.2 is quoted from ICH E 11. The subdivision provided in table 3.1 (i.e. 2-5 for pre-school and 6-11 for school children) is maintained, considering the fact that the individual

[1] Where applicable

	we broadly agree with the classification that 2-5 and 6-11, but wonder if it should be 2-6 and 7-11.	state of development of a child of 5-6 years will anyway vary.
1	Suggest the use of a more specific terms than babies and children. Moreover, the heading of ch 1 seems somewhat diffuse. The age definitions outlined in 1.2 is according to the guidelines, however considering the aspects of formulation, the subdivision of the age group 2-11 – as stated in tab. 3.1 – is of importance and could be mentioned at this point.	Agreed.
1.3.1 Page 4	The ability to effectively use different inhaler devices illustrates this well with a gradual progression from large volume spacer with mask, spacer, breath-activated device and metered dose inhaler from neonate to adolescent. 'Large volume spacer' should be 'holding chamber'.	Agreed. In addition, "neonate" is changed to "infant" as it is very unusual to use inhalers for neonates.
1.3.1	1.3.1 A recent published study showed that the average age of conversion from liquid antiretroviral preparations to solid formulation is 7.3. (1) However, it is important to note that these children were on long-term treatment and have "learnt" how to take their medicines; the results will not be applicable to children who have acute illness and require only short-term medicines. It is important to consider the nature of the illness being treated in order to determine the requirement of formulation.	The comment is taken note of. However, the wording is kept unchanged as it is intended to provide general guidance.
1.3.7 page 6	There may be differences in the acceptability of different routes of administration …. It cannot be the 'same' differences as referred to in the previous section. We suggest that the text should be 'Cultural differences may also arise with regard to taste'.	Agreed, text changed.
1.4	The summary of develop mental pharmacology is partly beyond the main scope of this paper, but, as stated in the cover note, this has been included following advices, and makes a nice, although maybe a bit too general, brief overview. As to the metabolic development, however, this part has to be included in the paper, as the changing ability of handling excipients may be of significant importance.	Agreed – no changes. .
1.4.1	Should include a paragraph on buccal absorption *Buccal* There is little information on developmental changes in the buccal mucosa. There may be a higher permeability of the mucosa in children compared to adults as shown in a study of lidocaine mucoadhesive patches (1). **References:**	Agreed – the following paragraph has been added "There is little information on developmental changes in the buccal mucosa but there may be a higher permeability of the mucosa in children compared to adults (1)".

	1. Leopold A. *et al. Pharmacokinetics of lidocaine delivered from a transmucosal patch in children*. Anesth Prog. 2002; 49 (3): 82-87.	
1.4.1, page 6	Developmental Pharmacology, Absorption We note that inhalation is not mentioned, and believe mention of deposition and uptake through the lung epithelium after inhalation could be included.	A short paragraph on pulmonary development has been added: 'Pulmonary – deposition and absorption through the lung mucosa may be a useful, non-invasive route of administration for systemic effect; drugs intended for local effect may be absorbed and produce systemic adverse effects.'
2.1	Perhaps mention "mini tablets"/innovative granule (those new straws containing drug granules) formulation which could be a key development. Taste, shorter shelf-life, cost and increased need for excipients are always going to be problematic with liquids. Innovative solid formulations could be the ideal solution – easily swallowed, possible to titrate dose, all the advantages of solid dos forms (long shelf-life, eliminates taste problems, m/r and e/c possible)	Agreed – text modified.
2.1	Oral Administration: Chewing gum should be mentioned as an example of dosage forms in the first paragraph:	Agreed – text changed.
2.1.1	Liquid formulations must be easy to redistribute/shake before use. The urge to inform about the need to shake suspensions, to ensure correct dosing, should be emphasised	Agreed – text changed.
2.1.1	Although, older children can take higher volume of liquid medicines, the manufacturers also need to consider it is unpleasant for children with chronic illness such as HIV infection to take large volume of medicines everyday and also inconvenient for parents to take home a large number of bottles of medicines (1). (1) Yeung VW, Wong IC. When do children convert from liquid antiretroviral to solid formulations? Pharm World Sci. 2005 Oct;27(5):399-402.	Agreed – text changed: 'Large volume doses may be inconvenient for both patient and carer'.

