3 January 2013
EMA/805826/2012
Committee for Human Medicinal Products (CHMP)
Paediatric Committee (PDCO)

Overview of comments received on 'guideline on pharmaceutical development of medicines for paediatric use' (EMA/CHMP/QWP/180157/2011)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	The Association of the European Self-Medication Industry (AESGP)
2	Agence Francaise de Securite Sanitaire des Produits de Sante *(*Afssaps)
3	AGE Older People`s Platform
4	Amgen
5	Astellas
6	Initiative of the German Medicines Manufacturers Association (BAH) to foster better Medicines for Children (BAH-Initiative Kinderarzneimittel) Bundesverband der Arzneimittel-Hersteller e.V.
7	BPI - German Pharmaceutical Industry Association, Commitee on Research, Development and Innovation
8	Prof Dr. Jörg Breitkreutz (individual)
9	The United Kingdom Commission on Human Medicines ('The Commission') in consultation with its Paediatric Medicines and Chemistry, Pharmacy and Standards Expert Advisory Groups
10	EFPIA – Véronique Davoust
11	European Paediatric Formulation Initiative (EuPFI)
12	Irish Medicines Board
13	Colorcon Ltd
14	International Federation of Associations of Pharmaceutical Physicians (IFAPP)
15	Faculty of Pharmaceutical Medicine

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Stakeholder no.	Name of organisation or individual
16	Medicines Evaluation Board in the Netherlands
17	Neonatal and Paediatric Pharmacists Group
18	UK NIHR Medicines for Children Research Network (MCRN) Pharmacy and Pharmacology Clinical Studies Group (P&P CSG)
19	NIHR Medicines for Children Research Network, UK
20	Medicines for Children Network, Norway
21	Novartis Pharma AG, Technical Research and Development
22	Prof Anthony Nunn (individual)
23	Pharmig
24	Prescrire
25	The Royal College of Paediatrics and Child Health (RCPCH) and the Neonatal and Paediatric Pharmacists Group (NPPG) joint Medicines Committee
26	Reckitt Benckiser Healthcare (UK) Ltd
27	Elisabeth Ricchi (individual)
28	F. Hoffmann – La Roche Ltd
29	Stallergenes S.A.
30	Swiss Agency for Therapeutic Products (Swissmedic)
31	Ursapharm Arzneimittel GmbH
32	vfa.Research-based Pharmaceutical Companies
33	Dr. Andreas Grummel (BfArM)

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The guideline calls for a re-evaluation of all products on the market to ensure that their products are state of the art i.e. meeting the requirements as described in this guideline within a period of 5 years following its date of coming into operation. Guidelines usually apply prospectively, not retrospectively. It should be noted that a re-evaluation of all paediatric products on the market within 5 years is very challenging particularly for well-established medicines which are well tolerated and have been satisfactorily used for years in children. The potential reformulation that may be entailed from the review would not be feasible for most companies and in particular SMEs which are particularly well represented in our sector. In addition, re-formulations of medicinal products established on the market for decades may create confusion for parents and care takers. We apply for the deletion of this requirement.	Accepted: According the Paediatric Regulation EC 1901/2006, before a medicine can be introduced to the market, it has to undergone extensive studies in order to ensure that it is safe, of high quality and effective for use in the target population. However, as practical evidence and scientific knowledge increases over the lifecycle of a medicine, it must be taken into consideration that a medicine the quality of which was suitable for use in a target patient population (i.e. age-appropriate) at the time the authorization was granted may not necessarily be so after many years later. The reference to 5 years transitional period has been deleted and the paragraph is revised. As it is a legal duty of Marketing Authorisation Holders to ensure that authorised products are *state-of-the-art* while being on the market, the following statement has been included in the revised Guideline: *As knowledge increases, the usefulness (practicality), quality, safety or efficacy of authorised paediatric medicines should be re-evaluated by pharmaceutical companies in the interest of children and their caregivers. This approach is in accordance with Art 23 of the Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a product and adapt or improve their products for the benefit of patients and maintain a positive benefit-risk balance.*

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2	Patient acceptability should be studied in children in the paediatric trials. Otherwise, the MAH should provide at least adult data and relevant paediatric data on acceptability of the paediatric formulation. Major impact on adherence / compliance is reported in antibiotics by the practitioners to the Afssaps, with reported bad adherence in generics in particular (but not only). **Patient acceptability** - 644 Patient acceptance can be defined as the overall ability of the patient to use a medicine as intended. Patient acceptability is likely to have a significant impact on the patient's adherence and consequently on the safety and efficacy of the medicine. It is determined by the characteristics of the medicinal product and the user. The product aspects involve the pharmaceutical characteristics of the medicine such as 1) palatability, size and shape; 2) the required dose e.g. the dosing volume, number of tablets etc.; 3) the required dosing frequency; 4) the selected administration device; 5) the primary and secondary container closure system and 6) the actual mode of administration to the child. For paediatric medicines, the user may comprise both the child and its adult caregiver. Evaluation of the patient acceptability of a medicine should be an integral part of the pharmaceutical development studies. For medicines falling under the scope of the Paediatric Regulation, patient acceptability of the medicine should be studied in children themselves as part of the clinical trials, unless to be duly justified. In justified cases where no clinical trials will be conducted or in justified cases where patient acceptability will not be studied in the clinical trials, the adequate patient acceptability of the medicinal product(s) as proposed for marketing should be demonstrated otherwise e.g. by	Accepted: The guideline, its relevant sections, has been revised to reflect the need for confirmation of acceptability of a paediatric medicinal product.

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	literature references or by studies in dedicated adult panels, taken into account that adult data is the first necessary step for improvement of palatability in medicines intended for paediatric use. It should be thoroughly investigated if drop outs and poor compliance during the clinical trials are due to a bad patient acceptability. For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient acceptability is also strongly encouraged to be tested during paediatric clinical trials if any, due to major impact on adherence / compliance. If not, adequate palatability should be demonstrated otherwise e.g. by data from literature, studies in dedicated adult panels or feedback from patients who have been using the same or a similar product. In lack of actual data in children, applicants are encouraged to confirm the adequate patient acceptability post 20/23 marketing by actual studies in children who are already under treatment or by a careful evaluation of voluntary patient feedback. Palatability is one of the main elements of the patient acceptance of an oral medicine. It may also be an aspect related to the use of nasal and inhalation medicines. Palatability is defined as the overall appreciation of an (often oral) medicine towards its smell, taste, aftertaste and texture (i.e. feeling in the mouth, on the tongue). It is determined by the characteristics of the active substance and the way it is formulated into a finished medicinal dosage form. Of note, some active ingredients (in particular with bitter or acid taste) are known to have a bad palatability and difficult to be masked by traditional techniques and an innovative age-appropriate formulation is necessary for their acceptance in children. Information on the palatability of the active substance should consequently be acquired	

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	at an early stage in the development of a medicinal product, e.g. from dedicated adult panels and children panels when necessary, literature or in-vitro measurements such as the electronic tongue (for bitter taste). The palatability of the active substance should contribute to the choice of the selected finished dosage form(s) and its excipients, and route(s) of administration. Unless otherwise justified, the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or beverages). The target quality product profile can be tailored at a paediatric medicinal product with a neutral taste or a paediatric medicinal product with a specific and generally acceptable taste. The choice for either of these profiles should be justified. Normally, development of medicinal products with no or neutral taste should be considered, especially for medicines used in the treatment of chronic conditions as strong flavours can become unpalatable on repeated administration. The development of the intended target palatability (neutral or a specific taste) should be clearly described and include information on relevant alternative compositions or dosage forms. The measures that can be undertaken to improve the palatability of a medicinal product e.g. involve the selection of the excipients including taste maskers, sweeteners and flavouring agents, a change in the particle size of the active substance or excipients, the choice of a different salt form of the active moiety, coating of the active substance, coating of the finished dosage form, the application of a complexing agent (i.e. beta cyclodextrines) or for liquid preparations by any means to lower the amount of free active ingredient in solution such as the choice of a different strength and subsequent change in volume. Any oral paediatric dosage form should by no	

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	means become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning. Mixing instructions with food or beverages may be recommended in the SmPC and PIL. The instructions can either be intended to mask the unsatisfactory palatability of a medicinal product in cases where it has been demonstrated that the palatability of the medicine cannot be further improved and where it is not an option to select an alternative dosage form. Mixing recommendations can also be applied as a further means to improve the patient acceptability and the ease of swallowing of an otherwise already palatable medicinal product. In cases where mixing instructions are provided to mask the unsatisfactory taste of a medicinal product, it should be discussed which foods mask the original taste best. The applicant should understand whether the medicinal product is likely to dissolve in the food. The applicant should demonstrate that the medicine becomes sufficiently palatable after mixing with the recommended foods or beverages. The patient should be informed that such mixing is not an option, but a necessity and the modalities of administration clearly stated (mixing, storage-time and temperature, etc.). In all other cases, mixing instructions with food or beverages do not need any further justification from the perspective of patient acceptance. However, certain foods of beverages may affect the bio-availability and/or therapeutic action of the medicine. Moreover, the lack of recommendations on mixing with food or beverages will not assure that caregivers will not employ this method in order to administer the medicine. Therefore, the effect of mixing the medicinal product with different types of common food or beverages for children should be discussed and/or studied in the development pharmaceutics targeting	

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	at in in-use with a maximum shelf-life of 30 minutes. The applicant should clarify and study if necessary the impact on pharmacokinetic-pharmacodynamic characteristics of the medicine. 21/23 Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately i.e. within 5 minutes. Positive mixing instructions with common food or beverages are recommended. Appropriate warnings should be added in cases where the medicine can not be mixed with certain food or beverages for even 5 minutes or shorter. The adequate palatability of a medicinal product should be studied as part of the patient acceptability studies. Otherwise, adequate palatability should be demonstrated by other means and confirmed post marketing in real patients. Actual palatability studies may be conducted in several ways. The suitability of the chosen method and the appropriateness of the limits to be applied should be discussed and justified in terms of risk to benefit considerations, including risks at population level (e.g. emergence of resistance), and should take in account the characteristics of the target age group, the condition relevant to the medicine, incidental and multiple use, co-medication and differences between countries.	
3	AGE represents older people, not children, but some of the things relevant for children are also relevant for older people: e.g. Problems to swallow, size of tablets, taste, formulation etc.	Response to comment not applicable
4	In general, the document does not emphasize strongly enough the vulnerabilities of this population given their ever changing internal environment. For example, the degree to which liver enzymes are produced to metabolize drugs varies with age, especially in very young infants. In addition, the importance of a safety program to	Partially accepted: The ICH terms for age classification of paediatric patients have been used trough out the guideline. Section 4 of the Guideline has been revised to emphasise

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	monitor growth and development needs to be underlined. "General Considerations" (Section 4) should contain language to emphasize that any paediatric drug development program should include detailed safety monitoring within a clinical trial development program that focuses on the impact of the drug on paediatric growth and development in addition to any potential risk posed by the drug itself. There should also be some reference to the potential impact of prescribing a given drug at various time points during childhood growth and development. Throughout the document, terminology changes are necessary. Newborn, young infant, etc are not used consistently. Consider using ICH terms for age classification of paediatric patients: • preterm newborn infants (<37 weeks gestational age) • term newborn infants (0 to 27 days) • infants and toddlers (28 days to 23 months) • children (2 to 11 years) • adolescents (12 to 16-18 years (dependent on region) Moreover, it should be mentioned how growth and development might be affected at the different chronological time points. The legal basis for the sentence: *"Pharmaceutical companies should have a re-evaluation of all their products on the market."* is unclear and should be provided. In addition, *"(...) have a re-evaluation"* could easily be misunderstood as a regulatory re-assessment rather than an internal judgement. Whilst the Paediatric Regulation as such has a broad scope, the paediatric obligations have a more narrow scope. In essence, such obligations relate to medicinal products required for paediatric use	paediatric specific aspects that need to be taken into consideration during development. A reference to ICH Q8 with relevant comments was included in to further clarify the approach for defining the pharmaceutical design of pediatric medicines. Retrospective applicability of the Guideline has been clarified and a reference to the 5 years transitional period has been deleted and the paragraph is revised Terms such as "dispersible tablets," "orodispersible tablets," "hard capsules" have not been defined in the Guideline as these are standard terms applicable also to medicines for adults. These terms are defined in the Ph. Eur. and in the Standard Terms. Editorial change: Not accepted. The comment is not endorsed. Section 10 of the Guideline was retained in the initial location

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	(refer to recital 6). This must be reflected in the guidance. Also, the cost implications must be taken into account as well as the need to avoid unnecessary trials or to delay or block the authorisation of medicinal products for other age populations (refer to recitals 4, 8, 10 and 14). To avoid misunderstanding, we suggest adding the words **with pediatric indication** after "products" so the sentence reads: "Pharmaceutical companies should evaluate all their products **with ~~potential~~ pediatric indication** on the market." Definitions: Define all dosage form terms such as "dispersible tablets," "orodispersible tablets," "hard capsules," etc. to provide clarity (some of these terms are not widely used in the industry). Editorial change: We suggest moving Section 10 "Patient Acceptability" to the beginning of the document as it defines terms that are used throughout the guidance.	
5	Astellas welcomes the current opportunity to comment on the draft guideline on pharmaceutical development of medicines for paediatric use. Astellas supports the development of a guidance document providing development principles for the pharmaceutical aspects of paediatric products. However we would like to draw your attention to some major concerns: The focus of the guideline on the pharmaceutical development seems to be to request justification of choices made throughout the development, whereas a guideline on pharmaceutical development is expected to give directions on development, set a framework and give factual guidance to all involved parties. The drug development process in general is already highly regulated. It is therefore	Partially accepted: It has been clarified in the guideline that any aspects of the pharmaceutical development of a paediatric medicine which apply equally to medicines for adult use are not discussed. The text of the Guideline has been further revised to remove unnecessary discussions. It has been further clarified that the Guideline should be read in conjunction with all other relevant EU legislative and guiding documents. The guideline has been revised to emphasise paediatric specific aspects which need to be taken into consideration

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	proposed to remove all information which is applicable to general pharmaceutical development and replace this with more factual guidance on paediatric pharmaceutical development. In case deviation from this guidance is required, this would then be subject to justification requirements. More factual guidance, especially on age appropriateness of dosage forms with regards to size, volume and amounts, dissolution testing pH conditions is welcomed. Throughout the guideline anecdotal evidence, words between brackets and assumptions not based upon factual evidence are postulated. It is proposed not to use this kind of wording in a guideline. The paragraph on “re-evaluation of all products on the market” (line 127 – 129) is strongly questioned. It is proposed to remove this paragraph in its entirety. The approval of new medicinal products is based on the assessment of quality, efficacy and safety. In contrast throughout this guideline the focus is on care-giver and patient acceptability and attributes like palatability. The selection of a dosage form and route of administration should be made based on pharmaceutical properties, pharmacokinetic and pharmacodynamic considerations in the first place. Consider change in priority setting to efficacy and safety (first priority) and in later stage to child friendliness and user acceptance. It is proposed to add a more extensive glossary to prevent differences in interpretation between parties. Throughout the guideline nomenclature is not used consistently. Especially descriptions of dosage types are open for several interpretations.	during development. A reference to ICH Q8 with relevant comments was included in to further clarify the approach for defining the framework for pharmaceutical design of the pediatric medicines. Retrospective applicability of the Guideline has been clarified and a reference to the 5 years transitional period has been deleted and the paragraph is revised Acceptability, including palatability, is an important factor in development of medicines for children. These aspects can not be disregarded and cannot be separated from discussion about age-appropriateness of pediatric dosage forms. Section 10 of the guideline has been revised to provide more detailed discussion on these aspects. Section 6 of the guideline was revised to provide more detailed information on dosage forms and their acceptability. With regards to the request to provide more factual guidance on development of pediatric medicines, it has to be acknowledged that publicly available data on paediatric formulations is still fragmented and that further development in this field is needed. The work on the guideline has been initiated in view of the public demand to have such document. The current status of the knowledge has been emphasised in the “Executive summary” section of the Guideline. The following statement is included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date*

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		of coming into operation.
6	In general the German BAH-Initiative to foster better Medicines for Children welcomes a proposal for a European Guideline on the pharmaceutical development of medicines for paediatric use as a compilation of actual facts to be considered when developing new medicinal products for the intended use in the paediatric population according to the mandatory procedures introduced by the Paediatric Regulation 1901/2006/EC. The BAH-Initiatives also welcomes the possibility to comment on this draft Guideline. Unfortunately the draft EU-Guideline seems not be harmonised with the content of an already existing WHO Points to Consider paper on the Pharmaceutical Development of Paediatric Medicines (QAS/08.257; latest Rev by Oct 2010). The BAH-Initiative suggest to revise the content of this Guideline accordingly. In addition to the following comments, the BAH-Initiative would like to draw the attention to the comments provided by the European Association AESGP and also to those made by Prof. Dr. Jörg Breitkeutz, member of the EMA PAEDCO and expert for paediatric pharmaceutical development and formulation.	Accepted: The WHO Guideline was considered and consulted in the preparation of this guideline however it is not referenced.
7	The Committee on Research, Development and Innovation of the German Pharmaceutical Industry Association (BPI) is grateful for the possibility to submit comments in regard to the public consultation on this guideline. The industry strongly supports the request, that paediatric medicines should be appropriately designed for the target age group(s).	Comment noted. Publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects. Often, the applicants may need to justify their choices and the development program. Numerous factors such as indications, age, dosing regimen and frequency will influence development of paediatric

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	The guideline requests justifications at many points. We strongly recommend focusing this request to points where a justification is really necessary. Otherwise, “justification of nearly every single decision” will lead to unnecessary bureaucratic burden.	medicines. Furthermore, in accordance with ICH Q8, the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications.
8	No general comments were raised	Not applicable.
9	The Commission considers that the draft guideline fails to meet its objective in that it does not provide specific and unambiguous regulatory guidance on the best practice for the development of medicines suitable for use in children. Clear, consolidated, evidence-based guidance should be provided which reflects the scope of the guideline in order to support the development of age-appropriate formulations for use in paediatric populations. There is particular concern regarding the retrospective nature of some aspects of the guideline (Lines 127-129) which go beyond the scope of the original reflection (Reflection paper on formulations of choice for the paediatric patient’ (EMEA/CHMP/PEG/194810/2005), paper and should be removed from the guideline. The Commission notes the guideline section on excipients and consider that well known issues of particular concern, such as the wide use of ethanol and propylene glycol in oral liquid paediatric medicines, should be raised. An opportunity exists to make strong, clear recommendations on the requirements to demonstrate the age-appropriateness of preparations. It would be therefore be helpful to provide guidance on the studies that should accompany applications to demonstrate the age-appropriateness of formulations, specifically focusing on what pharmaceutical studies should be included to demonstrate	Comment noted. Publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects. Furthermore, in accordance with ICH Q8, the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications. Retrospective applicability of the Guideline has been clarified and a reference to the 5 years transitional period has been deleted and the paragraph is revised. With reference to the excipients and in particular to ethanol and propylene glycol, it should be clarified that it was not within the remits of this guideline to provide detailed information on acceptability of ethanol and propylene glycol. Aspects relating to the use of these excipients and their acceptable limits will be included in the ongoing review of the Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use. This Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. It also explains in which situations additional studies or reformulation may be needed.

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	palatability, patient acceptability, mixing with food and accuracy of dosing. Clear guidance in these areas has not been provided. Guidance on studies to demonstrate age-appropriateness of formulations should be read in conjunction with existing clinical development guidelines such as CPMP/ICH/2711/99.	The importance of age-appropriateness of paediatric medicines is an important factor than needs to be considered during development. Section 10 of the Guideline has been revised accordingly to provide more details on the aspects that need to be considered. Within section 10 clear subsections have been included, one dedicated to palatability and one on mixing with food. Discussion on the need for accuracy of dosing is also included in section 11 of the Guideline.
10	Specific **areas of major concern**: 1. The draft guidance states that “Pharmaceutical companies should have a re-evaluation of all their products on the market.” It is not clear what are the criteria that a company should use to conduct such a re-evaluation (after all the products are approved) nor is it clear what is the legal basis for this recommendation in the draft guidance. Efpia proposes to remove wording that implies retrospective application of this draft guidance. 2. Add a short introductory statement or chapter emphasizing the fact, that the principle of **rational formulation development** includes justification (conscious decision making based on risk assessment, risk/benefit evaluation of formulation options, choice of routes of administration, excipient selection) and applies to the development of **all** pharmaceutical products in general and to paediatric products in particular, as paediatric populations have special needs with respect to the route and ease of administration and as they might react more sensitive to excipients.	Comments noted and partially accepted: 1. The reference to 5 years transitional period has been deleted and the paragraph is revised. 2. Where possible the unnecessary text of the guideline has been revised to improve the readability and clarity. 3. A reference to ICH Q8 with relevant comments was included in to further clarify the approach for defining the pharmaceutical design of the pediatric medicines. 4. Clear information on how to address the need for possible manipulations of the product has been added to the guideline. It is not intention of the guideline to ask for detailed discussion on possible off-label use for all paediatric medicines. 5. The need for a balanced approach in development is supported in the guideline. It is not the intention of the guideline to request too many age-appropriate dosage forms.

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	This would limit the need to indicate “justification” or “to be justified” more than **50** times in the text of this draft guideline. The highly repetitive use of these terms and some other occurrence of imprecise wording or speculative statements (for example unclear statements on excipient safety such as “avoidance of questionable excipients”) in the draft guideline leave significant room for interpretation and reflect a sometimes overcautious approach (e.g. safety and efficacy considerations after incorrect use of dosage forms). 3. The guideline should reflect more explicitly that the development of drug product manufacturing processes according to industry best practice follows sound scientific principles (see ICH Q8-11). 4. It should be a guiding principle of the document, that the developed formulation (drug product) has to be used as described and specified in the SmPC and as foreseen in Pharmacopoeias. Once the rationale for a dosage form has been accepted, this should be the dosage form to be adhered to by the patient. It cannot be expected from developers / manufacturers to cover the risks of all possible ways of unintended use, manipulation, or incorrect administration of dosage forms, and be responsible for the resulting consequences. 5. The guideline should highlight the need for a balanced approach to avoid too many age appropriate dosage forms. 6. There is insufficient hard data to support the age designations in relation to tablet-size provided in the draft guidance. Similarly, the lack of acceptability of formulations that are constituted in	The Guideline has been revised to emphasise paediatric specific aspects that need to be taken into consideration during development with a clear reference to ICH Q8 development concept. In addition, section 10 of the guideline dedicated to acceptability was further revised to provide guidance on how to approach this aspect. 6. In view of the limited data available on sizes of tablets and capsules the reference to the tablet (capsule) size has been removed from the Guideline in order not to stop development in this field. 7. It has been clarified in section 3 that the guideline should be read in conjunction with all other relevant directives and regulations, and relevant Commission, ICH and CHMP guidelines, Q&A documents and other documents as linked to or published on the EMA website (www.ema.europa.eu); this includes the reflection paper. 8. General discussion on formulations of choice is included in the Reflection Paper. Inclusion of the table could impede the development of medicines for particular age group(s). It is more appropriate to refer to the ICH Q8 approach. 9. Section 10 of the Guideline was retained in the initial location. 10. Section 6 of the Guideline has been substantially revised to address detailed comments received during consultation phase.

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	liquid to a given concentration and then dosed at an appropriate volume is too conservative as the concern for errors can be addressed by streamlining the procedure and showing ability to prepare reproducibly. **General suggestions** for improvement: 7. It should be clarified how the guideline for pharmaceutical development relates to the REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION, EMEA/CHMP/PEG/194810/2005 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf 8. A table summarizing which formulations are feasible by which age group (based on the guidance document) including major requirements/limitations to be considered for each formulation would be helpful. 9. Move Section 10 “Patient Acceptability” to the beginning of the document as it defines terms that are used throughout the guidance. 10. The level of detail varies greatly between sections; for example detailed guidance is provided in section 6.2.1, but very little in sections 6.24-6.5 (see detailed comments for more information). 11. Improve terminology: use ICH terms for age classification only (not newborn, young infant, etc.) 12. Use appropriate ICH terminology, e.g. *critical quality attribute*, and not: *critical to quality aspect*.	11. The ICH terms for age classification of paediatric patients have been used throughout the guideline. 12. A clear reference to ICH Q8, with its terminology, was introduced 13. The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur. and Standard Terms. 14. References have been removed from the guideline 15. No specific size limitations are applied to orodispersible and chewable tablets.

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	13. Use Ph. Eur. terminology for dosage forms; provide definition when not defined by Ph. Eur. (e.g. dispersible tablet, orodispersible tablet, effervescent tablets, hard capsule). 14. References included in the guideline are considered not specific enough. They should direct the reader to specific information e.g. on excipient safety, dissolution, excipient safety. Alternatively, the appropriate level of detail could be incorporated directly into this guideline. 15. No specific size limitations should apply for orodispersible tablets and chewable tablets. To clarify benefit/risk approaches it may be useful to refer to the forthcoming EuPFi publication in Int. J. Pharmaceutics highlighting work from the Efpia ad hoc formulations working group.	
11	The anticipated draft guideline is a welcomed contribution towards helping the industry developing better formulations and dosage forms for children. This current draft remains an advanced version of the Reflection Paper of Formulation of Choice for Children (2005). It could be further supported by other relevant documents such as the WHO points to consider document which should be referred to [DEVELOPMENT OF PAEDIATRIC MEDICINES: POINTS TO CONSIDER IN PHARMACEUTICAL DEVELOPMENT Working document QAS/08.257/Rev.3 (August 2011)]. The major comments from EuPFI are: • It oscillates between general pieces of advice and guidance with heterogeneous levels of details throughout. Where prescriptive, it is based on very little clinical/practical evidence especially	Comments noted and partially accepted: The WHO Guideline was considered and consulted in the preparation of this guideline however it is not referenced. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. In view of the limited data available on sizes of tablets and capsules the reference to the tablet (capsule) size has been removed from the Guideline in order not stop development in this field.

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	when it comes to *Acceptability of tablet/capsules size or oral volumes in relation to age (dispersible tablets, liquids, drops).* It should be less prescriptive until further data are available. *<u>List of references</u>* *Thomson et al. 2009 PEDIATRICS. 123(2): e235-e23* *Van de Vijver et al J Pediatr Gastroenterol Nutr. 2011 53(1):61-64.* *Polaha et al. 2008 Southern Medical Journal. 101(11): 1106-1112* *DeRoche et al. 2003 Pill Swallowing in America: A National Survey of Adults. Harris Interactive Survey. For Schwartz pharma* *Meltzer et al, 2006 Clin Pediatrics. 45(8): 725-733* • We agree that if a tablet is scored it is expected that it should comply with all relevant Pharmacopoeial tests. • General considerations on safety of excipients and how to approach the necessary risk assessment are informative. The prospect of an amendable annex is of interest but requires further discussion when the nature of the annex is further developed. • The re-evaluation of paediatric products on the market within 5 years is to be clarified as it concerns the pre PIP products already commercialised. (*Legal basis? Capacity of industry and regulators to manage this issue? Potential negative impact of availability of medicines for children?)* • The document should place more emphasis on the place of preliminary/enabling (clinical phase appropriate) formulation in clinical trials. • The pragmatic approach recognising, for example, that mixing	Aspects relating to the use of these excipients and their acceptable limits will be included in the ongoing review of the Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. It also explains in which situations additional studies or reformulation may be needed. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The reference to 5 years transitional period has been deleted and the paragraph is revised. Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the Guideline. It has been acknowledged in the scope that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated. A switch from a preliminary formulation to a commercial formulation should often be supported by relevant bridging studies between different formulations used throughout the development*. The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur and Standard Terms. Change in the salt form of an active moiety may change its

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	with food or using medicines differently than originally described will occur, is to be complimented. However more guidance on how industry should validate such practice with a defined range of foods or beverages should be provided. This is a current interest for EuPFI and we would be interested in further discussion. • The patient acceptability considerations are adequate as it is not the aim of this guideline to give methodological advice but to give a rational as of when and why palatability/acceptability assessment is required. • Generally the terminology should be aligned with the Ph. Eur. or standard terms according to EDQM and ICH. If no existing terms are available, they should be defined in the glossary. • Section 5 should be deleted as the change of the salt form would create a new entity. This is not specific to paediatrics and is covered elsewhere. Please note that many EuPFI members would have also contributed to other consolidated comments through other affiliations (EFPIA, MHRA, GRIP, UK MCRN, VfA, BAH, individual Pharma companies) to EMA. Specific comments were not repeated in the section below.	physico-chemical properties, i.e. solubility which may significantly facilitate the development of an age appropriate dosage form. It can not be accepted that change in the salt form would always create a new entity. Usually such change does not lead to significant differences in the (non)clinical properties of the substance. Such concept is commonly used in generic applications. The statement on the use of different salts has been modified, to make it optional, as one of the possibilities which could be explored.
12	The document provides very useful advisory guidance for companies developing paediatric formulations and also hopefully such companies will be encouraged and advised by this particular document. The document has been considered by Group of Experts No. 12 (Pharmaceutical Dose Forms) of the European Pharmacopoeia and a few useful and generally supportive comments were made. One point that was made was that perhaps to avoid such a guideline	Comment noted and partially accepted: It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	being seen as too restrictive or counter productive with its constant references to “justification” that the document might be presented as a “points to consider” document rather than a guidance note. Nevertheless, the specific comments provided hereunder are intended to be helpful. Line 122: Comment: Proposed change (if any): it is suggested to add “and the requirements of the European Pharmacopoeia” at the end of the sentence Line 134 Comment: Proposed change (if any): the reference to the Directive should say “relating to” rather than “relation”	The specific comments have also been considered.
13	There seems to be a difference in the terminology used to describe dosage form types in this document compared to the Reflection Paper EMA/CHMP/PEG/194810/2005. The Reflection paper gives a good description of all dosage forms and uses terms like multi-particulates with examples being beads, granules and mini-tablets. This paper only uses the term multi-particulates once in isolation and elsewhere refers to powders, granules and pellets. For clarity I think it would be advisable to have consistency in the terminology used in both papers, either within the document itself or in an attached glossary.	Accepted: The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur and Standard Terms.
14	This draft guideline is fine, no comments from IFAPP.	Response to comment not applicable.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
15	Overall, the Faculty of Pharmaceutical Medicine believes that this consultation document provides a very useful summary of all the aspects that need to be considered in developing paediatric formulations. We have a couple of specific comments to make below.	Response to comment not applicable. Responses to the specific comments are included in the latter parts of the document.
16	The development of a guideline on the pharmaceutical development of medicines for the paediatric population is highly welcomed and supported by the MEB. The guideline is expected to add to the global objective of “better medicines for children” and considered a logic and necessary follow-up measure to the EMA reflection paper on formulations of choice for the paediatric population. It should be acknowledged that scientific evidence on the relationship between pharmaceutical technology aspects of medicines for children and paediatric patient outcomes is scarce, but rapidly evolving. Such new evidence may result in different approaches than currently stated. Publication of the final guideline should not be upheld by discussion on such new evidence as this will be an ongoing process, but it should be made very clear to industry and assessors that any other approaches as stated in this guideline will be considered acceptable, if adequately justified. The MEB is particularly pleased that both the QWP and PDCO have contributed to this important work. Though, it remains a challenge to keep up with the scientific, clinical and regulatory developments in this field and to find the right balance between critical main issues and details. We anticipate that for these reasons the need for a constant monitoring, and if needed adjustment, of the up-to-dateness of this guideline in the coming years.	Comments noted. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. Often, the applicants may need to justify their choices and the development program. The current status in the knowledge has been reflected in the Executive summary. The following statement has been included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.* In view of the limited data available on sizes of tablets and capsules the reference to the tablet (capsule) size has been removed from the Guideline in order not stop development in this field. Tablets are discussed in the revised sections 6 of the Guideline. In addition section 10 provides further details on the acceptability testing. Aspects relating to the use of these excipients and their acceptable limits will be included in the ongoing review of the Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use. The Guideline explains

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The CHMP is asking specific attention to three points where further input is awaited. The MEB would like to respond as follows to item 1: Acceptability of tablet size and young children. Guidance on tablet sizes below 3 mm is currently missing and should be added to the guideline. The acceptability of such tablets should be identical as stated for powders, granules and pellets i.e. small tablets below 3 mm are normally acceptable from the moment the infant is able to accept solid food In the Netherlands, there is a long history of fluoride supplementation by 4 mm, round, uncoated tablets to children from very young ages i.e. often from the moment the child was having its first tooth. The tablets were the only dosage form that were (commonly?) available at that time. The Preventive Health Care clinics instructed parents to give the tablets as such or to crush the tablets between two spoons should the child not be willing to swallow the whole tablet. In the Netherlands, parents are currently recommended by preventive health care clinics to provide vitamin D supplementation to children from 0-4 years unless they are taking artificial baby milk which is already supplemented with this vitamin. The most commonly applied trade marks including vitamin D involve drops (no lower age limit), 4 mm round uncoated tablets (no lower age limit), bear shaped chewing tablets (from 1 year), sun shaped chewing tablets (from 1 year). Pending research of Utrecht University that was sponsored by the RIVM and MEB has shown that 4 mm round uncoated placebo tablets were well accepted by children from 12 months age.	a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. It also explains in which situations additional studies or reformulation may be needed. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	In conclusion, tablets from 3-5 mm are normally considered acceptable in children from the age of 1 year. It should be made more clear in the guideline that the acceptability of tablets that are to be taken whole and where accidental chewing will involve a potential risk to the child's health (either because of lack of adequate dosing or because of side effects) does not only relate to the size of the tablet but also to the ability of the child to follow precise instructions. The latter may justify a higher age limit than otherwise recommended in the guideline. *The CHMP is asking for specific attention to three points where further input is awaited. The MEB would like to respond as follows to item 2: Use of score lines to administer lower doses.* Both for adults and children, the application of a dose by a single tablet rather than a subdivided tablet is highly preferred in view of e.g. handling issues and dosing accuracy. Nevertheless, the application of subdivided tablets is generally accepted for adults and there is no reason to have a different approach for children other than palatability. On the contrary, subdivision of the lowest licensed strength of a tablet may be of particular interest to children as an "easy" manner to provide lower doses than currently authorised or to provide for an alternative dosage form in the lower dose. The guidance on palatability should also apply to subdivided tablets. Adequate subdivision i.e. dosing accuracy of a tablet should be proven by compliance to the Ph. Eur. test on subdivision of tablets, preferably irrespective as to whether or not the application of the subdivided dose has been approved by the authorities and preferably irrespective of the fact as to whether or not the line on the tablet was also intended by industry as a score line. Warnings in the SPC or PIL	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	that the line on the tablet is not suitable for breaking a tablet into equal parts are to be discouraged. The Ph. Eur. test on subdivision of tablets is based on a test for the uniformity of mass of the tablet parts and not on a test for uniformity of content. This approach seems to be questioned by some stakeholders. The MEB considers that age in itself is no reason to have a different approach to the test method for children as for adults as the impact of relative over- and under- dosing of medicines does not significantly differ between children and adults in general. Of course, compliance of the whole paediatric tablet to the Ph. Eur. test on content uniformity should be assured where relevant. The CHMP is asking for specific attention to three points where further input is awaited. The MEB would like to respond as follows to item 3: Safety of excipients. The safety of excipients is a critical issue for medicines for children. The guidance on the acceptability of commonly known excipients in children is highly welcomed. It is to be made fully clear to industry that the omission of such data would normally result in an objection.	
17	NPPG agrees with the overall aims of the document which is timely and sensible. There is a need for medicines which are better tailored for use in children. We note that the recommendations in the document are intended to be applied to the development of new medicinal products for use in children. However it is important that these recommendations are not applied inappropriately to the medicines which are already in use in this population, where necessary manipulation of the currently available products is undertaken in order to facilitate their	Partially accepted: The guideline should be applicable not only to the “new” medicinal products for children but to all products with paediatric indications. The companies are encouraged to consider this guideline during the life-cycle of a product, also post-authorisation. Where necessary appropriate improvements should be implemented, in accordance with the legal obligations imposed on MAHs by the legislation. It is acknowledged that for some medicinal products a

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	administration to children. We do welcome the intention to have the pharmaceutical industry re-evaluate existing products on the market to ensure that they are "state of the art" but this may lead to increased cost of some medicines which could cause affordability issues in some member states.	manipulation from an adult dosage form may be the only way of preparing products for children, e.g. due to the rarity of a disease, or properties of the active substance. However handling of dosage forms should be performed in a "controlled" environment and the proposed handling methods (approaches) should be validated. The revised guideline provides details on different types of handing of dosage forms. In addition, in section 10, discussion on aspects relating to mixing with food and beverages has been included.
18	The P&P CSG welcomes a guideline on pharmaceutical development of medicines for children. The group believes that the process of PIP application and speedy development for the benefit of children will be better achieved if the pharmaceutical industry understands the clear, regulatory guidance from EMA. However, the group is concerned that the draft guideline is written in the form of a review, rather than giving clear, distinctive guidance. However, unlike a scientific review, the evidence base is not always present to support the recommendations. The industry is frequently required to 'justify' aspects of pharmaceutical development which we take to mean that there is insufficient evidence or experience to make a more specific requirement. When this is the case the guideline should be transparent and recognise 'points to consider' and can become more prescriptive if necessary as evidence becomes available. The PIP and MA processes should be used to gather such evidence from those having to 'justify' their approach. Whilst the draft guideline is reasonably comprehensive of issues it is not sufficiently informative of methodologies to be used during pharmaceutical development. As currently written it does not meet	Comment noted. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. Often, the applicants may need to justify their choices and the development program. Furthermore, in accordance with ICH Q8 the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications. The reference to 5 years transitional period has been deleted and the paragraph is revised. The revised guideline provides details on different types of handing of dosage forms. In addition, in section 10, discussion on aspects relating to mixing with food and drinks has been included.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	expectations of a guideline. The group is concerned about statements requiring revisiting of existing medicines with a view to achieving 'state of the art' status for them all. Whilst this may be a laudable objective the P&P CSG questions whether either industry or regulator has sufficient resources to achieve this, that it may detract from research on new medicines and that older medicines may be withdrawn rather than update them. This would not be in the best interests of children unless specific quality, safety or efficacy concerns had been identified. The group welcomes recognition of the practical difficulties of administering any dosage form to some children and the lengths that carers may go to disguise administration of the medicine. Equally it recognises that it would not be feasible to test all medicines with all foods and beverages. There should be further discussion of the steps that industry should take to verify manipulation of medicines and their addition to food, beverages and confectionery. P&P CSG would like to see greater emphasis on the use of 'enabling' formulations (or clinical phase-specific formulations, definitions required) during clinical studies and methods of bridging to the final commercial formulation. The group also recognises that intermediate formulations (powders for reconstitution, granules or multi-particulates and other 'simple' formulations) may sometimes be appropriate as commercial formulations but also believes that the first intent of the industry should be to provide an age-appropriate, ready to administer preparation. In circumstances in which the commercial formulation is not appropriate for all children within an age group, the industry should be asked to have a strategy for	Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the Guideline. It has been acknowledged that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated. A switch from a preliminary formulation to a commercial formulation should often be supported by relevant bridging studies between different formulations used throughout the development*. The WHO Guideline was considered and consulted in the preparation of this guideline however it is not referenced. The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur and Standard Terms. It has been clarified in the revised Guideline that "minitablets" are classified as tablets and consequently relevant requirements for this dosage form should apply. Orodispersible film technology has not been specifically mentioned in the guideline as this technology is not frequently applied in medicines for children. Such technology would normally be accepted for paediatric patients but there are various aspects which need to be considered during development. It is not possible to discuss in the guideline all possible approaches for development of paediatric medicines therefore a general reference to ICH Q8 has been included