2.1.2	Effervescent formulations: useful to know what is the minimum volume they can be dissolved/dispersed in and what is the solubility of the drug so fractional doses can be given if necessary.	Agreed- text changed.
2.1.2	The rapid drug absorption rates stated for effervescent products – is it significant, - and as it is mentioned only for this particular form it gives the impression that this is a special feature for this dosage form. The examples of available products (see also 2.1.4 and 2.1.5) is in my opinion not really necessary or relevant, and the availability may vary between different MS	Point is well taken. Text changed. In addition to the potential difference in availability in different MS, the knowledge that a specific product has already been authorised for the paediatric population does not necessarily help the formulation scientist.
2.1.3	Oral powders and multiparticulate systems: Are "beads" a specific dosage form whilst not belonging to the European standard terms list[2] ? Are they pillules? Delete-" beads"	Disagree. Although "beads" may not yet be included in the list of Standard Terms, the term is frequently used in pharmaceutical technology and drug delivery.
2.1.3	2.1.3 and 2.1.4 Mini-tablets and oro-dispersible dosage forms have great potential in paediatric formulation. We would like to see more research on these areas. However, we are aware that the expertise of this type of research is mainly in innovative and international pharmaceutical companies; these companies are unlikely to investigate their resources in the off-patent medications. Small pharmaceutical companies are unlikely to have either the resources or the expertise in such formulation developments. We recommend the EU Commissioners and national government to fund such research.	Valid comment, however, the reflection paper is not the right platform.
2.1.4	The use of coated tablets/microparticulate formulations should be encouraged, as taste problems can be significant for certain drugs. As to the coating of particles of orodispersible drugs – is the stated problems of effects on pk relevant?	The sentence is included to add a note of caution. The impact on the specific product and relevance will very much depend on the biopharmaceutical properties of the active substance/formulation.
2.1.6	Simply making tablets scored or crossed will improve the usefulness for tablets (with acceptable taste) for children, although not being the perfect solution – and this should be mentioned	Agreed – this is already stated in the text.

[2] Standard terms , 5th edition. December 2004. Council of Europe / EDQM (European Directorate for the Quality of Medicines)

2.1.6	Should include a paragraph on chewing gum (The existing paragraph "Tablets and capsules" should be renumbered 2.1.7) 2.1.6 Chewing Gum Medical chewing gum has only been used for relatively few paediatric formulations such as Travvell® (dimenhydrinate) and Fluorette® (sodium fluoride) (1). However, it may be a highly suitable dosing form for children as most children of age 6 years or older are familiar with chewing gum and appreciate it as a confectionary. Chewing gum is easy to administer, does not require additional water and may be taken anywhere. The unpleasant taste of most active substances can be masked by sweeteners and flavours added to the chewing gum (2). The release of the active substances is controlled by various means such as solubilizers, ion exchange, encapsulation and the amount of gum base (2). The minimum chewing time needed to ensure complete release of the required dose should be stated on the package. References: 1. Imfeld, T. *Chewing gum – Facts and Fiction: A review of Gum-chewing and Oral Health*. Crit. Rev. Oral Biol. Med. 1999; 10 (3): 405-419. 2. Hyrup, B. *et al. The MediChew® technology platform*. Expert Opin. Drug Deliv. 2005; 2 (5): 927-933.	Agreed – slightly modified text included.
2.2.2	Oro-mucosal dosage forms and formulation considerations. This subsection should include a paragraph on chewing gum. <u>Chewing gum</u> releases the active substance to saliva during chewing and may be used for both local and systemic treatment. Chewing gum should be chewed for a certain period of time (usually 10-20 min.) to ensure release of the intended dose and afterwards the gum residue should be expelled. This dosage form is likely to be acceptable for children of 6 years or older. (Fertin)	Agreed – text included.