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	achieving administration in these children. There are some discrepancies in means of terminology between EMA Guideline Draft (May 2011) and WHO Development of Paediatric Medicines: Points to Consider in Pharmaceutical Development Working document QAS/08.257/Rev.3 (August 2011). It will be a good step forward to bring standardization. Dispersible tablets and orodispersible tablets can be given under the subsection of flexible solid oral dosage forms (line 281) by providing a definition. Another example for compliance between documents, cutaneous administration should be re-worded to dermal and transdermal administration. There is no information on mini-tablets under the section of `powder, granules, pellets and tablets`. It will be useful to have a short part on mini-tablets considering their potential in terms of ease of manufacture (compared to novel formulations), dose accuracy, acceptability. In this way, it will be possible to be informed on how the mini-tablets are classified by regulators (under multi-particulates or tablets) and accordingly, to clarify the requirements to fulfil for this dosage form (e.g. if considered under multi-particulates, requirement for particle size distribution or if considered under tablets requirement for uniformity of mass). The group welcomes that the guideline refers to new formulation development approaches such as oro-dispersibles but should also consider the application of oro-dispersible film technology. P&P CSG recognises that many of its members will have contributed to other sets of comments and has confined itself to general comments and specific comments that may not have been raised by other specialists.	in the guideline.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
19	We welcome the guidance document, which draws attention to the paediatric patients' needs and the challenges associated with the administration of medicines in this group of patients. Although the draft guideline presents a thorough exposition of the issues involved in paediatric formulation, and thus maybe useful for increasing awareness of these aspects for clinical audiences, it does not meet its objectives and takes us little further than the Reflection Paper on 'Formulations of choice for the paediatric population' in terms of 'specific regulatory guidance'. In places the document reads like a textbook on paediatric pharmaceutical development whilst in others the guidance is scanty, debateable and unreferenced. It does not seem to have taken into account much of the experience obtained from the PIP review process which has been underway now for nearly 5 years. Furthermore, terminology should be reviewed and agreed with stakeholders; WHO is working on a "Points to consider" guidance on pharmaceutical development of paediatric medicines and EuPFI has a paper in preparation exploring such terminology and provides suggestions for standardisation.	Comments noted. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. Often, the applicants may need to justify their choices and the development program. Furthermore, in accordance with ICH Q8 the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications. The work on the guideline has been initiated in view of the public demand to have such document. The current status of the knowledge has been emphasised in the "Executive summary" section of the Guideline. The following statement is included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.* The WHO Guideline was considered and consulted in the preparation of this guideline however it is not referenced.
20	No general comments were raised	Response to comment not applicable.
21	A table summarizing which formulations are feasible by which age group (based on the guidance document) including major requirements/limitations to be considered for each formulation would be helpful.	Not accepted: General discussion on formulations of choice is included in the Reflection Paper. Inclusion of the table in the Guideline was not considered appropriate as it could impede the development of medicines for particular age group(s). It is

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		more appropriate to refer to the ICH Q8 approach.
22	In general, this EMA guideline does not meet its objectives and takes us little further than the Reflection Paper on 'Formulations of choice for the paediatric population' in terms of 'specific regulatory guidance'. In places the document reads like a textbook on paediatric pharmaceutical development whilst in others the guidance is scanty, debateable and unreferenced. It does not seem to have taken into account much of the experience obtained from the PIP review process which has been underway now for nearly 5 years. Terminology should be reviewed and agreed with stakeholders – *preliminary* formulation; *manipulation* of an authorised medicine, for example, may be understood. EuPFI has a paper in preparation exploring such terminology and provides suggestions for standardisation.	Comments noted. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. Often, the applicants may need to justify their choices and the development program. Furthermore, in accordance with ICH Q8 the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications. The work on the guideline has been initiated in view of the public demand to have such document. The current status of the knowledge has been emphasised in the "Executive summary" section of the Guideline. The following statement is included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.* The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur and Standard Terms.
23	No general comments were raised	Response to comment not applicable.
24	See document submitted by Prescrire, with lots of general comments and examples on risk of medication errors associated with inappropriate packaging, inappropriate dosing devices and choice of	Comments noted. Responses to specific comments are included in the latter part of the document.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	excipients. Encourage pharmaceutical companies to submit their paediatric investigation plans (PIPs) as early as phase II of drug development, rather than just before applying for marketing authorisation. PIP submission in phase II increases the chances that paediatric medicines will become available whose pharmaceutical forms (including excipients) and packaging have been properly evaluated. For medicines that are candidates for a 6-month extension of their supplementary protection certificate (SPC) under the European Paediatric Regulation, impose stricter obligations and closer supervision by European medicines agencies with respect to the safety, convenience and availability of paediatric medicines, and provide for financial penalties that shall apply when these obligations are not met. For medicines that are no longer protected by a patent or SPC, encourage national medicines agencies to be much more vigilant and to set stricter requirements for the pharmaceutical aspects of medicines (dosage form, dose strength, package leaflet, excipients) in European worksharing procedures to re-assess medicines in children (Article 45 of the Paediatric Regulation) and in European referral procedures, particularly for the harmonisation of marketing authorisations (Article 30 of Directive 2001/83/EC). Publish detailed data on overdoses and accidental poisoning with drugs or excipients in SmPCs and public assessment reports; make them publicly accessible on the websites of European Union medicines agencies.	Potential for medication errors and need for an appropriate administration and dosing were further considered in the revised version of the Guideline. Various sections of the Guideline have been updated with requirements to include clear instructions in the SmPC and PIL about appropriate handling, dosing and administration of a product. Critical aspects of various dosage forms that should be considered during development as well as patient's characteristics are discussed in the Guideline. Other general aspects listed in the letter, such as submission of PIP applications and supplementary protection certificates, do not fall within the scope of the Guideline and therefore were not reflected in the revised text.
25	We agree with the overall aim of the document which is timely and	Partially accepted:

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	sensible. There is a great need for medicines better tailored for use in children. This document is intended to be applied to the development of new medicines for children but it is important that it is not applied inappropriately to prevent necessary manipulation of current products to facilitate administration to children. We welcome the intention to have industry re-evaluate existing products on the market to ensure that they are “state of the art” but this may lead to an increase in the cost of paediatric medicines which may cause some affordability issues in some member states.	It is acknowledged that for some medicinal products a manipulation from an adult dosage form may be the only way of preparing products for children, e.g. due to the rarity of a disease, or properties of the active substance. However handling of dosage forms should be performed in a “controlled” environment and the proposed handling methods (approaches) should be validated. The revised guideline provides details on different types of handing of dosage forms. In addition, in section 10, discussion on aspects relating to mixing with food and beverages has been included. Retrospective applicability of the Guideline has been clarified and a reference to the 5 years transitional period has been deleted and the paragraph is revised.
26	This guideline will be very useful to support the pharmaceutical development of medicines for use in children. We agree with the overall approach, but have a few specific comments.	Response to comment not applicable. Responses to the specific comments are included in the latter parts of the document.
27	This guideline should mention the case where a product has to be reconstituted before oral administration. And more specifically the quality of the marking that indicate the volume of reconstitution or the need for a measuring cup. Cases have been seen where the marking was not adequate to ensure an accurate reconstitution of the product. The paragraph dedicated to excipients should include ‘processing aids’ which are removed during the manufacturing process but remain in the finished product as traces. We had to assess a dossier recently for the paediatric population in	Partially accepted: Section 11 of the guideline which is dedicated to administration devices has been revised and updated to flag critical aspects that need to be considered during development of medicines for children. Processing aids were not included in the section on excipients as these are not considered excipients in the finished dosage form. If processing aids can not removed from the product they should be regarded as impurities and their limits should be controlled in accordance with relevant

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	which the drug product is manufactured with processing aids that have never been used as excipients in any of the drug products available on the French market.	guidelines.
28	No general comments were raised	Response to comment not applicable.
29	No general comments were raised	Response to comment not applicable.
30	The document is highly appreciated by its broad scope, describing development of an age appropriate dosage form. We see a potential for misunderstanding between a product passing a profound quality evaluation and the clinically justified wish of a recommendation for an extemporaneous preparation. As an example, it is imperative that a capsule could not be opened. Either the information should be clearly separated or in case of a conflicting statement the recommendation should be put in the right perspective. Moreover, by the highly supported intent to make child size medicines available also for older products, industry's interest in developing age appropriate dosage forms (PUMA) would be weakened. Since no agency can enforce industry making recommendations for such use and to do the appropriate testing (such as stability and accuracy) the guidance document may, if not carefully worded, deterioriate quality standards.	Comments noted. Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the Guideline. It has been acknowledged that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated. A switch from a preliminary formulation to a commercial formulation should often be supported by relevant bridging studies between different formulations used throughout the development*. A more detailed section on handling of dosage forms has also been introduced. It has been acknowledged that for some medicinal products manipulation from an adult dosage form may be the only way of preparing products for children, e.g. due to the rarity of a disease, or properties of the active substance. However handling of dosage forms should be performed in a "controlled" environment and the proposed handling methods (approaches) should be validated. The revised guideline provides details on different types of handing of dosage forms. In addition, in section 10,

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		discussion on aspects relating to mixing with food and beverages has been included.
31	No general comments were raised	Response to comment not applicable.
32	vfa acknowledges the necessity to update the REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION and welcomes the initiative of the Quality Working Party. The publicly available scientific data on paediatric formulations are still scarce. Guidelines should be based on sound knowledge. vfa believes after consultation of various stakeholders (including scientific bodies) that the scientific basis is not yet sound enough to justify the drafting of a guideline at this point of time. Further investigations are required to build a robust scientific basis for this guideline. The document offers some guidance for the development of paediatric formulations but primarily provides lists that give the impression of conclusiveness. This might potentially narrow the room for future developments. The draft should better reflect the current scientific knowledge of the European Pharmacopoeia (Ph. Eur.) and available EMA documents. All pharmaceutical formulations listed in the Ph. Eur. should be included (or at least referred to) in this document. The described aspects leave the impression that the development of pharmaceutical formulations for children might be handled too restrictive if this document were to be applied in the current form and structure. **vfa highly recommends to revise it and to use the contents for an update of the existing reflection paper.** Companies should also be advised to seek scientific advice or to	Comments noted. It has been acknowledged in the guideline that publicly available data on paediatric formulations is still fragmented and it is not always possible to provide a precise guidance on all aspects relating to the development of medicines for children. Often, the applicants may need to justify their choices and the development program. Furthermore, in accordance with ICH Q8 the approach for defining the pharmaceutical design requires thorough analysis and justification and often it will not be possible to avoid justifications. The work on the guideline has been initiated in view of the public demand to have such document. The current status of the knowledge has been emphasised in the “Executive summary” section of the Guideline. The following statement is included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.* The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur. and Standard Terms.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	discuss individual applications with the experts of the PDCO to ensure that new scientific knowledge is being applied.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
55-63	10	This is not an Executive Summary of the guideline, just a very short introduction why the guideline is needed	Comment noted. Executive summary section has been revised.
55-63	10	Children cannot be considered scaled-down adults, since they go through complex non-linear transformations before becoming an adult. The group of children is even more heterogeneous than that of adults.	Comment noted. It is acknowledged in the guideline that children are not scaled-down adults and that this is a heterogeneous group; Section 1 of the Guideline has been revised accordingly.
55-63	10	It is not the need to develop child appropriate clinical dosage forms that drives the change, it is the need to have appropriate products on the market. This requires adequate investigation planning of paediatric clinical studies.	Accepted: It has been clarified in Executive Summary that the critical objectives for the development of age-appropriate paediatric medicines is to ensure that children in the target age groups have access to medicinal products with a positive benefit - risk balance, of a consistent quality, assuring adequate patient's adherence and which do not put an unnecessary burden on the patient and/or its caregivers.
58-60	5	"As a result of this Regulation, the number of paediatric formulations that the pharmaceutical industry will have to develop to support their clinical trials will increase. It is expected that the number of medicines applying for a marketing authorisation for paediatric use will increase as a result." The statement about the number of formulations that industry	Accepted: The statement has been moved form Executive Summary to Section 1: "[…] *it is expected that the number of authorised paediatric medicinal products and the knowledge on the quality aspects critical to*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		will have to develop seems to contain assumptions and conclusions and is therefore open for multiple interpretations. Support of clinical trials is not what the Regulations aims to achieve - the aim of the Regulation is to facilitate access to better medicines for children. Proposed change (if any): Proposal to remove: As a result of this Regulation, the number of paediatric formulations that the pharmaceutical industry will have to develop to support their clinical trials will increase. It is expected that the number of medicines applying for a marketing authorisation for paediatric use will increase as a result. Proposed text: "It is expected that as a result of this Regulation, the number of available paediatric formulations will increase and access to better medicines for children is facilitated."	*these products will rapidly increase*."
63 and 174-175	1	The ICH classification of age groups related to paediatric patients goes up to 17. (Neonates: 0-27 days, Infants and toddlers: 28 days-23 months, Children: 2-11 years, Adolescents: 12-17 years). If this ICH classification is referenced, line 63 should be updated to refer to medicines for use in children between birth and 17 years of age (or <18 years of age). (The current wording in line 63 refers to children between birth and 18 years of age.) Proposed change (if any):	Comment noted. The age bands have been aligned with the ICH terminology, the term "*from birth to less than 18 years of age*" has been introduced to the text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Editorial update to align with the age range per ICH.	
63 and 174-175	23	The ICH classification of age groups related to paediatric patients goes up to 17. (Neonates: 0-27 days, Infants and toddlers: 28 days-23 months, Children: 2-11 years, Adolescents: 12-17 years). If this ICH classification is referenced, line 63 should be updated to refer to medicines for use in children between birth and 17 years of age (or <18 years of age). (The current wording in line 63 refers to children between birth and 18 years of age.) Proposed change (if any): Editorial update to align with the age range per ICH.	See above.
65-67	4	”*The physical, metabolic and psychological processes* ***peculiar*** *to growth from birth into adulthood reveal that children cannot be regarded as small adults nor can they be regarded as a homogeneous group in themselves.”* Is there a better word for “**peculiar**” in this sentence? Proposed change (if any): Replace by (alternatively) “inherent”, “unique” or “related”.	Accepted: The term “peculiar” has been replaced with “inherent”
65-67	10	”The physical, metabolic and psychological processes **peculiar** to growth from birth into adulthood reveal that children cannot be regarded as small adults nor can they be regarded as a homogeneous group in themselves.”	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Is there a better word for "**peculiar**" in this sentence? Perhaps unique?	
67	10	Proposed change (if any): (for consistency) suggest changing "studies" into "trials"	Accepted: The term "studies" has been replaced with "trials"
68	10	Proposed change (if any): Change "Thus, clinical trials may be needed" to "Thus, clinical trials in many cases will be needed".	Accepted: The text has been revised; "*in many cases clinical trials will be needed*" has been added.
73-76	5	It is proposed to include specifications on sizes of tablets and capsules and age dependent volume administration (I.V. and oral) per state of the art and age appropriate dosage type. The reference to age appropriateness is very often made throughout the document whereas actual guidance or instruction on what are age appropriate dosage forms is lacking. Proposed change: inclusion of a table with data	Comment noted but not accepted: In view of the limited data available on sizes of tablets and capsules the reference to the tablet (capsule) size has been removed from the Guideline in order not to inhibit development in this field.
73	10	Typo/grammar Proposed change (if any): …for **o**lder children and adults. Neonates **especially** pose….	Accepted: The term "elder" has been replaced with "older"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
73, 372, 373, 755	11	Comment: Importance of comment: Elder Proposed change (if any): Older	See above.
73	18	Comment: throughout the text, “elder” should be “older”. Proposed change (if any): replace “elder” with “*older*”.	See above.
73	22	throughout the text elder should be older Proposed change (if any): older	See above.
77-81	5	“Knowledge on the critical….products.” “As a consequence….other caregivers and children”. It is proposed to change this statement as it is unclear what is meant by the paragraph. The word “might” suggests that an assumption is made. This makes the paragraph unclear. Proposed change (if any): Proposed text: “Knowledge of the quality aspects critical to paediatric medicines is still limited especially when considering these aspects in a multidimensional approach to the best attainable and affordable paediatric medicinal products. As a consequence, as knowledge increases, some of the currently	Comment noted. It has been acknowledged in Section 2 that the authorised paediatric medicinal products could benefit from further optimisation and it is the responsibility of MAHs to undertake such re-evaluation. Relevant reference to the legal framework has been added: “*As knowledge increases, the usefulness (practicality), quality, safety or efficacy of authorised paediatric medicines should be re-evaluated by pharmaceutical companies in the interest of children and their caregivers. This approach is in accordance with Art 23 of the*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		available paediatric medicines could benefit from further optimisation in the interest of parents, other caregivers and children"	*Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a product and adapt or improve their products for the benefit of patients and maintain a positive benefit-risk balance.*"
77 – 81	10	Paragraph appears incomplete (word – "approved" ? - missing between 'currently' and 'paediatric' on line 79). Of great concern, is that the paragraph seems to suggest that currently approved paediatric medicines may need to be redeveloped. This seems to be a counterproductive comment and will need further elaboration to understand when / which current products are 'questionable'. Proposed change (if any): Remove this paragraph from the guidance.	Accepted: Statement referring to questionable and based on minimum standards formulations has been removed.
77	18	The wording "Knowledge on the critical to quality aspects of paediatric medicines is still limited" requires re-wording. Proposed change (if any): *Knowledge on the aspects of paediatric medicines critical to quality is still limited.*	Accepted: The text has been revised accordingly
77	22	Knowledge on the critical to quality aspects of paediatric medicines is still limited,	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Knowledge on the aspects of paediatric medicines critical to quality is still limited,	
77-79	32	Art. 15 No. 2 sent 2 of the Paediatric Regulation gives details for the Paediatric Investigation Plan (PIP): “In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.” Proposed change: A clarification of the scope is needed. The wording should reflect the legal text of the regulation: “Knowledge on the critical to quality aspects of paediatric medicines is still limited, especially when considering these aspects in a multidimensional approach to ~~the best attainable and affordable paediatric medicinal~~ **adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.**	Accepted: Statement referring to questionable and based on minimum standards formulations has been removed; further updates were introduced in section 2
78	9	It is not clear what is meant by the term “multidimensional approach”. The statement should be clarified. Proposed change (if any):	Comment noted. The term “multidimensional approach” is not used in the rephrased section.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
79-81	4	The meaning of the sentence *"As a consequence, the usefulness (practicality) of some of the **currently** paediatric medicines might be questionable / based on minimum standards and could consequently be subject to further optimisation in the interest of parents, other caregivers and children"* is not clear and may lead to confusion. Proposed change (if any): Editorial change for clarity – Suggest changing "currently" to "current" so sentence reads: *"As a consequence, the usefulness (practicality) of some of the **current** paediatric medicines might be questionable / based on minimum standards and could consequently be subject to further optimisation in the interest of parents, other caregivers and children."*	Comment noted. The comment is not reflected in the guideline because the text has been further modified. The term "authorised paediatric medicines" has been used in the revised text.
79	18	The wording "some of the currently paediatric medicines" does not make sense. Proposed change (if any): Some of the currently *authorised* paediatric medicines	See above.
79	22	Comment: 'some of the currently paediatric medicines' does not make sense Proposed change (if any):	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		some of the currently *authorised* paediatric medicines	
81	5	Since it is acknowledged that knowledge is limited, the guideline should make provision for future revisions to be implemented as knowledge increases. Also, from this acknowledgment, the limitations of the guideline should be indicated. Proposed change (if any): Proposal for additional text: This guideline is based on the limited current knowledge and will be updated as further experience is gained.	Accepted: The current status in the knowledge has been reflected Executive summary. The following statement has been included: *The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.* There is no need to explain that the guideline will be updated as further experience is gained as it is a standard approach with regulatory guidelines. It is a standard practice to initiate a revision of a guideline when new evidence, significantly changing the approach discussed in a guideline is available.
88-91	5	It is advised to rephrase this statement as it should be factual rather than an expectation. Proposed change (if any): Proposed text: Since the Regulation became into force, the number of paediatric formulations under development and the knowledge about critical aspects to these formulations is increasing rapidly.	Not accepted: The comment is not endorsed