2.3.2	Nasal Drops: Why are nasal drops only applicable for infants whereas there are nasal drops for adults? To replace "nasal drops may only be applicable for infants " by "nasal drops may be preferred for infants ".	Agreed – text changed.
2.4.1	2 We are aware that culture differences within the EU have significant effect on the use of rectal preparation. MENCAP (a UK disability charity) has reported that a child who required rectal diazepam was unable to attend school because the school was unable to administer the drug when required (2). It is difficult for the caregiver to give as well as patients to be given rectal diazepam. As a result, the unlicensed preparation of buccal midazolam, is being used in some patients. We agree that in some situations eg premature babies, it is necessary to use rectal products; however, we believe that the manufacturers should encourage developing alternative formulations or drugs to avoid the use of rectal products in some patients. 2) MENCAP Campaign report. Don't count me out. The exclusion of children with a learning disability from education because of health needs. http://www.mencap.org.uk/download/dont_count_me_out.pdf	No change. A reference on potential cultural differences in the acceptance of rectal dosage forms is already included in the text.
2.4.2	Enemas: The use of scaled devices (prefilled syringes with "rectal tip") will facilitate individual dosing, in contrast to the "all or none" devices, and may reduce the need for several strengths/dosages.	Already reflected in the present wording.
2.5	The reduced capacity in children for biotransformation and elimination of active substances absorbed by the cutaneous route: what is actually meant by this statement? To me, it gives the impression that this is a particular problem for drugs absorbed by the cutaneous route, is that so? The transdermal monolithic matrix type patches: if efforts are made to ensure proper precision when dividing doses of transdermal patches, this should be useful for children	The comment makes a valid point. However, in the context of this section the present wording is intended as a note of caution. Agreed and changed.
2.5.2	"a transdermal patch should always be favoured …" There is no reason to always prefer transdermal patches, as creams ointments and gels were justified and authorised through their respective application for any indication. In the same way, the first sentence at the top of page 15 should be withdrawn (" Creams, ointments and gels for transdermal delivery should be considered only in cases where no adequate transdermal	As the dosing precision of transdermal is much more accurate than the one of creams or ointments, the wording is maintained.

	patch or system is available.”).	
2.5.2	A transdermal patch has great potential in paediatric drug delivery; however, research and development of transdermal patches is limited by the similar factors as mini tablets and orodispersble tablets please see 2.1.3 and 2.14.	Acknowledged, however this is not the rightplatform.
2.6.1	The documents should use Ph. Eur terms for expressing concentrations, i.g. mg/ml instead of percent	Although there are some benefits for using the Ph. Eur. standards, branded products normally use percentage. The wording is therefore kept unchanged.
2.6.2,	Separate issues on central lines and peripheral lines should be addressed, especially concerning osmolarity	This is covered in 2.6.1 but a short paragraph has been included: “Hyperosmolar injections may be appropriate for central venous administration without further dilution. Rate of administration must be stated.”
2.6.5	The potential use of transcutane needle-less systems – why not more enthusiastic and encouraging?!	Agreed but no change needed.
2.7.2	Advantages and disadvantages We propose that this section should mention that the efficiency of the inhaled route is dependent on the age group. Younger children treated with nebuliser therapy may only get 1 to 2 % of the dose put into the nebuliser (metered dose) and neonates even less. However, the dose /kg may be substantial. This is very different from adults or adolescents. This might be usefully conveyed in a table	Basically, the information is already included in 2.7.3.
2.7.3	Older children can be trained to use an autohaler. ‘Autohaler’ is a trade name and should be replaced by ‘breath- actuated pMDI’	Agreed – text changed.
	Older children can be trained to use an autohaler. Even rather young children may be able to use a breath actuated pMDI so we suggest ‘Many children…’	Agreed – text changed.
	When referring to treatment of very young children we believe the text is incorrect as a (valved) holding chamber is meant and not a spacer. The first and last sentences seem to say the same. The second sentence is ambiguous. The use of a spacer or holding chamber does not always reduce the dose to the lung, although it will reduce the overall dose. Therefore we propose a revised text ‘Spacers and Holding Chambers’ The use of a spacer or holding chamber with a pMDI avoids issues of patient co-ordination and means that less medication impacts on the oropharynx. Using a face mask attached to a holding chamber	Agreed – text changed