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
90	18	The wording “the knowledge on the critical to quality aspects of paediatric medicines is expected to increase rapidly” requires re-wording. Proposed change (if any): the knowledge on the aspects of paediatric medicines *critical to quality* is expected to increase rapidly.	Accepted: The text has been revised
90	22	Comment: the critical to quality aspects of paediatric medicines is expected to increase rapidly. Proposed change: the aspects of paediatric medicines *critical to quality* is expected to increase rapidly.	See above.
92	10	This paragraph does not mention “safety, quality or efficacy”.	Accepted: Terms “safety, quality or efficacy” have been included in the revised Section 2.
93-95	4	The meaning of the sentence: *”Therefore, this guideline aims to provide additional tools for the rationale pharmaceutical development of medicines for children between birth and 18 years of age to those already described in the current CHMP and ICH guidelines”* is not clear.	Accepted: The text has been revised and included in Executive summary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Editorial change for clarity – delete the word “rationale” so the sentence reads: “Therefore, this guideline aims to provide additional tools for the pharmaceutical development of medicines for children between birth and 18 years of age to those already described in the current CHMP and ICH guidelines.”	
94	5	“rationale pharmaceutical” Proposed text: “rationale for pharmaceutical”	See above.
94	10	The meaning of the sentence: ”Therefore, this guideline aims to provide additional tools for the rationale pharmaceutical development of medicines for children between birth and 18 years of age to those already described in the current CHMP and ICH guidelines” is not clear. Proposed change (if any): Either change rationale into rational, or remove the word rationale.	See above.
94	18	The wording “additional tools for the rationale pharmaceutical development of medicines” does not make sense. Proposed change (if any): replace “rationale” with “*rational*”.	See above.
94	22	rationale	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): *Rational*	
96-97	4	The meaning of the sentence: *"The guideline intends to balance between predictable and consistent regulatory assessments of paediatric medicines ..."* is not clear. Proposed change (if any): Editorial change for clarity – Add the word **provide** before balance so the statement reads: *"The guideline intends to **provide** balance between predictable and consistent regulatory assessments of paediatric medicines ..."* - <u>if that is indeed the intention of the statement.</u>	Not accepted: There is no need to include "provide" in the statement.
96-100	4	The meaning of the sentence: *"...the speed of development, industrial feasibility and the need to develop medicines that are better tailored for use in children than the currently authorised, but "questionable"* paediatric medicines or the currently applied off-label or pharmacy compounded medicines" is not clear. Proposed change (if any): Change statement to read: *"The guideline intends to balance between predictable and consistent regulatory assessments of paediatric medicines (either generic, innovative, existing or new), the speed of development, industrial feasibility and the need to develop formulations intended for use in children rather than continuing the practice of unapproved pharmacy compounded medicine and off label use"*	Accepted: The text has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
96-98	10	It is appreciated that the guideline will take into consideration industrial feasibility. An imbalance between requirements and industrial feasibility/costs would risk to inhibit rather than to increase pharmaceutical development for children.	Response to comment not applicable.
96-99	9	Currently, this section seems to imply that all medicines currently authorised for children are 'questionable'. This is not the case and these lines should be reworded.	Accepted: The text has been revised. Part of the statement referring to questionable formulations has been reworded.
97-100	10	The meaning of the sentence: "...the speed of development, industrial feasibility and the need to develop medicines that are better tailored for use in children than the currently authorised, but "questionable" paediatric medicines or the currently applied off-label or pharmacy compounded medicines" is not clear. Proposed change (if any): The term "tailored" conveys that every medicine may need redesign for children regardless of its properties. A medicine may not need to be modified or tailored if it meets the needs for both adult and paediatric patients, e.g. small tablets or oral liquids.	Accepted: The text has been revised. Part of the statement referring to questionable formulations has been reworded. The term "tailored" has been replaced with "*more appropriate*"
99	5	"questionable". If paediatric medicines are authorized they have been assessed by regulatory authorities and the benefit-risk has been concluded to be positive, therefore they cannot be questionable. It is proposed not to use any quotation signed word to avoid misunderstanding or interpretation errors. The word questionable will raise doubts around the paediatric	Accepted: The text has been revised. Part of the statement referring to questionable formulations has been reworded.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		medicines currently on the market. Proposed change (if any): Proposed text: “The guideline intends to…. And the need to develop medicines that are better tailored for use in children in line with state of the art knowledge and methods, whenever possible avoiding off-label use or the need for pharmacy compounded medicines.”	
99	10	Again, the draft guidance uses the surprising phrase “currently authorised but ‘questionable’ paediatric medicine”. Proposed change (if any): Remove this phrase, since authorized medicines cannot be considered questionable.	See above.
99	11	Importance of comment: Applied Proposed change (if any): Used	Comment noted.
99	18	“than the currently authorised, but “questionable” paediatric medicines” is a rather broad statement. Proposed change (if any): than *some* of the currently ……	Accepted: The text has been revised. Part of the statement referring to questionable formulations has been reworded.
99	21	It would be helpful to provide a definition of “questionable”	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		paediatric medicines.	
99	22	This is a 'sweeping' statement. There are plenty of currently authorised medicines that are age-appropriate as well as many that are not. Proposed change (if any): *some of* the currently authorised…	See above.
100-101	5	It is not clear what this statement is meant to indicate, but it could be interpreted as if medicines developed following this guideline are sub-standard. Proposed change (if any): Proposal to remove text: “The outcome of this balanced approach should not necessarily result in a “gold standard” paediatric medicine”	Accepted: The statement has been removed as per recommendation.
100-101	10	The draft guidance states “The outcome of this balanced approach should not necessarily result in a ‘gold standard’ paediatric medicine. This principle is welcomed and could be usefully supported by a general statement of what standards will be approvable – e.g. products should be safe and efficacious. Please avoid however the term "gold standard", since nobody knows exactly what this means. Proposed change (if any): Suggest the guidance includes statement that products should	Accepted: The text has been revised accordingly and the term “gold standard” removed. Furthermore, the need to develop products which are designed to be safe, efficacious and fit for their intended purpose has been emphasised in the revised Executive summary. The following text has been included: “*Critical objectives for the development of age-appropriate paediatric*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		be designed to be safe, efficacious and fit for their intended purpose'.	*medicines is to ensure that children in the target age group(s) will have access to medicinal products with a positive benefit-risk balance, of a consistent quality, assuring adequate patient's adherence and which do not put an unnecessary burden on the patient and/or its caregivers."*
100-101	9	The following sentence requires clarification: *"The outcome of this balanced approach* ***should not*** *necessarily result in a "gold standard" paediatric medicine"*. It is acknowledged that compromises are often required in the development of medicines and that a less than ideal, but licensed, paediatric medicine is generally better than no medicine at all. However, those involved in the development of paediatric medicines should still strive to ensure that the final product is age-appropriate and as close to ideal as possible for the benefit of the paediatric patient.	See above.
103	10	"The principles of this guideline are to be applied …" can be agreed upon when the principles refer to the need to provide a comprehensive development rationale, taking into account the relative benefits and risks of a number of possible and feasible alternatives (text Line 513 and 514). Proposed change (if any): It is our suggestion to place such as statement upfront e.g. in the	Not accepted: The comment is not endorsed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Executive Summary.	
103-105	32	The Paediatric Regulation does apply to NEW medicinal products. (11) ….However, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. There is no legal basis for this wide scope of "all medicinal products". This scope would neglect the principle of a balance between requirements and incentives that forms the basis of the Paediatric Regulation. In addition guidelines are not legally binding. The language in this sentence seems to give another impression. Development of medicinal products requires flexible approaches. Any restriction should be limited to legal requirements. Proposed change (if any): Change to: "The principles of this guideline ~~are to~~ **should** be ~~applied~~ **taken into consideration** during the pharmaceutical development of ~~all~~ paediatric medicines." ~~as proposed in Marketing Authorisation Applications (MAA) or applications to extend or vary the marketing authorisation to the paediatric~~	Not accepted: The scope of this guideline is not restricted to the PIP applications and it should be considered during development of medicines for children, regardless of the legal basis which is used for MAA. Even for generic applications, when the product is to be used in children, applicants should ensure that the proposed product is suitable and appropriate for use in the proposed population.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		~~population (MAVs).~~	
105	11	Importance of comment: MAVs? Proposed change (if any): MAV	Accepted: The abbreviation (MAVs) has been explained in the text.
106-112	5	It is not clear where these considerations should be discussed. If the scope of the guideline are MAAs or MAVs covering paediatric medicines, final formulations should be available and discussed. If however the intent is to provide guidance as to acceptability of different types of formulations during different phases of development, the guideline should be further expanded accordingly.	Accepted: The scope of the guideline has been updated to emphasise that it is also applicable in the early phase of the development, at the time of PIP applications. A statement linking the life cycle of a product with initial PIP development has been added: "*Depending on the phase of the development, the principles of this guideline should also be considered for the purpose of the Paediatric Investigation Plan (PIP) applications.*"
106-119	10	*Impact on development* In our opinion this paragraph deserves to become its own (sub-)chapter, as the concept of enabling (preliminary) formulations is an important approach, in particular in the context of development of NMEs. Actually two important things are addressed here: (1) the fact that in early phase PIPs not enough information might be available to propose a final paediatric medicine (for the	Comment noted: Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the revised Guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		market), and (2) the concept of using preliminary (enabling) formulations in early clinical trials incl. the opportunity to switch later from the enabling formulation to the commercial form. It should be added that preliminary formulations may not only be based on manipulation of existing (commercial) dosage forms, but might also be developed / applied as simple formulations (e.g. granulates, powder mixes). Proposed change (if any): Restructure paragraph as outlined in the comment above – see points (1) and (2) - and move into a new separate (sub-) chapter.	
111	18	The forum for discussion is not specified and it is unclear why the PIP process is not included in the scope section.	Accepted: The forum for discussion has been clearly specified in the scope of the Guideline:" *The principles of this guideline should be considered during the pharmaceutical development of all paediatric medicines as proposed in Marketing Authorisation Applications (MAA) or applications to extend or vary the marketing authorisation to the paediatric population (MAV).*" In addition, a statement linking the life cycle of a product with initial PIP development has been added: "*Depending on the phase of the development,*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			the principles of this guideline should also be considered for the purpose of the Paediatric Investigation Plan (PIP) applications."
111	22	to be discussed where? There is no mention of the PIP process in the 'Scope'.	Accepted: The scope of the guideline has been updated to emphasise that it is also applicable in the early phase of the development, at the time of PIP applications. A statement linking the life cycle of a product with initial PIP development has been added: "*Depending on the phase of the development, the principles of this guideline should also be considered for the purpose of the Paediatric Investigation Plan (PIP) applications.*"
112-116	4	The sentence: *"The use of preliminary (also called enabling) paediatric formulations in the early clinical trials may be considered acceptable if appropriately justified, however it is not exempting from the requirement to develop a formulation which will be industrially-manufactured and controlled. Thus, preliminary formulations which are based on instructions for the manipulation of an authorised medicine will normally n*ot be considered acceptable for marketing authorisation." is too restrictive. Proposed change (if any): Consider re-wording to allow for current compounding procedure	Comment noted. Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the revised Guideline. The purpose of the Paediatric Legislation is to stimulate development of age appropriate formulations. Pharmacy compounded formulations in exceptional cases can be considered. Using "may" and "could" is not restrictive and does not exclude such options for development (if justified).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		per pharmacy and medical practice. Line 212 contradicts this statement as it points out that different dosage forms "may be" needed for targeted age groups. The statement needs to be broad enough to work for both small molecules and other types of medicinal products e.g. biologics.	Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the Guideline. It has been acknowledged that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated. A switch from a preliminary formulation to a commercial formulation should often be supported by relevant bridging studies between different formulations used throughout the development*.
113	10	The draft guidance states that "The use of preliminary paediatric formulations in the early clinical trials may be considered acceptable if appropriately justified". EFPIA considers that the expectation that the investigational product be safe and has appropriate quality is sufficient for early investigational clinical studies in paediatric patients. Further rationale should not be required. Proposed change (if any): Modify the wording to "The use of preliminary … may be considered provided such products fulfil appropriate quality	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		criteria for investigational products."	
113	18	Terminologies such as "preliminary" or "enabling" formulations should be reviewed and defined. Standardisation of terminology with other stakeholders would be important.	Accepted: Terms "preliminary" and "enabling" formulations have been defined in the 'Definitions' section of the Guideline.
113	18	We agree that the use of preliminary paediatric formulation in early clinical trial setting is acceptable. However, there should at least a minimum requirement for these preliminary formulations to ensure dosing accuracy and safety of the participants. Formulations requiring preparation prior to administration should be supported by validated method of preparation (e.g. the reproducibility of the dose) in order to maintain the integrity of the clinical trial data.	Accepted: Information and role of primary (enabling) formulations in the life-cycle of a product has been clarified in the Guideline. It has been acknowledged that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated.*
114-117	8	Some preliminary formulations may be acceptable for marketing authorisation in some age groups after manipulation, e.g. scored tablets (with demonstrated accuracy of dosing) or a multiparticulate drug formulation in a capsule shell, and may not be included in the SmPC yet (see definition of 'manipulation' l. 809-812). Proposed change (if any):	Comment noted. Information and role of primary (enabling) formulations in the life-cycle of a product has been further clarified in the Guideline. It has been acknowledged that the *preliminary formulations which are based on instructions for pharmaceutical handlings of an authorised medicine will normally not be considered acceptable for marketing authorisation,*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Delete the sentence.	*unless sufficiently justified and appropriately validated.*
114 and 805	10	*Preliminary formulations* The concept to use preliminary (enabling) formulations to facilitate preclinical and early clinical development studies is only explained in the definitions section (line 804 - 807). Proposed change (if any): Move explanation of concept of use of preliminary formulations to facilitate preclinical and early clinical development studies to main section as part of suggested new chapter on enabling formulations (see comments to lines 106-119)	See above.
114	21	The guideline suggests the acceptability of preliminary formulations if appropriately justified. A guidance should be provided outlining in which case such formulations would be acceptable as illustrated in the following examples: industrially verified extemporaneous formulations, small patients population, life threatening disease for which a preliminary formulation would enable a fast market access …	Not accepted: An outlining in which case such formulations would be acceptable has not been included in the guideline as it is acknowledged that such exceptions would require a justification. It is the applicant's responsibility to discuss and justify the proposed development strategy. Possibility for justification has been included in the revised statement.
115-114	5	"Thus, preliminary formulations which are based on instructions for the manipulation of an authorised medicine will normally not be considered acceptable for marketing authorisation."	Accepted: The statement "unless sufficiently justified"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		This text suggest that it is standard practice not to accept formulations that are derived from the adult formulation. Such statement in itself seems to exclude the possibility that there may be formulations derived from the adult formulations that are perfectly suitable for treatment in children and therefore contradicts with the intention of the this guidance to increase number of better medicines for children and may unnecessarily delay (or prevent) treatment of severely ill children. Proposed change (if any): Proposed to revise text into: "Thus, preliminary formulations which are based on instructions for the manipulation of an authorised medicine may not be considered acceptable for marketing authorisation unless sufficiently justified."	included in the revised text.
115-116	10	Dilution of an authorised medicine can be -in some circumstances- the only possibility of preparing medication for children, when for example, long time storage of a low concentration product is not feasible. In that case instruction for manipulation of an authorised medicine should be acceptable.	Comment noted. If handling of a dosage form is unavoidable it should be clearly described in the SmPC and PIL. When additional handling is necessary the approach should be validated. These requirements have been further emphasised in the revised guideline.
115	11	Importance of comment: L Extent of what is considered *'Manipulation'*	Not accepted: The term "manipulation" has been deleted from the guideline in view of different

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Refer to Definitions [808-814]	interpretation by different stakeholders. Term "handling" has been introduced instead.
117-119	5	"A switch from ... including bioequivalent studies if necessary". This statement 'if necessary' should be elaborated to prevent confusion and referred to appropriate existing guidance on this topic, since extensive in vivo studies are not always necessary. For example if the formulation change is minor (e.g., change in quantity of an excipient) during late phase development an additional Safety/ Efficacy study would not be required if it can be demonstrated that the pharmaceutical properties of the product are unchanged. Proposed text: "dependent on the clinical phase and timing of formulation change could include in vitro testing or bioequivalence studies or relative bioavailability studies if required by the existing guidance"	Comment noted. The text has been revised: "*A switch from a preliminary formulation to a commercial formulation should often be supported by relevant bridging studies between different formulations used throughout the development.*"
118	11	Importance of comment: On *Bioequivalence studies* Proposed change (if any): For guidance purposes, add when (depending on: age groups concerned?, type of dosage form: IR vs MR?, BCS classification of API?) and how this is required and should be done (adult vs.	Comment noted. The purpose of this guideline is not to indicate what type of studies are needed during development of a paediatric formulation, e.g. if a bioequivalence study is needed but rather to indicate that these aspects should be discussed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		children) to provide guidance.	
122	30	"may require further justification and adaptation" this may be misunderstood. Proposed change (if any): Additional considerations need to be applied to the development of paediatric dosage forms	Comment noted.
127-129	1	According to the Community Code, Marketing authorisation holders (MAH) are required to regularly monitor their medicinal products, notably for quality and safety aspects, taking into account new technical and scientific evolution, as appropriate. There is no legal basis for this requirement and a re-evaluation of all products on the market within 5 years would be extremely challenging, if not impossible particularly for well-established paediatric medicines and for SMEs which are particularly abundant in the self-care sector. From a patient/parent/care-taker point of view, reformulation of well-established medicines on the market since a long time may create confusion which may negatively impact patients. Proposed change (if any): The entire paragraph should be deleted.	Comment noted and partially accepted: According the Paediatric Regulation EC 1901/2006, before a medicine can be introduced to the market, it has to undergone extensive studies in order to ensure that it is safe, of high quality and effective for use in the target population. However, as practical evidence and scientific knowledge increases over the lifecycle of a medicine, it must be taken into consideration that a medicine the quality of which was suitable for use in a target patient population (i.e. age-appropriate) at the time the authorization was granted may not necessarily be so after many years later. The reference to 5 years transitional period has been deleted and the paragraph is revised. As it is a legal duty of Marketing