	facilitates the use of pMDI with very young infants, although this may sometimes reduce the dose reaching the airways, (1). Wherever possible children should inhale through the mouth rather than the nose.' It would aid clarity if the above was set out as a sub-section of the pMDI text.	
	The survey data presented in the draft text, as well as the labelling of some marketed products, support the use of DPIs in children younger than 5 years. We suggest that the first sentence is changed to 'DPIs can be efficient delivery systems for children old enough to achieve the necessary inspiratory flow.'	Agreed – text changed.
	As above The penultimate sentence is awkward and we think it is unhelpful to speculate on the probable age range for new devices. We suggest: 'New DPIs appearing on the market may provide dispersive energy and will assist disaggregating the powder. Subject to suitable evidence, these devices might be appropriate for younger children.	Agreed – text changed.
	Nebulisers with air compressors are bulky and inefficient aerosol delivery systems. Newer nebulisers are computer controlled and deliver the drug only during effective inhalation. There are new compact air compressor nebulisers as well as those using other atomization principles. We suggest: 'Traditional air compressor nebulisers are bulky and inefficient aerosol delivery systems. Newer nebulisers of both air compressor and other designs are more compact. They may offer more efficient delivery of medication to the lung because of novel features including computer control.	Agreed- text changed.
	There is no reference to metered dose liquid Inhalers, except under nebulisers. 'New devices for nebulised medicines are available, which are as convenient as pMDIs concerning the size and the duration of inhalation. The whole dose is nebulised instantly and can be inhaled at once.' We suggest removing this sentence from the nebuliser section because the devices referred to are not nebulisers, but handheld inhalers just like DPIs/ pMDIs. We propose the introduction of a new section	Partially agreed. However, the European Pharmacopoeia Inhalanda terminology does not provide an appropriate classification. The sentence has therefore been removed from the nebuliser section and has been included as a separate paragraph.

	based on proposed European Pharmacopoeia Inhalanda terminology).	
2.7.4	Age and device This section seems to add little to the document that is not already covered in section 2.7.3 where the impact of age on inhalation device usage is treated and we suggest it is deleted. However, we believe that the discussion in the document shows that a range of different devices are necessary to ensure that different treatment options are available in order to allow treatment of different paediatric populations and it would be useful to make this general point. If the section is retained then we question why nebuliser therapy is not mentioned at all here as a recommendation when it is covered in previous sections. Either say that it is not recommended or to what extent it should be recommended with any limitations that may follow.	Agreed – section deleted.
Section 3 Table 3.1	The text caused considerable confusion because it is inconsistent with previous sections in several particulars and it was interpreted as a recommendation from EMEA. However, proper review of the text shows that it is a compressed presentation of data from a very limited survey that is described as 'not an in depth, evidence-based piece of work'. In the light of this qualification, we question the value of including the table in the document, although the information might be worth publishing elsewhere. If it is intended to provide a statement of preferred means of administration of medication to different paediatric populations then we believe this requires very considerable further work	A "disclaimer" has been added to the text to clarify that the table does not present a recommendation of licensing authorities, but is intended to provide basic information. Clearly further research is required.
Section 4,	Excipients We suggest that developers are also recommended to consider the possible implications of paediatric use of formulations not specifically developed for this group.	Agreed – text changed.
	It would be much valuable and useful for formulators to list or establish an acceptable range/level for the most common excipients used in paediatric formulation products in the guideline if available, such as for instance the EADI (Estimated Acceptable Daily Intake) for adult in USP, Ph. Eur, and JP.	Valid comment, but outside the scope of this document.

	This reflection paper should be in accordance with the existing regulation, in particular with the guideline "Excipients in the label and package leaflet of medicinal products for human use." which is in the literature references 3. So some wording changes specifically relevant to children can be proposed:	Agreed.
	4.1 Benzyl alcohol: It ~~can be toxic in~~ ***must not be given to*** neonates and pre-term neonates due to their immature metabolism. In developing pharmaceutical preparations for use in ~~pre-term infants, neonates and~~ young children ***up to 3 years old*** benzyl alcohol should be carefully evaluated…..	Agreed- text changed.
	4.1. Add: Benzoic acid (E210), sodium benzoate (E211) and potassium benzoate (E212) when used in parenteral dosage forms "may increase the risk of jaundice in new born babies" .	Agreed – text modified. For consistency, reference to E numbers has been deleted throughout the chapter.
	4.1. Add: Organic mercury compounds (such as thiomersal, phenylmercuric nitrate, acetate, borate) when used for the parenteral route can induce allergic reactions. The parents should tell the doctor if their child has any known allergy.	Disagree. Organic mercury compounds should now be avoided for children.
	4.2 Sucrose : Are sucrose adverse effects specifically relevant to children?	No, but a general note of caution seems worthwhile having.
	4.2 Fructose : Are fructose adverse effects specifically relevant to children?	See above.
	4.2 Sorbitol/xylitol: Are Sorbitol/xylitol adverse effects specifically relevant to children?	Disagree. This section is not the right place for the level of detail proposed. However, reference to the guidance provided by the European Commission has been included in the beginning of the chapter on excipients.
	4.2 Aspartame: Supplementary information can be supplied to implement the initial version. "Children without dietary restrictions **and even if less than 3 years old** can safely ingest ~~10~~ **40** mg/kg/d [4].	
	4.3 Ethanol: Add after "…in the range 1-100 mg/ 100ml." : "Up to 100 mg per day is considered as a small amount of ethanol"	Disagree – the proposed text is considered dangerous.