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Authorisation Holders to ensure that authorised products are *state-of-the-art* while being on the market, the following statement has been included in the revised Guideline: *As knowledge increases, the usefulness (practicality), quality, safety or efficacy of authorised paediatric medicines should be re-evaluated by pharmaceutical companies in the interest of children and their caregivers. This approach is in accordance with Art 23 of the Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a product and adapt or improve their products for the benefit of patients and maintain a positive benefit-risk balance.*
127-129	5	"Pharmaceutical companies ... the date of coming into operation of this guideline." The legal basis for this statement is not clear. Adequate provisions already exist in the legal acumen that indicate that medicines and medicine development should be state of the art. It is stated in this guideline that knowledge is limited. Therefore, it seems unreasonable and untimely to impose this obligation until improved recommendations can be made based on improved knowledge. Please explain with regards to the statement that if the authorized product on the market does not meet this guideline, industries then should change or have to	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		develop the alternative formulation? Please explain also if during this process, the authorized product will then be un- available on the market? Proposed change (if any): It is proposed to remove the statement in its entirety.	
127-129	6	According to the European drug law and also according to the national legislation in the member states, each marketing authorisation holder (MAH) is bounded by law to continuously monitor his products in the aspects of Quality and patient safety. This implies the compliance of his products also to new technical and scientific aspects, written down e.g. by Guidelines like this. So, it is not necessary to put a deadline for re-evaluation in a Guideline. Such procedure is triggered automatically after the publication of each Guidance/Guideline. Nevertheless, a re-evaluation of all the products cannot be the intention of this guideline. This paper addresses only the development of paediatric medicines. Proposed change (if any): This paragraph should be deleted or at least be amended to address only products on the market with an intended use in the paediatric population.	See above.
127-129	7	The request for a re-evaluation of all products on the market describes an unspecified retrospective application. Guidelines are	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		normally prepared for application prospectively (See EMEA/P/24143/2004 Rev. 1 corr – Procedure for European Union Guidelines...). A retrospective application should be only made in exceptional situations. This is not the case, as the addressed medicines are already specially approved for children. **We therefore recommend deleting this paragraph.**	
127-129	8	I appreciate a continuous monitoring of the properties of licensed medicinal products for children. However, to my knowledge there is no legal basis for a 5 y re-evaluation period. I am afraid that the entire process will bind huge capacities at the regulatory body, various industry departments and external reviewers such as myself. Some existing products with small patient populations might be withdrawn from the market if the financial efforts are too high. All this may have a negative impact on the access of children to approved paediatric medicines and this would be in sharp contrast to the Directive Regulation 1901/2006/EC. Re-evaluation of the approved medicinal products may be performed by the agencies in the usual procedure. This may be triggered by new guidelines of the agencies or at the time-point of SmPC changes submitted by the companies. There is no need for an additional deadline in my opinion. Proposed change (if any): Delete this paragraph.	See above.
127	10	The draft guidance states that “Pharmaceutical companies should have a re-evaluation of all their products on the market.” It is not clear what are the criteria that a company should use to conduct	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		such a re-evaluation (after all the products are approved) nor is it clear what is the legal basis for this recommendation in a guidance; one would expect such a statement rather in a directive. We propose to delete the first sentence of this line. The Article 23 of the Directive 2001/83/EC already mentions this obligation to take into account scientific and technical progress during the whole product life. Unless problems have been identified/reported with existing products there should be no need to re-evaluate the formulation. Proposed change (if any): Remove wording that implies retrospective application of this draft guidance.	
127-129	11	*Pharmaceutical companies should have a re-evaluation of all their products on the market. They should ensure that their products are state of the art i.e. meeting the requirements as described in this guideline within a period of 5 years following the date of coming into operation of this guideline.* Is it a legal obligation? Proposed change (if any): If this is a binding element of this guideline this should get much more attention	See above.
127-129	15	Although the Faculty agrees that products on the market should be reviewed with regards to the aspects of formulation outlined,	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		we believe that it would be a concern if a product's marketing authorisation was withdrawn because it did not comply with these guidelines. We believe that this could be counterproductive for availability of children's medicines. We recommend that the EMA provide industry with some reassurance that they would work with the respective companies to develop an appropriate plan to address any issues with formulation rather than to withdraw the MA. Proposed change (if any):	
127-129	18	Whilst this statement may be legally sound, has the statement been tested for feasibility? Would failure to comply lead to licence being revoked - this could be counter-productive for children?	See above.
127-129	9	*"Pharmaceutical companies should have a re-evaluation of all of their products on the market. They should ensure that their products are state of the art i.e. meet the requirements as described in this guideline within a period of 5 years following the date of coming into operation of this guideline"*. It is not reasonably practical for companies to redevelop product unless there is a specific reason to do so such as a quality failure or safety issue. Re-evaluating all medicines on the market and developing new age-appropriate pharmaceutical forms and licensing them would be extremely resource intensive for both industry and regulators. It is unusual for guidance to be applied retrospectively and concept paper (EMEA/138931/2008) is intended to be	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		prospective. As development pharmaceutics occur prospectively, re-evaluation of existing products might be considered beyond the scope of this guidance document. Proposed change (if any): It is recommended that the statement on retrospective application of the guideline is removed.	
127-129	21	Is the re-evaluation only applicable for pediatric formulations out in the market?	See above.
127-129	33	The legal basis for the re-evaluation of all products on the market is not given and therefore the demand is not acceptable.	See above.
127	23	• A re-evaluation of all products on the market within 5 years is very challenging particularly for small and established products. • To our understanding this corresponds to all “paediatric products on the market”. Proposed change (if any): • A clarification regarding the re-evaluation of all market products is recommended. • “Pharmaceutical companies should have a re-evaluation of all their paediatric products on the market.” • Suggest to call it “pediatric remediation program of the	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		marketed product” • A longer transition period, e.g. 10 years, is recommended.	
127-129	22	Whilst this statement may be legally sound, has the statement been tested for feasibility? If companies do not comply will they lose MA - this could be counter-productive for children?	See above.
127-129	32	The Paediatric Regulation refers to NEW medicinal products and does not apply to medicines already on the market. This scope would neglect the principle of a balance between requirements and incentives that forms the basis of the Paediatric Regulation that expresses the will of the legislative bodies. An administrative document cannot go beyond existing legislation. There is also no legal basis in any other legislative document (i. e. Directive 2001/83/EC) to require any re-evaluation unless the benefit-risk balance of a medicinal product is not favourable anymore. Proposed change (if any): Delete these sentences	See above.
127-129	33	The legal basis for the re-evaluation of all products on the market is not given and therefore the demand is not acceptable.	See above.
128	30	if there is a legal basis for this a reference would strengthen this postulate	See above.
128	9	The term “state of art” is not a term that should be used in a regulatory guideline as it is open to interpretation.	Accepted: The term “state of art” has been deleted from

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): “Age-appropriate” may be a more suitable term.	the guideline.
129	21	The company has to re-evaluate existing products within 5 years in order to comply with this guideline. There is no clarity about the procedure and incentive.	Comment noted. According the Paediatric Regulation EC 1901/2006, before a medicine can be introduced to the market, it has to undergone extensive studies in order to ensure that it is safe, of high quality and effective for use in the target population. However, as practical evidence and scientific knowledge increases over the lifecycle of a medicine, it must be taken into consideration that a medicine the quality of which was suitable for use in a target patient population (i.e. age-appropriate) at the time the authorization was granted may not necessarily be so after many years later. The reference to 5 years transitional period has been deleted and the paragraph is revised. As it is a legal duty of Marketing Authorisation Holders to ensure that authorised products are *state-of-the-art* while being on the market, the following statement has been included in the revised Guideline: *As knowledge increases, the usefulness (practicality), quality, safety or efficacy of*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			authorised paediatric medicines should be re-evaluated by pharmaceutical companies in the interest of children and their caregivers. This approach is in accordance with Art 23 of the Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a product and adapt or improve their products for the benefit of patients and maintain a positive benefit-risk balance.
130-131	32	This sentence is directly related to the first sentence and should be the second sentence of the scope. Proposed change (if any): The principles of this guideline ~~are to~~ **should** be ~~applied~~ **taken into consideration** during the pharmaceutical development of paediatric medicines. **The examples listed should not be regarded as providing exhaustive information and do not preclude the existence of other aspects relevant to the pharmaceutical development of paediatric medicines or alternative ways of development.**	Comment noted.
131	18	Clarification on “other aspects” would be useful. Are they known or unknown aspects?	Comment noted. The term “other aspects” means aspects not discussed in the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
131	22	what are the other 'aspects'? This should be made clear. Are they known or unknown?	See above.
133-168	32	Guidelines are not legally binding documents. Proposed change: Other guidelines list guidelines to be read in conjunction under the heading "References" which might be more appropriate.	Comment noted. The list of regulatory guidelines has been deleted form the guideline. However a general statement that guideline should be read in conjunction with all other relevant directives and regulations, and relevant Commission, and CHMP guidelines, Q&A documents and other documents as linked to or published on the EMA website, remains.
134	12	Proposed change (if any): the reference to the Directive should say "relating to" rather than "relation"	Accepted: The text has been revised accordingly.
138-140	5	It is advised to replace the current open statement with a list of applicable documents to improve clarity.	Not accepted: The list of regulatory guidelines has been deleted form the guideline as it may not be possible to provide an exhaustive list of all documents that need to be consulted.
138-140	8	The development and production of medicinal products for paediatric use has to undertaken according to the European legislation for Good Manufacturing Practice (GMP); EudraLex Vol. 4.	Not accepted: It is not a paediatric-specific requirement. Manufacturing in accordance with GMP is required for all medicinal products. GMP aspects are addressed in relevant directives

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Add a reference to GMP as general principles also for the production of Medicines for Paediatric Use.	and regulations.
138-140	6	In general the development and production of medicines for paediatric use has to follow the same standards and principles like the production of all other medicinal products in the European Union. These basics are outlined in the European legislation for Good Manufacturing Practice (GMP); EudraLex Vol. 4. Proposed change (if any): Add a reference to GMP as general principles also for the production of Medicines for Paediatric Use.	See above.
140	12	Proposed change (if any): “emphasis” rather than “emphasise”	Comment noted. However, the text has been revised and the word was removed.
140	5	Correction: emphasis	See above.
141-168	6	The WHO published already several years ago a Points to Consider paper on the Pharmaceutical Development of Paediatric Medicines (QAS/08.257). The latest Revision is from October 2010 and available on the WHO Homepage. http://www.who.int/entity/medicines/services/expertcommittees/pharmprep/Rev2-PaediatricMedicinesDevelopment_QAS08-	Not accepted: The WHO Guideline was considered and consulted in the preparation of this guideline however it is not referenced.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		257Rev1_8102010.pdf Proposed change (if any): Add a reference to the WHO PtC paper	
161	1	This is the wrong number for the paper. EMEA/196218/05 is an additional Note of explanation. The correct number for the paper "REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION" is EMEA/CHMP/PEG/194810/2005 Proposed change (if any): Replace "EMEA/196218/05" with "EMEA/CHMP/PEG/194810/2005"	Comment noted. However, the list of regulatory guidelines has been deleted from the guideline.
161	6	This is the wrong number for the paper. EMEA/196218/05 is an additional Note of explanation. The correct number for the paper "REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION" is EMEA/CHMP/PEG/194810/2005 Proposed change (if any): Replace "EMEA/196218/05" with "EMEA/CHMP/PEG/194810/2005"	See above.
161	8	EMEA/196218/05 is a false citation. Proposed change (if any):	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Replace 'EMEA/196218/05' by 'EMEA/CHMP/PEG/194810/2005'	
162-165	5	It is unclear how reference to the guideline on PIPs is relevant if the intent of this guideline is to indicate the content of the pharmaceutical development section for MAAs or MAVs for paediatric medicines It is proposed to remove this reference.	See above.
168	20	Under 3. Legal basis, there should be a reference refer to the sources mentioned under 9. Excipients in the formulation, see line 533 - 580. Proposed change (if any): Add relevant sources, i.e. like EFSA and JEVFA.	See above.
170-172	9	The term "state of art" is not a term that should be used in a regulatory guideline as it is open to interpretation. Proposed change (if any): A more specific term such as "age-appropriate" would be a more suitable term.	Accepted: The term "state of art" has been replaced with "age-appropriate".
174, 178-179	4	It is not appropriate to oblige companies to develop formulations for potential off-label use in paediatric patients. "Indicated" target age groups are understood to mean "authorized" patient population(s).	Comment noted. The term "target age group(s)" refers to the age groups of patients for which medicinal product is being developed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The term “indicated” should be replaced by “authorized”. The term “targeted” age group also needs an explicit qualifier: it should be*: “The authorized target age group(s)”*	
174	10	We assume this is referring to ICH E11, so recommend making specific reference to it here for clarity.	Comment noted. The age bands have been aligned with the ICH terminology and there is no need to include specifically that it is in accordance with ICH E11.
174-175	23	The ICH classification of age groups related to pediatric patients goes up to 17. (Neonates: 0-27 days, Infants and toddlers: 28 days-23 months, Children: 2-11 years, Adolescents: 12-17 years). If this ICH classification is referenced, line 63 should be updated to refer to medicines for use in children between birth and 17 years of age (or <18 years of age). (The current wording in line 63 refers to children between birth and 18 years of age.) Proposed change (if any): Editorial update to align with the age range per ICH.	Accepted: The age bands have been aligned with the ICH terminology, the term “*from birth to less than 18 years of age*” has been introduced to the text.
176-177	5	For improved readability alternative text is suggested: “In deciding the suitability of the pharmaceutical design of a paediatric medicine, the following should be considered:”	Accepted: The text has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
176-196	9	Factors in deciding the appropriateness of pharmaceutical design are listed. There are many other factors. It would be helpful to list the chapters of the guideline. Proposed change (if any): The following additional factors (chapters of the guideline) should be added to the list of focus points which may provide some additional clarity with respect to the contents and structure of the guideline: • characteristics of the active, • route of administration, • dosing frequency, • excipients, • patient acceptability • container closure system and administration device.	Comment noted. It has been clarified that the list includes factors in addition to those discussed in sections 6-12 of the guideline. Factors such as characteristics of the active, route of administration, dosing frequency, excipients, patient acceptability and container closure system/administration device are discussed in sections 6-12 of the guideline therefore these have not been listed in section 4.
176-192	17	Additional considerations for appropriateness are: 1. ease of measurement of doses across the age range 2. safety of the presentation e.g. use of glass ampoules for oral medicine	Comment noted.
176-192	25	Additional considerations for appropriateness are 1. Ease of measurement of doses across the age ranges indicated. 2. Safety of presentation e.g. use of a glass ampoule for oral	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		medicine.	
178–192	10	There is overlap with adult considerations for “the condition to be treated”, and all the criteria in lines 186 -191. Proposed change (if any): Suggest making a cross reference to other references supporting adult documentation e.g. IMPD, IB, etc.	Comment noted. Comment considered however not reflected in the text. Making a cross-reference to other references supporting adult documentation would significantly decrease the readability of the guideline.
178-192	10	Suggest to add 1) a request for special considerations on medication, which has to be given daily by injection either by the child self or by a care giver 2) on line 181 climate/geography 3) after line 187: “Additional general considerations include: • Pain of injection • Dosage volume / paediatric diluted SKU or device for small volume injections”	Comment noted.
180-181	20	We don’t think that the activity of the child is relevant Proposed change (if any): Delete line 180 and 181	Not accepted: The age associated activities of children in the target age group(s) (e.g. school, nursery, etc.) and the environment setting where the product is likely to be used (e.g. hospital) are important factors which should be taken into

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			consideration when developing medicines for children.
181	8	'...or community' is an inappropriate wording. The focus of attention should be also place on the person who administers the medicinal product. Proposed change (if any): ... (e.g. hospital and domestic environment) and the person who administers the medicinal product.	Comment noted.
183-185	4	*"the condition related characteristics of the child (e.g.* ***likely disabled****, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to centrally nervous system diseases (e.g. epilepsy) or to critical illnesses)…"* Proposed change (if any): Editorial Change – "likely disabled" should be changed to "**children with physical or mental disabilities**" so the statement reads: "*the condition related characteristics of the child (e.g.* ***children with physical or mental disabilities…****"*	Accepted: The term "likely disabled" is replaced with "children with physical or mental disabilities".
183-185	4	"the condition related characteristics of the child (e.g. likely disabled, **aggressive**, fluid restriction, high degree of co-medication including inability to swallow due to centrally nervous system diseases (e.g. epilepsy) or to critical illnesses);"	Not accepted: The word "aggressive" was removed from the revised text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please clarify what aggressive means.	
183-185	4	"the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to **centrally** nervous system diseases (e.g. epilepsy) or to critical illnesses)…" Proposed change (if any): Editorial change to correct grammar – The word "centrally" should be changed to "central" so the statement reads: "the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to **central** nervous system diseases (e.g. epilepsy) or to critical illnesses)…"	Comment noted. The text has been revised.
183-185	5	For improved readability alternative text is suggested: "the condition related characteristics of the child (e.g. likely disabled, aggressive, under fluid restriction, with a high degree of co-medication, unable to swallow due to central nervous system diseases or to critical illnesses);"	Comment noted. The text has been revised
183-185	10	"the condition related characteristics of the child (e.g. **likely disabled**, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to centrally nervous system diseases (e.g. epilepsy) or to critical	Accepted: The term "likely disabled" is replaced with "children with physical or mental disabilities".