[3] **Guideline CPMP/QWP/463/00 rev1. July 2003 ("Excipients in the label and package leaflet of medicinal products for human use.")**
[4] European Commission report on dietary food additive intake in the E.U. October 2001; ref COM (2001) 542 final (Annex V table 2)
[5] European Commission report on dietary food additive intake in the E.U. October 2001; ref COM (2001) 542 final (Annex III table 2 and Annex V table 2)

	As it is mentioned on page 23 of the guideline "formulations of choice….", ethanol is a very common solvent which is toxic for children. Therefore, it would be necessary to establish satisfactory thresholds of ethanol concentrations in children's medication. The reflection could start on the basis of the thresholds stated in the paper of the American academy of pediatrics (Committee on drugs 1984) which could be summarised as follows: - no ethanol should be included in medicinal products for use in children. However, when ethanol is required to solubilise the active ingredients, the following is proposed: - over-the-counter (OTC) liquid preparations should be limited to a maximum of 5% ethanol. - Children under age six should be under physician supervision when using OTC medicines containing alcohol, - The amount of ethanol in any medication should not be able to produce a blood concentration greater than 25 milligrams per 100 milliliters (the point of nervous system toxicity) after a single recommended dose. 4.3 Propylene glycol: Add after "…should not be administered to children below the age of 4 years.":" **if more than 200mg/kg/day"**	Disagree. It will be difficult to completely avoid the use of ethanol in medicinal products for use in children. As regards the proposed options, reference is made to the guideline on excipients. The information provided in the guideline in combination with the present wording in the reflection paper is deemed appropriate.
	4.4 Colouring agents: Acceptable daily values for young children (less than 3 years old) are presented in the European Commission report[5] with a safety ratio usually 100 and summarised in the following table.(see page 8/8) It should be added at the end of this §4.4 : "Attention should be paid that coloured dosage forms may help to differentiate the drug product one another thus enhancing the children compliance to their treatment".	Disagree. It is felt that the table provides too much information for the reflection paper. Reference to the document itself has been included in the introductory section to the chapter on excipients. Disagree – could also lead to confusion with candies.
4.1 Preservatives	The problems associated with pain caused by injecting benzyl alcohol should be mentioned. The toxicity problems (also mentioned in ch 1) is does dependent and to our knowledge not necessarily a major problem, and could may be modified. The use of parabenes can be mentioned as an option for injections, however for this substance taste problems may limit the use in oral liquid forms. For both benzyl alcohol/benzoic acid, parabenes and propylene glycol, references	Already mentioned in the text. The WHO guidelines referred to in the comment are not easily available. Therefore, reference to a number of publications on the use of excipients in paediatric formulations has been added under "further readings" in the

	should be made to guidelines (WHO Accepted Daily Intake/Neonatal Formulary), enabling risk evaluation for a particular product	excipients chapter as this provides similar information..
Section 4.1	Benzyl Alcohol / Benzoic Acid / Sodium Benzoate Benzyl alcohol is often used as a preservative in injectable medicines. The title mentions 3 compounds but the text refers only to benzyl alcohol; we assume that this should refer to benzyl alcohol and its derivatives. It is not clear whether there is a specific risk of benzyl alcohol and its derivatives for paediatric patients, or just a general concern.	Text revised.
Section 4.3	…sensitivity to lactose varies widely in severity and the intake of considerably less than 3 g may provoke the described symptoms. At the very low quantities of lactose commonly administered in DPI (≤25mg dose) one would not anticipate any issues with lactose intolerance. It would be helpful to add a suitable comment on inhaled products	Disagree – no need to include this specific comment.
Section 4.4	There are severe acute and chronic concerns in the use of ethanol containing medicines in the paediatric population, … At the very low quantities of ethanol commonly administered in pMDI (<10µl) one would not anticipate any issues. It would be helpful to add a suitable comment on inhaled products	Disagree – no need to include this specific comment.
Section 5	Include other references that can bring more evidences on the common usage of the taste sensor/electronic tongue in the pharmaceutical industry. E.g., scientific posters written by companies (as BMS, Takeda, Barr Laboratories, Eli Lilly, Merck, Janssen…). which can be downloaded on this page: http://www.alpha-mos.com/en/pharma/pharma_meeting.php Moreover, you didn't mention the electronic nose, which is an useful tool to assess flavour quality/quantity/identity, assessments useful for formulation scientists that can not be done thanks to taste sensor or electronic tongue as flavour are volatile compounds and are more relative to odour and retro-olfaction than to taste.	Disagree as the proposed change is considered to be too promotional.
Section 5	For taste evaluation for paediatric formulations, the reflection paper mentions that the in-vitro taste could be evaluated through E-tongue instrument and the in-vivo taste evaluation could be performed by selected children. In fact, there should be another valuable way to perform such in-vivo taste evaluation for optimizing formulation through a professional taste evaluation panel. In certain levels, the	Reference is already included in 5.3.1.