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		illnesses)…" Proposed change (if any): Editorial Change – "likely disabled" should be changed to "**children with physical or mental disabilities**" so the statement reads: "the condition related characteristics of the child (e.g. **children with physical or mental disabilities…**"	
183-185	10	"the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to **centrally** nervous system diseases (e.g. epilepsy) or to critical illnesses)…" Proposed change (if any): Editorial change to correct grammar – The word "centrally" should be changed to "central" so the statement reads: "the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to **central** nervous system diseases (e.g. epilepsy) or to critical illnesses)…"	Comment noted. The text has been revised.
183-185	20	We don't think that the environment is relevant Proposed change (if any): Delete line 183-185	Not accepted: The environment setting where the product is likely to be used (e.g. hospital) is an important factor which should be taken into consideration

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			when developing medicines for children.
184	18	"centrally nervous system diseases" is incorrect. Proposed change (if any): Replace "centrally" to "*central*".	Comment noted. The text has been revised.
184	22	centrally Proposed change (if any): *central*	See above.
186	5	For improved readability alternative text is suggested "The accuracy required in the dose"	Not accepted: It is not only a dose accuracy but also its criticality.
186-187	8	'...the criticality of the dose' is an inappropriate wording. The key words 'dose titration' and/or 'flexible dosing' are missing. Proposed change (if any): * the therapeutic regimen (i.e. dose calculation method, dose titration, flexible dosing), especially in cases of a narrow therapeutic window or high risk of adverse effects.	Partly accepted: The text has been revised. The dosing regimen (i.e. dose calculation, dose titration, flexibility of dosing) has been added to the text.
187	4	Consider adding the following statement. Proposed change (if any):	Comment noted. The proposed factors have been addressed in section 6.8 Parenteral administration.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"Additional general considerations include: • Pain of injection • Dosage volume / paediatric diluted SKU or device for small volume injections"	
189-190	8	The sentence lacks some potential hazards in the medicinal product (except, this was meant by '...and the finished medicinal product'). Proposed change (if any): ... active substance, known impurities, excipients, other known related products (e.g. degradation products, residual solvents, heavy metals, leachables) and the finished medicinal product;	Not accepted: Known impurities, other related compounds, residual solvents constitute either part of the active substance or finished product and there is no need to list them separately.
191	10	Also biopharmaceutical properties are important Proposed change (if any): Add "biopharmaceutical properties"	Comment noted.
192	4	"patient acceptability i.e. child friendliness." Proposed change (if any): "Patient Acceptability" and "Child Friendliness" need to be better defined.	Partially accepted: "Patient acceptability" is discussed and clarified within section 10 of the Guideline. Term "child friendliness" has been deleted form the Guideline.
192	10	"patient acceptability i.e. child friendliness."	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "Patient Acceptability" and "Child Friendliness" need to be better defined. What about the role of parent/care-giver?	
192	22	there are many others e.g. food habits; pragmatic approach of care givers to methods of achieving administration in the uncooperative child - addition to food/liquid; manipulation of dosage form.	Comment noted. Dedicated paragraph on mixing with food and drinks has been included in the guideline within section 10.
193	5	For improved readability alternative text is suggested ~~On this basis,~~ "The most sensitive development aspects…"	Comment noted.
193-196	20	"Long term" should be defined or deleted. Excipients that are known to have undesirable effects should not be used. Proposed change (if any): On this basis, the most sensitive development aspects are likely to arise in paediatric medicines for the use in neonates, infants and young children, particularly with relation to excipients. Excipients for which the safety data are of concern, should not be used. Excipients for which the clearance is reduced because of the ontogeny of involved enzymes in the age group should not be used in that age group.	Comment noted. Relevant updates have been introduces in Section 9 Excipients in the formulation.
195	18	Presumably 'safety data' refers to safety of excipients (since	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		safety of the active should have been established. Consider rewording this sentence for clarity.	
195	22	presumably 'safety data' refers to safety of excipients (since safety of the active should have been established. This should be made clearer.	See above.
197	10	General comments for Section 5 There is a need for a general, high level, introductory statement to address drug success in the paediatric population and the special considerations in this group. Proposed change (if any): Consider adding the following text at the beginning of this section: "The characteristics of a drug to help ensure its success in the paediatric community should consider, 1) ease of administration: the age at which children are able to swallow tablet is variable and offering a liquid formulation that may be used even in older children is important, 2) taste must be acceptable, 3) solubility must be consistent and directions clear with respect to solubility in different foods (i.e. applesauce), 4) dosage frequency especially in school age children may affect compliance, 5) effect on appetite even if short lived may be very important in the paediatric population, especially in infants where intravascular volume depletion is a increased risk with small reductions in oral intake."	Comment noted. Section 5 has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
197-206	4	There is a need for a general, high level, introductory statement to address drug success in the paediatric population and the special considerations in this group. Proposed change (if any): Consider adding the following text at the beginning of this section: “There are several drug characteristics which should be considered when planning paediatric medicines e.g., 1) ease of administration: the age at which children are able to swallow tablet is variable and offering a liquid formulation that may be used even in older children is important, 2) taste must be acceptable, 3) solubility must be consistent and directions clear with respect to solubility in different foods (i.e. apple sauce), 4) dosage frequency especially in school age children may affect compliance, 5) effect on appetite even if short lived may be very important in the paediatric population, especially in infants where intravascular volume depletion is a increased risk with small reductions in oral intake.”	See above.
197-206	1	Changing the salt form of the drug substance for paediatric formulations may lead to increased development efforts and significant delays as well as to operational challenges. Child acceptability of a specific active ingredient in a medicine should mainly be covered by the development of suitable dosage forms. If it is not possible to equally satisfy the needs of different paediatric age groups by only one dosage form, several forms might be developed – based, however, on the use of only	Partially accepted: The statement on the use of different salts has been modified, to make it optional, as one of the possibilities which could be explored.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		one form of API Proposed change: Delete lines 198-206 and replace by “In cases where no suitable paediatric formulation can be developed using the existing salt form, the use of a different salt form or free form of the active moiety may be considered.”	
197-206	5	This section implies that development of a different salt, change from salt to free base (and vice versa) should be considered. This may have a significant impact on the development of paediatric formulation, which may end the development of the novel drug product in itself. A full assessment on toxicology and ADME is required upon changes. Please delete this section or add more clarification on to what extent and under which conditions the existing data on adults can be used for the paediatric development in the proposed situation.	See above.
197	10	<u>General comments for Section 5</u> There is a need for a general, high level, introductory statement to address drug success in the paediatric population and the special considerations in this group. Proposed change (if any): Consider adding the following text at the beginning of this	Comment noted. Section 5 has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		section: “The characteristics of a drug to help ensure its success in the paediatric community should consider, 1) ease of administration: the age at which children are able to swallow tablet is variable and offering a liquid formulation that may be used even in older children is important, 2) taste must be acceptable, 3) solubility must be consistent and directions clear with respect to solubility in different foods (i.e. applesauce), 4) dosage frequency especially in school age children may affect compliance, 5) effect on appetite even if short lived may be very important in the paediatric population, especially in infants where intravascular volume depletion is a increased risk with small reductions in oral intake.”	
197-203	9	The dose-response curve and therapeutic window, although not physicochemical characteristics of the active, are critical properties of the active in the development of a paediatric formulation and should be discussed early in the development pharmaceutics section. Proposed change (if any): The concept paper (EMEA/138931/2008) confirms the importance of this aspect as it states: *“The first issue to be established is the ‘criticality’ of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window, etc.) and how the dose is to be calculated. These aspects in turn may determine the choice of pharmaceutical form, the formulation, and the dosage administration system,*	Comment noted. The ‘criticality’ of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window, etc.) and how the dose is to be calculated has been listed in section 4 as one of the points which need to be considered when developing medicinal products.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(e.g. fixed 'quantised' doses vs a continuously variable dose)" It is suggested that this statement, from the concept paper, is included in section 5.	
197-203	9	It would be helpful to include solubility in this section. The solubility of the active in various media should be discussed. As the pH of the gastro-intestinal tract can change with the growth and development of the child, a discussion of the solubility of the drug in the gastro-intestinal tract would be very useful. If the medicine is intended to be mixed with food, the solubility should be discussed. As liquid paediatric medicines are often in solution or suspension, solubility is critical. It may be helpful to include a statement on the more practical impact that solubility might have on the taste of an oral medicine, as taste is also often dependent on how much active is in solution. Proposed change (if any): Addition of solubility to section 5. (Characteristics of the active substance)	Comment noted. Solubility is one of the characteristics of the active substance, and there is no need to explicitly mention it in this section as there are also other characteristics, equally important.
198	10	These lines (which seem to suggest the first thing that should be done is to re-select an active substance) are suggestive of a 'gold standard' approach. Development of a paediatric medicine by using a new salt form (different from the form of the API used for the adult product) might require a re-start of the full tox / DMPK program, as per definition, a new molecular entity (NME) is created. This might have a significant impact on	Partially accepted: The statement on the use of different salts has been modified to make it optional, as one of the possibilities that could be explored.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		development timelines and chances of success. It would seem more reasonable in the first instance to use the pre-existing drug substance if this can be formulated into a product that is safe, efficacious and fit for purpose. Thus an applicant that has a particular safe and efficacious product as one product type (e.g. a sprinkle) should not necessarily have to have explored other salts to produce a different formulation (e.g. a solution). Proposed change (if any): "Selection of form/salt of active during early phases of (adult) development should also take into account paediatric formulation requirements where possible." The choice of the form of the API will also be significantly impacted by the proposed dosage form. Also PK characteristics may determine the choice of form of the active substance.	
200-201	4	It is assumed that this is general guidance and that in considering the Active Substance during pharmaceutical development for both adults and children, that the acceptability for children is considered. However the guideline could be interpreted to read that company may need to develop a parallel form of the Active Substance specifically for the paediatric population. A different Active Substance base / salt could be considered a new active substance and could trigger a completely separate drug development pathway – specific non-clinical and clinical studies – and require its own MA.	Partially accepted: The statement on the use of different salts has been modified to make it optional, as one of the possibilities that could be explored.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		It is indeed necessary to ensure that the guidance reflects the Paediatric Regulation, which in turns refers to the need avoid unnecessary trials and to delay or block the authorisation of medicinal products for other age populations (refer to recitals 4, 8, 10 and 14). Also, the Paediatric Regulation does not seem to provide a solid basis for requiring the development of a specific Active Substance for the paediatric population (refer for instance to article 31(4)). Proposed change (if any): Recommend to reword the conclusion paragraph (line 204) to read: *'Therefore, the choice of the form of the active substance in the paediatric medicine should* ***CONSIDER*** *its use in the indicated target age group.'*	
200	32	The use of a different salt for paediatric formulations than for other populations can only be an exemption in rare cases as it might lead to the requirement of additional pre-clinical studies and to additional bioequivalence or even clinical studies because bridging from adult data might not always be possible. For all these reasons the original drug substance should be used also for the paediatric development. It should not be mandatory to test different forms in case the original drug substance is not suitable for all age appropriate dosage forms. However, in the (probably exceptional) case that a company wishes to use an alternative it could be acceptable.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): **In some exceptional cases** the manufacture of a liquid medicine **may require** a substance with improved solubility i.e. a different salt, or a salt instead of the base. However, a different salt might lead to additional preclinical and stability tests and bioequivalence or even clinical studies (also with children). The choice of another dosage form might be the better alternative in these cases (e.g. mini tablets).	
201-206	8	Although I appreciate all modifications that improve the characteristics of the active substance (better called 'active pharmaceutical ingredient', API), other salt forms are usually considered as new APIs. Therefore, there is no free selection of 'a salt form' as this would require new pre-clinical (related products, detailed synthesis route, residual solvents) and clinical data on efficacy and safety. This data may not even be available for adults. Proposed change (if any): p. 201: Child acceptability may be improved by the selection of excipients (e.g. pH modifiers, counter-ionic excipients, complexing agents) which may improve the solubility and/or taste properties of the active pharmaceutical ingredient.	Comment noted. Section 5 is dedicated to the active substance and excipients should not be discussed within this section. In some cases due to properties of the active substance various excipients need to be used to solubilise the substance. These excipients not always are neutral and safe. There should be always a discussion on what is better the use of an alternative salt or unsafe excipients.
201 – 202	12	The sentence in lines 201-202 is not really clear. Why should trial acceptability be favoured by the selection of a less soluble form of the active substance? This is not clear and could	Comment noted. Less soluble form may have implications on taste, one of mechanisms to mask the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		perhaps be explained.	unpleasant taste of the active substance.
203	10	"..patient safety in children may be improved by avoiding a particular inorganic counter-ion or organic salt structure" – sentence is unclear Proposed change (if any): Would be useful to know what inorganic counter-ion or organic salts should be avoided in paediatric medicines. Please provide a reference. A common data base or similar would be valuable.	Partially accepted: Mesylates have been added as an example of a particular counter-ion which should be avoided.
204-206	5	Please clarify if, in case different drug substance forms between paediatric formulation and the drug substance form applied for the adult formulation are used, novel preclinical safety studies would be required. If the form change of drug substance during the manufacturing process is incorporated, what kind of studies would be required?	Comment noted. It is not the role of Quality guideline to define criteria for clinical and non-clinical development. Depending on the impact of the change in the active substance the non-clinical and clinical program may vary.
204-206	32	The first choice is the active substance used in adults as it is well defined and thoroughly studied. A different salt might lead to additional preclinical and stability tests and bioequivalence or even clinical studies (also with children). Another active substance should only be the "ultima ratio". Proposed change (if any): Delete sentences	Partially accepted: The statement on the use of different salts has been modified to make it optional, as one of the possibilities that could be explored.
Section 6	32	In this chapter many statements require further scientific justification. It is not clear which data could be useful to be	Comment noted. Comment concerns many sub-sections and will

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		provided. The different requirements for acute/short-term treatments versus long-term treatments should be explained more explicitly. Many chapters include recommendations for complex testing and considerations about incorrect use (e.g. line 297/298, 340/341). Proposed change: Delete lengthy considerations about incorrect use; instead the following sentence could be included: "Companies should strive for clear instructions and tests to establish the correct use of medicines by parents and caregivers."	be reviewed for each and revised, where appropriate. Agreed in principle that correct use should be ensured.
Section 6	10	The section does not address the possibility and acceptability of developing depot formulations. Depot formulations could be appropriate, for example in schizophrenia. Therefore we would suggest adding a sub-section to discuss and provide guidance on this type of formulation.	Comment noted. Modified release preparations are included in the guideline and discussed in a separate section (Section 8).
Section 6	33	A lot of dosage forms which are listed in the standard term list are missing e.g. orodispersible film, minitablets, rectal (foam) and vaginal (foam) dosage forms, nebuliser, etc.	Comment noted. Further amendments to section 6 to address some of the missing dosage forms have been introduced.
207-221	5	The selection of a dosage form and route of administration should be made based on pharmaceutical, pharmacokinetic and pharmacodynamic considerations in the first place.	Comment noted. The text has been revised to reflect that user aspects are one aspect among the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The guideline gives unbalanced importance to user aspects like child friendliness and user acceptance. Consider change in priority setting to efficacy and safety (first priority) and in later state to child friendliness and user acceptance.	considerations to be taken. Revised text: *"The rationale for the choice and advantages and disadvantages of a particular paediatric dosage form via a particular route of administration should be discussed and justified for children in each of the target age group(s). Aspects to be considered at least include condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients in a paediatric preparation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and users aspects such as the ease of administration and patient acceptability."*
209-210	4	*"The advantages and disadvantages associated with the administration of a particular paediatric dosage form via a particular route of administration should be discussed and justified for children..."* Proposed change**:** The terms *"Advantages and disadvantages"* are subjective terms. Consider instead stating the *"characteristics"* of the paediatric administration of a dosage form being discussed.	Comment noted. Although subjective, the 'advantages and disadvantages' have been kept in the text. Instead the aspects to be considered have been specified more clearly, as this will reflect on what can be regarded as an advantage or disadvantage. See above for revised text.
209-214	9	The pros and cons of various dosage forms are considered but	Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		one major factor not considered is how long the medicine will be given for. The duration of treatment will be a major factor in determining the acceptability of the dosage form.	Treatment duration added to considerations. Revised text: "*The rationale for the choice and advantages and disadvantages of a particular paediatric dosage form via a particular route of administration should be discussed and justified for children in each of the target age groups. Aspects to be considered at least include condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients in a paediatric preparation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and users aspects such as the ease of administration and patient acceptability."*
209 – 221	10	This section suggests that a different formulation is pursued for each target age group and health condition. From an industry feasibility viewpoint this is not a realistic point of departure. From a cost containment and development perspective, it is better to aim for a formulation that can be used by as many patients as possible. Reference is made to the EFPIA position paper on this topic.	Comment noted. Agreed in principle that one formulation that can be used across as many age sub-sets/patients as possible would have benefits. However, the paragraph/sentence intends to highlight that the same dosage form may not always be applicable for all age sub-sets.
210	10	The draft text stating that advantages and disadvantages (benefits and risks?) associated with the administration of a	Partially accepted: The word *"discussed"* when used in a

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		particular dosage form via a particular route of administration "should be discussed" is unclear. Does this refer to discussion within the sponsor company with clinicians as part of agreement of the target product profile OR is it intended that some discussion with the PDCO should take place. If regulator engagement is intended it would be useful to note which elements of the regulatory process (e.g. agreeing on the PIP with the PDCO, scientific advice) would satisfy this guidance expectation.	regulatory guideline, refers to presentation of a justified rational in the relevant documentation, which in this case may include MAA, as well as PIP or Scientific Advice procedure, as the guideline applies to all medicines developed for children. The text has been clarified to include more specifically aspects that at least need to be considered.
Lines 211-214	9	Different dosage forms may be necessary for children in the same age group. For example: if a single dosage form is proposed (e.g. tablets for 6-12 years), the way in which children who cannot manage that dosage form can be treated should be discussed e.g. can the tablet be dispersed in water?	Comment noted. Sub-sections of 6.2. and in section 10 have been revised accordingly. Children may not be able or willing to swallow a specific dosage form and/or paediatric formulation, even when the dosage form/formulation/preparations itself is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms/formulations to the market (e.g. oral liquid as well as tablets). When not feasible, alternative strategies for intake of the preparation should be discussed (see subsection "Handling of dosage forms to facilitate administration" and section 10).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
214	22	If a single dosage form is proposed (e.g. tablets for 6-12 years), the applicant should propose alternative strategies for administration for children who cannot manage that dosage form e.g. can the tablet be crushed and given with food. Any such manipulations must be validated. An alternative dosage form should also be considered.	See above.
215-221	22	It is unclear in this paragraph as to what is the 'specific regulatory guidance'.	Comment noted. Most of the paragraph in question has been deleted and the text in sub-section 6.1 has been revised. Revised text: *"Aspects to be considered include at least the condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients in a paediatric preparation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and users aspects such as ease of administration and patient acceptability."*
215-221	19	It is unclear in this paragraph as to what is the 'specific regulatory guidance'.	See above.
215-216	4	"*The justification for the choice of the route of administration and dosage form should include user aspects as e.g. adequate palatability, tablet size etc."*	Accepted: The paragraph has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change**:** Suggest to keep in general terms to make guideline more widely applicable and improve clarity, i.e., rather than “tablet size” use terms such as “ease of administration” or “dosage requirements.”	Revised text: *“Aspects to be considered include at least the condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients in a paediatric preparation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and users aspects such as ease of administration and patient acceptability.”*
219	30	Comment: liquid dosage forms are parenteral solutions and oral liquid dosage forms under general aspects in addition to the need of preservation other critical aspects such requirement of special storage conditions (e.g. low temperature), size of packaging (storage space) may be added.	Comment noted. The paragraph has been revised accordingly. See above.
221- and foregoing (215 – 221)	12	It is also suggested to make reference to accuracy and ease of use of the devices.	Comment noted. The paragraph has been revised accordingly. See above.
222	30	Critical aspects of oral liquid dosage forms such as syrups or oral suspensions, would be desirable to be read in conjunction with critical aspects of oral solid dosage forms. Proposed change (if any): move from 219 to 230 For example, the choice for an oral liquid formulation normally requires a	Comment noted. The paragraph in question has been deleted and the text in 6.1 revised to discuss more general aspects. See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		dosing device.	
222	7	The guideline may additionally take into account the following aspects for oral administration: - Chewing Gums - Gum-Pastilles - Small Syringes - Small Syringe-Pumps	Not accepted: Not all dosage forms are specifically addressed in the guideline.
222-237	9	Section 6.2 should explicitly state that crushing tablets should be avoided where possible, particularly in order to provide less than a single unit dose.	Comment noted. Crushing of tablets is addressed under a new sub-section added under 6.2.1 Solid oral preparations under the heading of “Handling of dosage forms to facilitate administration”.
223-225	10	“Oral administration can be achieved via several types of dosage forms. In general, the main choice is between the application of an oral liquid preparation, an oral solid unit dosage form (e.g. normal sized tablet, capsule) or an oral flexible solid dosage form (e.g. powder, granules, pellets).” In addition, tablet shape may also have an impact on ease of swallowing. Proposed change : Please define “normal tablet” and “flexible” dosage forms or rephrase as stated below: Replace by “oral solid dosage forms, which allow dosing	Not accepted: The paragraphs covering general considerations have been largely reworded. The term flexible dosage forms is no longer used, instead dosing flexibility is used in relation to ability for dose adjustment. As discussed for comments related to section 6.2.1 and tablet size, there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups. Hence