	professional taste panel will be more appropriate to perform such test and there are several commercially available paediatric formulation products (and more and more paediatric products in the development stage) which have been evaluated by a professional taste panel. Therefore, in our view it will be appropriate to also suggest or recommend the professional panel to perform the pediatric product taste evaluation/optimization in the future guideline.	
Section 6	MR formulations like prolonged release granulas with specified dose per granula should be mentioned (Valproate MR granulas Orfiril Long being a good example). Such formulation might be of significant value and makes it possible to use an "adult product" in children.	Agreed – text changed.
7.2.3 and Annex 1 Section 2	Possibly replace the term "highly-potent" used in places such as 7.2.3 and Annex 1 section 2 (flucloxacillin could be regarded as highly potent in that it kills susceptible Staphylococci, but as the therapeutic index is wide: do we really need to measure its dose accurately?) I think this needs replacing with "narrow therapeutic index".	Partly agreed – text changed in 7.2.3. In Annex 1, the context clearly is "low dose preparations". Low dose preparations are not necessarily narrow therapeutic index.
Section 8	Include discussion of bioavailability/safety problems with specials vs. extemp vs. altered adult formulations at the bedside. If the majority of medicines are unlicensed and therefore given as specials/extemps, then bioavailbatility (Notterman Pediatrics 1986; 77: 850-2) may be altered and risk of errors with extemps (peppermint water case) could be mentioned	Agreed. In fact, the awareness of the risks of extemporaneous activities is the whole reason for drafting this section! – "Usually there is little information on the bioavailability of the manipulated dosage form' has been added.
Section 8	This chapter is of major importance and focuses on many essential issues. very good! However, we don't share the general major concern about splitting tablets, as an intra dose variation test should be prerequisite.	Agreed – the monograph "Tablets" of Ph. Eur. does require demonstration of mass or content uniformity. Thus, testing content uniformity is part of batch release in those cases where it is applicable.
Section 8 and Annex 1	Section 8 "Additional issues to be considered" and Annex 1 "Risks associated with manipulation of 'adult' dosage forms for administration to paediatric patients" propose that Industry should be encouraged to make available relevant information to improve the quality of formulations which are prepared by manipulation of authorised 'adult' dosage forms. While some companies see that this section might have value, before such a section could be incorporated into a guideline this would need significant further discussion from technical, legal and intellectual property considerations. Our members are not prepared to support off-label use and see	The reflection document is intended to highlight the manipulations of adult medicines which may and do occur in the absence of appropriate paediatric dosage forms. It highlights the risks around common manipulations and indicates information which may be useful to reduce these risks. The provision of relevant pharmaceutical information to support extemporaneous preparation of a paediatric formulation, either in the SPC or in response to a request by a health-care practitioner is an option which industry can consider. To clarify that this is an option, Annex 1, sections 2, 3, 4, 5, 6, 7 and 8

	potential off-label use exclusively being the responsibility of the prescribing medical doctor. To support manipulation of licensed dosage forms, e.g., by data not contained in a drug product application, will need a reliable legal framework that clarifies the respective responsibilities and liabilities of providers and users of such data. Any manipulation of dosage forms constitutes a manufacturing step, which would require adherence to GMP and may confer unpredictable results if not carried out with sound technological knowledge	have been slightly modified.
Section 8, first point	Companies are encouraged to make available as much relevant information as possible: How to manage to deliver physico-chemical data to the health professionals (solubility, stability in common solvents, pH-solubility, stability profile, microbiological quality, potential for solid-state transitions in suspension)? We disagree with this use of information as the applicant would be implicated in the liability by the health authorities in any case. On the other hand some of this information are confidential and will not be disclosed to health professionals. To delete the first point.	The comment is well taken. However, the document only provides recommendations deemed necessary from the point of view of a pharmacist facing the need to prepare an extemporaneous formulation. It is up to industry to decide whether they are willing to share the described type of information. For clarification, the wording in Annex 1 has been slightly modified (see above).
8., third point	What will be the information about interaction with food or drinks (grapefruit ?) in the SPC § 4.5? Data should be available To put some information in the SPC to help manipulators/parents in the extemporaneous preparation. ***: "Depending on the evaluation of such data by the competent authorities validated formulations for extemporaneous dispensing may be considered acceptable for inclusion in the SPC and package leaflet."*** Validation could not be faced for extemporaneous preparations. To delete: “validated formulation”. ***"The industry should also consider making available their pure active substances in order to improve the quality of extemporaneous preparations "*** We disagree with this use as the applicant would be implicated in the liability by the health authorities in any case. To add: “in exceptional	Again, this is only a recommendation. If a company is willing to include data on a validated formulation for extemporaneous dispensing in the SPC and package leaflet, that would be optimal. However, it it’s the company’s choice. Again, this is only a recommendation – see above.

	cases, the industry should also consider….."	
Annex 1	In Annex 1, the documents recommended that the manufacturers should provide information on the formulations. We welcome these recommendations. We have the following comments: 1) It is important to clarify the differences between providing useful information to health professionals to use these medicines and "promotion of unlicensed use of medicines" 2) There is no formal mechanism to feedback to either the regulatory authorities or the manufacturers what drugs are being use in children and what types of data are required. Therefore, it is important to set up data collection mechanism to collect such information and feedback to both the regulatory authorities and manufacturers. We would recommend the EU Commissions-funded network "Task-force European Drug Development for the Young" (TEDDY) to collect such information. 3) The Paediatric Expert Group should provide guidance of what type of data and tests are need. Current literature suggests that most investigators only focus on the chemical stability and ignoring the physical and microbiological stabilities. 4) It is important to consider the health and safety issues when patients/carers are cutting and crushing tablets or opening capsules at home. We suggest a comprehensive review is required to tackle these issues.	Yes, but "..unlicensed.." is too negative. It is important to accept that extemporaneous preparations are not necessarily outside the law; there is nothin illegal here. EU law allows that a 'license' is simply not necessary under certain (e.g. magistral) conditions. This is already explained in the text on p31, line 1 *et seq.* Comment is well taken, but this is the wrong platform. Disagree – this is not the function of this document. Adequately covered by the type of information to be provided. This is not the forum to suggest a 'comprehensive review'.
Annex 1.	o The first § " Whilst…. Patients." is repeated in the second part of § 1.Background o Delete this first § o The second § " The purpose…. unavoidable." is unnecessary for the understanding of the scope o Delete the second § o 1. Background point V.	Agreed and changed. Disagree. It is felt that the paragraph provides useful clarification.

	I. Add:" if more excipients are necessary for the paediatric formulation, it is better to use the same as in the adult formulation to avoid any incompatibility with any untested excipient" .	Agreed – text changed. "Since the adult medicine will probably already contain excipients, reformulation for paediatric use should not add unnecessarily to this burden, i.e. it should be kept as simple as possible by avoiding additional excipients, e.g. extraneous colouring matter, etc. Due consideration should be given to active substance/excipient compatibility."
Annex 1.	Background next to last § : "Liability for the magistral preparation seems to be different in the Member States but as might be expected, responsibility rests mainly on the manipulators themselves." We do not agree with this approach; there is a shared responsibility between "manipulators" and the pharmaceutical company. To delete this part	Disagree – text unchanged.
Annex 1., 8. Injection solutions administered by other routes, 4th §.	"Also the stability of injection solutions may be compromised on dilution, and in the absence of reliable technical information from the original manufacturer, it should not be assumed that the stability profile of the original product will be duplicated on dilution. More explanation has to be formulated To add after: …".The same dilution medium should be used as for parenteral use to avoid unstability of the solution.".	Disagree – para already reflects the general stability issue. As regards dilution, even the use of the same diluent as in the original preparation may impact stability.
Annex 2, second section, last para	"The methodology is well established for almost all paediatric dosage forms….. screening new substances for bitterness and monitoring the stability of taste over time." The paragraph is rather promotional and should be deleted.	Partly agree. First sentence changed to read 'The methodology may be applicable to many paediatric dosage forms….'