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		adjusted to age or body weight either in multiple units (granulates, pellets, mini tablets), or which can be divided into sub-doses (sub-division of tablets)". Add specifics of sizes, and information on tablet shapes if available.	detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
223-225	4	"Oral administration can be achieved via several types of dosage forms. In general, the main choice is between the application of an oral liquid preparation, an oral solid unit dosage form (e.g. normal sized tablet, capsule) or an oral flexible solid dosage form (e.g. powder, granules, pellets)." Proposed change**:** Please define "normal tablet" and "flexible" dosage forms. These are not common terms.	See above.
223 – 225	5	"Oral administration ….an oral solid unit dosage from … or an oral flexible solid dosage form (e.g. powder, granules, pellets)." For improved readability alternative text is suggested: "The most widely used oral dosage forms are oral solid unit dosage forms (e.g., tablets, capsule), or an oral flexible solid dosage from (e.g., powder granules pellets, mini-tablets and mini-capsules) and oral liquids."	Not accepted: Pellets, mini-capsules or –tablets are not defined dosage forms and are therefore not specified as examples. A paragraph introducing the concept of mini-tablets has been introduced under 6.2.1.
223-237	17	It should be noted that standard tablets may also disperse well and quickly. We agree that correct dosing requires a fully dissolved solution or homogeneous dispersion and it is important to consider the	Comment noted. The text has been revised accordingly. Revised text: "*Taking part of a liquid prepared*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		dispersibility of the product and the solubility of the active ingredient when an aliquot is used to obtain a proportion of the dose. We agree that new products should not be formulated anticipating dispersion and then administration of an aliquot of the resultant liquid. This remains necessary for some existing products and this guideline should not be a barrier to that continuing until products are re-evaluated.	*from such dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduces an increased risk for dosing errors, and should generally be avoided."*
223-237	25	Oral Administration It should be noted that standard tablets may also disperse quickly and well. We agree that new products should not be formulated anticipating dispersion and then administration of an aliquot of the resultant liquid. This remains necessary for some existing products and this guideline should not be a barrier to that continuing until products are re-evaluated.	See above.
224	8	An 'oral liquid preparation' is not adequately defined. Suspensions do not necessarily belong to liquid drug formulations. The term 'formulations' should be used instead of 'preparation'. Proposed change: ...of an oral liquid formulation (solution,	Not accepted. Oral liquid preparations was used based on EDQM Standard Terms. However, the text has been revised and now the term oral liquid dosage forms is used.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		syrup, emulsion or suspension).	
224-225, 229-230	8	An 'oral solid unit dosage form' is not adequately defined. I assume 'single-unit dosage forms' is intended. Moreover, an 'oral flexible solid dosage form' is not adequately defined, too. Mini-tablets and orodispersible formulations as new promising dosage forms are not considered in the present text. Proposed change: ...an oral solid single-unit dosage form (e.g. normal sized and/or modified-release tablet or capsule), an oral solid multiple-unit dosage form ≤ 3 mm (e.g. powder, granules/pellets, small-sized tablets) or an orodispersible form (e.g. orodispersible tablets, orodispersible films).	Not accepted. The text in section 6.2 has been re-worded/the paragraphs re-structured for content. Mini-tablets are not a separate dosage form, and are not mentioned as a specified example. The concept of 'mini-tablets' has been introduced under section 6.2.1. Tablets. Revised text: *"Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
225	22	Include dispersible tablets as an example here - important for links to the WHO equivalent document.	Comment noted. The text in section 6.2 has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Dispersible preparations are included. Revised text: *"Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided."*
225	19	Dispersible tablets should be included as an example. This provides important links to the WHO document on "Points to consider" on pharmaceutical development of paediatric medicines. Minitablets should also be included.	Comment noted. The text in section 6.2 has been revised. Dispersible preparations are included in the revised text. See above. Mini-tablets do not represent a separate dosage form. However, the concept of 'mini-

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			tablets' has been introduced under section 6.2.1. Tablets. Revised text: "*Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
225, 227, 229, 230, 232	11	**flexible solid dosage forms** *e.g. powder, granules, pellets* In the WHO document(August 2011): DEVELOPMENT OF PAEDIATRIC MEDICINES: POINTS TO CONSIDER IN PHARMACEUTICAL DEVELOPMENT Working document QAS/08.257/Rev.3 It is defined as follows: 3. DOSAGE FORMS TO BE CONSIDERED IN PARTICULAR a) Dosage forms that, in general, are likely to prove most	Partially accepted: The text in section 6.2 has been revised. The term "flexible oral dosage form" is no longer used. Flexibility is discussed in relation to ability for dose adjustment; the term dosing flexibility is used. Revised text: "*Oral solid single-unit dosage forms may provide a stable and easy dose approach. However, where individually adapted dosing is necessary the number of strengths*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		suitable for global use, including for developing countries, and which should be prioritized, are **flexible solid dosage forms** such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for various APIs. They may not be suitable for medicines requiring a precise dose titration. The lack of uniformity of definition might create confusion Suggestion - Proposed change / suggested text (if any) It has to be agreed what 'flexible' is used for - to emphasise the practicality of administration, or - to describe that it provides dosing flexibility (for example, to deliver precise doses mg/kg or SA). 226 – mention monolithic dosage form? (in opposition to multiparticulate)	*that are needed to treat patients in the target age group(s) will increase. Alternatives which may provide dosing flexibility for tablets include addition of score lines enabling the administration of a fraction of the full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose (see section 6.2.1)* *Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
226	5	“Children may be unable to swallow… forms.” Proposed text: “Children may be unable to swallow solid unit dosage forms due to disease state or age”.	Not accepted: The text has been revised.
226	10	The guidance text says “Children may be unable to swallow solid unit dosage forms” – it would be important to put this comment in the context of age-groups of children (as is done in lines 247).	Comment noted. In section 6.2.1 Tablets, detailed guidance have been removed from the guideline as there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups. A more general requirement for justifications by applicants has been introduced instead.
226-235	19	It is unclear in this paragraph as to what is the 'specific regulatory guidance'. The paragraph says on the one hand, a particular dosage form can achieve what is desired but on the other, it is not normally acceptable.	Comment noted. The paragraph has been reworded for better clarity. Revised text: *“Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided."
226-235	22	Unclear as to what 'specific regulatory guidance' is being given. The paragraph says on the one hand that it can achieve what is desired but on the other that it is not normally acceptable.	See above.
228	10	Comment: Style Proposed change: … may be a problem **where** dosing is weight..	Comment noted. The text has been revised.
229-230	28	The term "oral flexible dosage form" is neither common nor used in the Ph. Eur., and needs to be either defined (in the glossary) or replaced. Proposed change**:** Replace by "oral solid dosage forms allowing flexible dosing" or "oral solid dosage forms, which allow dosing adjusted to age or body weight either in multiple units (granulates, pellets, mini tablets), or which can be divided into sub-doses (sub-division of tablets)".	Comment noted. The paragraphs have been revised. The wording 'oral flexible dosage form' is no longer used, whereas dosing flexibility, i.e. ability for dose adjustment is discussed. Revised text: *"Oral solid single-unit dosage forms may provide a stable and easy dose approach. However, where individually adapted dosing is necessary the number of strengths that are needed to treat patients in the target*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			age group(s) will increase. Alternatives which may provide dosing flexibility for tablets include addition of score lines enabling the administration of a fraction of the full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose (see section 6.2.1). *Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
230-231	10	"However, the application of a large range of doses with an oral solid flexible dosage form may necessitate the need for a dedicated device in order to avoid dosing errors." "dedicated device" is difficult to imagine for a solid dosage form. Examples of such dedicated devices will be appreciated. Proposed change: Sentence is not completely clear. Is the following meant? "However, the application of a large range of doses with an oral ~~solid~~ flexible dosage form may necessitate the need for a dedicated device in order to avoid dosing errors."	Comment noted. The text has been revised. The sentence in question has been removed from section 6.2 and measuring devices are discussed, when relevant, under the specific sub-sections for different preparations and in Section 11 (11.3).
230-231	11	What does it mean? *However, the application of a large range of doses with an oral solid flexible dosage form may necessitate the need for a dedicated device in order to avoid dosing errors*. Proposed change: Rephrase / explain	Comment noted. The text has been revised. The sentence in question has been removed from section 6.2 and measuring devices are discussed, when relevant, under the specific sub-sections for different preparations and in Section 11 (11.3).
230-231	4	*"However, the application of a large range of doses with an oral solid flexible dosage form may necessitate the need for a dedicated device in order to avoid dosing errors."* Proposed change: Guidance should allow for use of conventional measuring devices such as measuring spoons that are not "dedicated" or "co-packaged" to be used with liquid preparations if justified	Comment noted. The text has been revised. The sentence in question has been removed from section 6.2 and measuring devices are discussed, when relevant, under the specific sub-sections for different preparations and in Section 11 (11.3). The text has been revised to include aspects that could allow the use other than a dedicated measuring device.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
231	10	Paragraph starting “Solid oral dispersible… ” is not completely clear. Why would a dispersion of tablets be considered ‘not acceptable’ whereas dispersions of granules etc. are acceptable (lines 240 – 241)? Clarification is needed.	Comment noted: The text has been revised to clarify that the issue is linked to taking a part of the dispersed unit dosage form, which would result in a multiple step handling and hence introduce an increased risk for dosing errors. Revised text: *“Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided.”*
231-232	11	Regarding “*Solid oral dispersible tablets will also enable dosing*	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		flexibility, if parts of the dispersed solution are taken". Proposed change: *'dispersed solution'* should be more elegantly rephrased as it is not possible This statement is confusing. Soluble/dispersible tablets are different than orodispersible tablets.	The text has been revised. See above.
231 – 232	1	Proposed changes: • Delete "oral" from the term solid oral dispersible tablets to be consistent with later definition (line 281 ff.) • Add "or capsules" after tablets, since also capsules may be dissolved or dispersed in water	Comments noted. The text has been revised. See above. For general considerations, dosage forms are mentioned as examples and not all concerned listed.
231-232	8	'Solid oral dispersible tablets' is neither a Ph. Eur. nor a EDQM standard term. Further, it is unclear whether effervescent tablets, soluble tablets, dispersible (prepares dispersion before administration) tablets and orodispersible (forms dispersion in the mouth) tablets are meant. Small-sized orodispersible dosage forms such as orodispersible tablets or orodispersible films may be a better alternative, but are not yet addressed in this paragraph. Proposed change: Use 'Solid effervescent, soluble or dispersible tablets will also enable dosing flexibility, if …'.	Comments noted. The guideline has been revised to use standard terms in the text as well as headings for sub-sections and does not necessarily specify each dosage form under a certain type of preparation.
231 – 234	5	"Solid oral dispersible tablets….dispersion to be taken"	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		This sentence is in contradiction with itself. Proposed text: “Solid oral dispersible (mini-)tablets will also enable dosing flexibility if a fully dissolved solution or a homogeneous suspension is generated upon addition of liquids and if the correct volume of the dispersed drug product can be administered.”	The paragraph has been revised to clarify that the issue is linked to taking a part of the dispersed unit dosage form, which would result in a multiple step handling and hence introduce an increased risk for dosing errors. Revised text: *“Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided.”*
231-235	32	There might be solid oral dispersible tablets that could be divided with sufficient accurateness. The example does not take into account that there might be ways to overcome the	Comment noted The paragraph has been revised to clarify that

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		described shortcomings with new technologies. Proposed change: The example should be clearly marked as an example for multiple step-handling and not mention one particular dosage form.	the issue here is related to the multiple step handling. See above.
232-233	4	*"However, correct dosing will then require a fully dissolved solution or a homogeneous dispersion..."* Proposed change**:** Please clarify what is a fully dissolved solution?	Comment noted. The paragraph has been revised. See above.
232-235	21	The guidance states that the oral dispersible tablets are not acceptable as mean to administrate a flexible dose. There is a lack of rational in this as it would be the responsibility of the pharmaceutical company to demonstrate the dose accuracy.	Comment noted. The paragraph has been revised with addition of the need to validate the procedure where this type of approach could be found acceptable. Revised text: *"Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			introduce an increased risk for dosing errors, and should generally be avoided."
233-235	10	Are dispersible tablets desirable from an EMA perspective (as they are from a WHO perspective)?	Comment noted. It is not the purpose of the guideline to express general preferences but to emphasise the aspects to be considered in the choice of an age appropriate dosage form.
234-235	10	Is the terminology as used in this draft guideline in line with E.P. definitions, distinguishing e.g. between dispersible tablets and orodispersible tablets? Proposed changes**:** "*Solid dispersible tablets will also enable dosing flexibility, if parts of the dispersed solution are taken. However, correct dosing will then require a fully dissolved solution or a homogeneous dispersion, the correct volume of water to be added and the correct volume of the dissolved solution or dispersion to be taken. Clear instructions for use should be provided, stressing the need to fully dissolve / disperse the tablets prior to administration and the minimum volume of liquid required to do so. ~~Such handling is prone to errors and normally not considered acceptable~~*. Solid orodispersible tablets could be an appropriate alternative since they may enable the same dosing flexibility and do not need water. In addition they are easy to administer and are generally difficult to spit out."	Comment noted. The text has been revised. Standard terms are now used where applicable. Revised text: *"Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			resulting liquid and the possibility to withdraw the correct volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided."
235	10	The guidance text notes that a range of (previously listed) manipulations are 'normally not considered acceptable'. It would be important to note when they could be accepted – e.g. if the product is being administered in e.g. hospital and prepared by a hospital pharmacy. Proposed change: Please clarify in the text the circumstances when such manipulation would be acceptable.	Comment noted. This aspect is discussed in a new subsection on "Handling of oral solid preparations to facilitate administration" in section 6.2.1.
237	21	Reference should be 6.9 (not 4.3.9).	Comment noted. Reference corrected to 6.2.3 (previous sub-section 6.9)
Line 237	9	Reference to section 4.3.9 is given. This section does not exist. Proposed change: Remove or amend reference as appropriate.	See above.
237	5	see 4.3.9 incorrect reference should be see 6.9	See above.
237	10	Reference should be 6.9 (not 4.3.9)	See above.
237	19	There is no paragraph 4.3.9	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
237	22	There is no paragraph 4.3.9	See above.
Section 6.2.1	4	Comment: Tablets don't belong to granules and powders and pellets? Proposed change: Suggest grouping Tablets and Capsules together as they are "unit-dose" dosage forms.	Comment noted. The structure of Section 6 has been changed: 6.2 Oral administration 6.2.1 Oral solid preparations 6.2.2 Oral liquid preparations 6.2.3 Administration through feeding tubes 6.2.4 Oromucosal preparations 6.3 Nasal preparations 6.4 Preparations for inhalation 6.5 Rectal preparations 6.6 Cutaneous and transdermal preparations 6.7 Eye and ear preparations 6.8 Parenteral administration 6.9 Fixed dose combinations
238	10	Mini tablets are not discussed in the guidance – these should be included in the 'tablets' section, including guidance on age-appropriateness. Proposed change: include guidance on mini tablets.	Comment noted. Section 6.2.1 has been revised. The term "minitablet" is not a separate dosage form but the concept is discussed under 6.2.1, subsection "Tablets": Revised text: *"Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."
238	11	Orodispersible tablets should have section where they are discussed. Oral thin films/wafers are not discussed at all in the guideline. Proposed change: add	Not accepted: The guideline has been revised to use standard terms in the text as well as headings for sub-sections and does not necessarily specify each dosage form under a certain type of preparation. Orodispersible tablets are included in the guideline.
238	19	A section on minitablets and the specific regulatory guidance should be included in this section (e.g. whether minitablets should meet the same requirements as stated for miniparticulates or tablets?)	Comment noted. Section 6.2.1 has been revised. The term "minitablet" is not a separate dosage form but the concept is discussed under 6.2.1, subsection "Tablets": Revised text: *"Small tablets containing a fraction of the dose may be considered as a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."
239	23	Comments to 6.2.1. Acceptability: • A dosage form especially suitable for children is the "spoon tablet". Spoon tablets are relatively small (up to 6 mm), fast dispersible tablet, designed to be put on a spoon with water directly before intake. They disintegrate within a period of maximum 30 seconds on the spoon and can be taken as a fine suspension. • A dosage form proving dose flexibility and easy to swallow performance is a micro tablet (3-4 mm), containing only a fraction of a single dose. The total single dose is obtained by counting a certain number of micro tablets and taking them at the same time. A low number is easier to count than a large number; counting up to 10 tablets seems to be acceptable.	Comment noted. Section 6.2.1 has been revised. "Spoon tablet" not included as it is covered by dispersible tablets. Term "minitablet" is not a separate dosage form but the concept is discussed under 6.2.1, subsection "Tablets": See above. Effervescent tablets are addressed under 6.2.2 Oral liquid preparations. The Na/K load is not explicitly mentioned in the Guideline but should be considered as indicated in section 9. Excipients in the formulation.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• The suitability of effervescent dosage forms for children should be addressed, especially referring to the high sodium/potassium load of those dosage forms.	
240	11	It will not be a solution very often (suspension/dispersion rather). The same restriction applies as above (233-235) unless the whole dose (volume) is taken at once (and not an aliquot corresponding to the dose) Proposed change: Use 'liquid', Rephrase accordingly	Accepted: The text has been revised accordingly.
240	10	The guidance text states: 'If appropriately justified, the application of a liquid dispersion may be acceptable from birth as well.' – It is unclear why a suspension/dispersion formulation approach needs to be specifically justified, as this dosage form is generally considered suitable for children from birth. Proposed change: Remove 'if appropriately justified'.	Accepted: The text has been revised accordingly.
240	10	"….administered as a solution.":- Some formulations will not form solutions Proposed change: Should this be "….administered as a solution or dispersion."	Comment noted. The text has been revised. Word "solution" was replaced by "liquid".
240-241	19	This appears to be 'specific regulatory guidance'. However, it is unclear what is the evidence for the statement.	Comment noted. Giving this guidance is considered possible without referring to specific evidence.
240-241	22	This appears to be 'specific regulatory guidance'. What is the evidence for the statement?	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
240 -246	1	To our point of view, the pharmaceutical form “pillules”, specific to homeopathy, should be addressed in this Guideline in addition to the pharmaceutical forms “Powders, granules and pellets”’. Pillules consist of spherical solid preparations made of lactose and sucrose, intended to be administered by sublingual or oral route. As a reminder, “Pillules” and “Pillules in single-dose container” are listed in the “Standard terms” (ID number 10231000 and 50041000 respectively). The European Pharmacopeia monographs no. 2079 “Homeopathic pillules, impregnated” and no. 2153 “Pillules for homeopathic preparations” will be in force in April 2012. Pillules are often used in the paediatric population. In infants, it is recommended to dissolve the pillules in water before administration. Therefore, the Draft guideline proposal as regards the use of powders, granules and pellets from birth when administered as a solution thus fully applies to pillules. In older children, pillules can be administered in their solid form. In that case, pillules are allowed to dissolve in the saliva, preferably after being placed under the tongue (i.e. sublingual route). Having regard to the following elements: - no risk of obstruction linked to the shape is expected given the spherical form of pillules,	Not accepted: The comment is not endorsed. The purpose of the guideline is not to deal with every dosage form, but to cover the major ones.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		- the diameter of pillules (2 mm in single-dose container and 4 mm) is smaller than the internal diameter of trachea in newborns (i.e. 7 mm), the risk of aspiration and choking is very low in newborns and is quasi-inexistent for children over 6 months of age. Therefore, the Draft guideline proposal as regards the use of powders, granules and pellets in their solid form from the age of 6 months also applies to pillules. Proposed change: "Powders, granules, pellets and homeopathic pillules may be given to children from birth when administered as a solution (…). If powders, granules, pellets or homeopathic pillules are administered in their solid form, they will normally be considered acceptable from the moment the infant is able to accept solid food. This is usually around 6 months. The risk of aspiration, chocking and where relevant chewing should be considered depending on the target age group, size, shape, quantity (volume) and the type of active substance and dosage form.	
241	10	Could you provide an example for an appropriate justification?	Comment noted. Section 6.2.1 has been revised. The respective text on appropriate justification is deleted.
242-243	21	It is our understanding that the terms "pellets, granules powder" encompass minitablets but this should be mentioned	Comment noted. Section 6.2.1 has been revised. The term

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		explicitly. Proposed change: "If powders, granules, **minitablets** or pellets are administered in their solid form, …"	"minitablet" is not a separate dosage form but the concept is discussed under 6.2.1, subsection "Tablets". It is a solid unit dosage form and complies with the Ph. Eur. monograph "Tablets".
242-243	19	This appears to be 'specific regulatory guidance'. However, it is unclear what is the evidence for the statement.	Comment noted. Giving this guidance is considered possible without referring to specific evidence.
242-243	22	This appears to be 'specific regulatory guidance'. What is the evidence for the statement?	See above.
242-253	8	Pellets are spheronized granules and not yet specified in the Ph. Eur. Small-sized tablets ≤ 2 mm (also called mini-tablets) have recently been demonstrated to be very suitable for young children, starting with 6 months of age (Spomer et al. Arch.Dis.Child. 2012, *accepted*; Klingmann et al. 3rd EuPFI conference, Strasbourg 2011), but are not considered in the present draft. Safe use of small-sized tablets with 3 mm diameter has been demonstrated for children of at least ≥4 years (Thomson & Tuleu, Pediatrics 2009). While there is acceptance data available for these mini-tablets there is no scientific evidence for acceptance of tablets with higher diameters. Required integrity should be considered because biting on or crushing coated dosage forms may result in loss of safety or	Partially accepted: Section 6.2.1 has been revised. Pellets are a veterinary dosage form and have been deleted from this guideline. Small-sized tablets ("mini-tablets") are discussed in section 6.2.1 subsection "Tablets". Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		efficacy. Unpublished data on the acceptance of uncoated and coated 2 mm mini-tablets, in comparison to 3 ml glucose syrup, are available in my group for the QWP/EMA on request. Proposed change: Change to 'If powders, granules/pellets and small-sized (≤ 2 mm) tablets in their solid form,...' and '...depending on the target group, size, shape, required integrity (in case of modified-release dosage forms), quantity...'	
243	11	Comment: solid food Proposed change: Semi solid food, Usually min 6-8 months. There are some cultural aspect to that I guess.	Accepted: Section 6.2.1 has been revised accordingly.
244	5	"six months age" Proposed text: "six months of age"	Accepted: Section 6.2.1 has been revised accordingly.
244	30	The various aspects should be separated Proposed change: The risk of aspiration, choking should be considered depending on the target age group, size, shape, quantity (volume) and the type of the active substance and dosage form. Preventive measures to avoid chewing of gastro-resistant and modified release dosage forms should be elaborated dependent on age.	Partially accepted: The text has been revised accordingly. Revised text: *"The risk of aspiration, choking and where relevant chewing (see section 8) of powders/granules should be discussed in relation to the target age group(s), size, shape and quantity (volume) of the powders/granules and any specific characteristics of the active*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			substance or the formulation."
244	20	If powders, granules and pellets are administered in their solid form, they will usually be spread on food, and the risk of aspiration, etc. will be reduced. Proposed change: Delete "normal sized". The risk of chewing should be considered for products that are enteric coated to avoid degradation by gastric acid, and for modified released products.	Comment noted. The text has been revised. Risk of chewing was added to the text. Revised text: See above.
244 478	15	With regards to oral preparations, mention is made in section 6.2.1 (line 244) and section 8 (line 478) of the "risk of chewing" a tablet. Line 247 onwards discusses the ability of a child to swallow a tablet, and appropriate tablet size, however we don't see any mention of a chewable tablet preparation, which may be of benefit for younger children who cannot swallow tablets whole.	Comment noted. Chewable tablets are not specifically mentioned as beneficial to younger children, but a separate paragraph has been introduced on orodispersible and chewable preparations. Revised text: *"Orodispersible and chewable preparations involve oral solid unit dosage forms that do not need to be swallowed intact and may be swallowed without a liquid. Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.* *If there is a risk associated with direct swallowing of an orodispersible or chewable*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL."
244 -246	5	More guidance would be welcomed as to the risks mentioned per age group for the attributes mentioned.	Comment noted. Section 6.2.1 has been revised. It is unclear what guidance is asked for.
245	10	Please replace size and shape by tablet size and tablet shape in order to be more precise.	Not accepted: Text in this line refers to powder and granulate.
247	20	Proposed change: The tablet size is fundamental to the ability of a child to swallow a tablet whole.	Not accepted: The comment is not endorsed. The addition of "whole" was considered superfluous.
247	10	Since orodispersible tablets and chewable tablets are not supposed to be swallowed, size limitations do not need to be specified for these pharmaceutical forms. <u>Proposed change</u>: "*The tablet size is fundamental to the ability of a child to swallow a tablet. Young children may be able to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or clinical evidence, small tablets [..] will not be considered acceptable for children below the age of 2 years, medium sized tablets […] for children below the age 6 years; large tablets […] for children below the age of 12 years and very large tablets […] for children below the age of 18*	Partially accepted: The text has been revised accordingly. Revised text: *"Where tablets are not intended to be swallowed intact, e.g. (oro)dispersible, chewable or effervescent tablets considerations specific to tablet size and shape are of less importance. However, palatability issues may significantly affect the acceptability of these tablet types."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		years. Since orodispersible, effervescent and chewable tablets are not supposed to be swallowed these limits do not apply to these dosage forms."	
247-248	4	*"The tablet size is fundamental to the ability of a child to swallow a tablet. Young children may be able to accept small tablets, but not large tablets."* It is difficult to assess the right tablet size for each age group. Each patient's needs may be different regardless of age. Proposed change: Discussion should focus on ensuring the tablet can be crushed, split, or dissolved into liquid and under what circumstances this would be allowed - i.e. when entire unit dose will be delivered.	Comment noted. This aspect is discussed in a new subsection on "Handling of oral solid preparations to facilitate administration".
247-253	32	The acceptable tablet size varies between individuals. As long as studies have not clearly shown scientific justification for them, these tablet sizes should only be mentioned as examples and not represent any kind of absolute limits. Other forms should also be mentioned (e.g. very small tablets, so called "mini tablets").	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Regarding very small tablets a new text has been introduced: Revised text: "*Small tablets containing a fraction of the dose may be considered as a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."
247-253	21	There is no indication if multiple tablets are acceptable. Proposed change: (addition of one sentence at end of paragraph): "A single dose may involve multiple tablets."	Comment noted. The test has been revised. The use of multiple tablets for a single dose has been mentioned. Revised text: *"If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
247-253	21	It would be helpful to know on which reference or data the size of the tablets is considered for the different age groups?	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
247-253	17	No mention is made of tablet shape which will influence ease of swallowing. We are unable to comment on the size ranges for age suggested in the document but would agree that generally there is a relationship between the age of the child and the size of tablet they are able to take.	Comment noted. The text has been revised. Shape was added as an aspect that influences the ability of a child to swallow a tablet. However, since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
Lines 247-253	9	The guideline recommends small tablets for children above 2 years of age. It would be helpful if it was clarified if this means what are commonly referred to as 'mini-tablets'. Although, with training, some children can accept tablets at a young age, it may not be appropriate to encourage the development oral tablet medicines for such young age groups. It is noted that Table 3.1 in the reflection paper (EMEA/CHMP/194810/2005) considers the low acceptability of oral tablets in sub-populations below 6 years. Proposed change: The guideline should state that where a solid dosage form is developed for a young age group evidence of its	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Section 6.2 has been revised. The need for alternative strategies has been addressed. Revised text: *"Children may not be able or*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		acceptability should be provided. Furthermore, where a solid dosage form is the only option alternative strategies should be provided should administration as a solid dosage form not be acceptable to some children.	*willing to swallow a specific dosage form and/or paediatric preparation, even when the dosage form/formulation/preparation itself is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms/formulations/preparations to the market (e.g. oral liquid as well as tablets). When not feasible, alternative strategies for intake of the preparation should be discussed (see subsection "Handling of dosage forms to facilitate administration" and section 10)."*
247- 253	25	6.2.1 acceptability No mention is made of tablet shape which will influence ease of swallowing.	Comment noted. The text has been revised. Shape has been added as an aspect that influences the ability of a child to swallow a tablet.
247-253	10	There is no indication whether multiple tablets are acceptable. Proposed change: (addition of one sentence at end of paragraph): "A single dose may involve multiple tablets."	Comment noted. The test has been revised. The use of multiple tablets for a single dose has been mentioned. Revised text: *"If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
247-253	10	It would be helpful to know on which reference or data the size of the tablets is considered for the different age groups.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
247-253	33	The scientific basis for the proposed accepted tablet size in the different age group is not justified.	See above.
247-253	19	This appears to be 'specific regulatory guidance' on acceptable tablet sizes. What is the evidence for this paragraph? We are aware of the work by Tuleu *et al.* using mini-tablets in normal children from 2 years when 50% tolerated the tablets in the youngest age group.	Comment noted. See above.
247-253	22	This appears to be 'specific regulatory guidance' on acceptable tablet sizes. What is the evidence for this paragraph (other than the work by Tuleu *et al* using mini-tablets in normal children from 2 years when 50% tolerated the tablets in the youngest age group)?	See above.
247-253	1	It is difficult to understand which size is suitable for which age. Proposed change: Unless otherwise justified by appropriate	Not accepted: The comment is not endorsed. Since there is limited data available in the literature on the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		studies or clinical evidence, the following sizes of tablets are acceptable for the following age groups: - below the age of 2 years: tablets will not be considered acceptable - 2-5 years: small tablets (i.e. round tablets from 3 to 5 mm diameter)' - 6-11 years: medium sized tablets (i.e. tablets from 5 to 10 mm) - 12-17 years: large tablets (i.e. round tablets from 10 to 12mm or oval/oblong tablets from 10 to 17 mm length) - 18 years or older: very large tablets (i.e. round tablets larger than 12 mm or oval/oblong tablets larger than 17 mm)	influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
247-253	23	It is difficult to understand which size is suitable for which age. Proposed change: • Unless otherwise justified by appropriate studies or clinical evidence, the following sizes of tablets are acceptable for the following age groups: below the age of 2 years: tablets will not be considered acceptable 2-5 years: small tablets (i.e. round tablets from 3 to 5 mm diameter)' 6-11 years: medium sized tablets (i.e. tablets from 5 to 10 mm)	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		12-17 years: large tablets (i.e. round tablets from 10 to 12mm or oval/oblong tablets from 10 to 17 mm length) 18 years or older: very large tablets (i.e. round tablets larger than 12 mm or oval/oblong tablets larger than 17 mm)	
247-253	18	Robust evidence should be provided for the sizes of tablet or capsule that can be accepted by children of different ages. The industry should be asked to demonstrate acceptability of tablets for a given age range and to state how children who do not find the sizes manageable will be accommodated.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Section 6.2 has been revised. The need for alternative strategies has been addressed. Revised text: *"Children may not be able or willing to swallow a specific dosage form and/or paediatric preparation, even when the dosage form/formulation/preparation itself is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms/formulations/preparations to the market (e.g. oral liquid as well as tablets). When not feasible, alternative strategies for intake of the preparation should be discussed*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			(see subsection "Handling of dosage forms to facilitate administration" and section 10)."
247-253	11	Comment: Tablet size Proposed change: Take out size or label carefully e.g. 'indicative size range' as there is no clear clinical evidence.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
247-253	26	The current text regarding appropriate size of a tablet versus the child's age is not very clear. Clear guidance of size versus age would be more useful, for example in the form of a table. The guideline could then state that additional safety / acceptability studies for tablet size would only be required if the size was outside the recommendations.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
247-253	12	It is suggested that this paragraph could be written in a positive rather than negative way, i.e. below the age of two years, no tablets, 2-6 years – small tablets 3-5 millimetre, 6 – 12 years tablets 5-10 millimetre	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Children over 12 years – large tablets could be used. Very large tablets should not be used in children and are intended for adults over the age of 18 years.	applicants has been introduced instead.
247-253 282-285	15	Re: lines 247-253. We believe that it makes sense that smaller children require smaller tablets but think that mentioning specific diameters should be backed up by evidence. Re: lines 282-285. Similarly we would also like to see the evidence for the volumes referred to in this section for dispersible tablets. The FPM believes that the wording in this section should probably discourage crushing of tablets more strongly than it does. Other methods of administration are preferable wherever possible.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups as well as the acceptability of different liquid volumes, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. The crushing of tablets is addressed in a new subsection “Handling of dosage forms to facilitate administration “: Revised text: *“In lack of any alternative age appropriate dosage forms, alternative strategies for administering the oral solid preparations should be considered (e.g. dispersing or crushing tablets, mixing with food or drinks). If such an alternative strategy is proposed, the approach should be validated and clear instructions on the handling(s) to be conducted should be given in the SmPC and*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			PIL. Validation of the handling should include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risks for the person who will handle the dosage form (see section 10).”
247-258	30	The correlation between a certain age and ability to swallow a tablet of a certain size is to strict, and based on an average may mislead development, since shape coating and other things, such as training, disease are relevant. Moreover it certainly does not apply to a dispersible tablet. Proposed change: Large tablets with a size above 10mm usually cause problems to be swallowed by children (below 11years). Young children may need much smaller tablets. For chronic diseases, tablet size acceptability in children may be improved by adequate training techniques. Tablet size acceptability may also be improved by adequate instructions for joint intake with semi solid food. In order to avoid a wide range of strengths, a single dose may involve several small sized tablets.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
248	20	Unless otherwise justified by appropriate studies or clinical evidence, mini tablets (i.e. tablets of 2-3 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, tablets of 5 mm diameter, (width or length whichever longest) will not be considered acceptable for children below the age of 5 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		below the age 10 years; large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years.	applicants has been introduced instead.
248	10	GENERAL COMMENT: Regarding the acceptability of tablet size for various child age groups the opinions within industry differ. Rather than giving here a harmonized position, Efpia provides two sets of comments. As you can read below, there are companies that see the benefit to have some kind of general guidance for tablet size, whereas other companies emphasize that every case is different. Both groups of companies however agree, that hard evidence is lacking and that the text in the guideline should take this into account.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
248 – 253	10	Although we acknowledge that tablet size may be a factor when deciding if a formulation is suitable for a certain age category, the proposed text is far too prescriptive. There is insufficient hard data to support the designations provided in the draft guidance. Several other factors (child training, medical indication) also play a role in determining if a child can swallow a certain tablet. Furthermore, the state-of-the-art of pharmaceutical development is evolving and new developments have shown that minitablets can be given to children with no issue if uncoated (Breitkreutz et al). Reference is also made to an EFPIA position paper on this matter. Proposed change: The tablet size ~~is fundamental to~~ *plays a role in* the ability of a child to swallow a tablet. Young children may	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		be able to accept small tablets, but not large tablets. *Tablet size should be appropriately justified, taking into account e.g. child training, disease state). This may require studies or clinical evidence.* ~~Unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length, whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years) and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years.~~	
248 – 253	5	Please consider including a table containing the information to replace this paragraph. Please consider the inclusion of data on capsule sizes related to age groups.	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.
248–253	10	Information in this section is consistent with the experience of some companies; however the wording regarding appropriate size of tablets could be clarified to avert any potential confusion. The statement could provide enhanced clarity regarding which size of tablet is appropriate for a certain age. <u>Proposed change</u>: Unless otherwise justified by appropriate	Comment noted. Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by

<table>
<tr><th>Line number(s) of the relevant text</th><th>Stakeholder number</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>studies or clinical evidence, tablets for swallowing are not considered acceptable for children below the age of 2 years. Small tablets (i.e. tablets from 3 to 5 mm diameter ... etc.) are considered acceptable only for children 2 years of age and older, medium sized tablets (i.e. tablets from 5 to 10 mm) are considered acceptable only for children 6 years of age and older, large sized tablets (i.e. tablets from 10 to 15 mm) are considered acceptable only for children 12 years of age and older, and very large tablets (i.e. tablets larger than 15 mm) are not considered acceptable for children below the age of 18 years.</td><td>applicants has been introduced instead.</td></tr>
<tr><td>249 – 253</td><td>10</td><td>We would propose to rephrase and reformat this paragraph as follows:

“Unless otherwise justified by appropriate studies or clinical evidence the following tablets as presented in the table below are considered acceptable for swallowing taking into account the age of children”.

We would suggest to implement an additional tablet size for children of 0.5 – 2 years of age based on information gained on the 3rd EuPFI Conference 2011, Strasbourg.
<table><tr><th>Age of children</th><th>Acceptable tablet diameter, width or</th></tr><tr><td>0.5 - 2 years</td><td>2 mm</td></tr><tr><td>≥ 2 years</td><td>≤5 mm</td></tr><tr><td>≥ 6 years</td><td>≤10 mm</td></tr></table></td><td>Comment noted.

Since there is limited data available in the literature on the influence of the size, shape and number of tablets on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead.</td></tr>
</table>

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		≥ 12 years | ≤15 mm	
254	10	This statement is beneficial for companies conducting these studies and should be maintained within the final guideline.	Comment noted. Sentence is maintained with only a minor adjustment.
254	11	Comment: Adequate training as well as acquired tolerance Proposed change: Add acquired tolerance	Comment noted. The proposal for change is not fully understood.
254-255	10	"For chronic diseases, tablet size acceptability in children may be improved by adequate training techniques." It's not clear to me what 'training' means and when we could use this for "larger size" tablets Proposed change: "Training techniques" seem to be out of scope of dosage form pharmaceutical development.	Comment noted. However, the sentence is not intended to imply that this is an expectation for the pharmaceutical development, but rather pointing to a factor that could be taken into consideration when justifying the age appropriateness of a formulation.
254-255	4	*"For chronic diseases, tablet size acceptability in children may be improved by adequate training techniques."* Proposed change: "Training techniques" seem to be out of scope of dosage form pharmaceutical development.	See above.
254-258	10	It could be made more clear that taking multiple small tablets (indicating how many at maximum) is also a measure to improve acceptability *versus* a larger tablet.	Comment noted. Section 6.2.1 has been revised. The use of multiple small tablets has been discussed. Revised text: *"Small tablets containing a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (addition of sentence at end of paragraph): "Multiple small sized tablets per dose should be taken also considered as a measure to improve the acceptability compared to the administration of one single larger tablet."	*fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
254-258	5	It is welcomed that larger tablet sizes may be acceptable in some cases. It should then be clarified in what circumstances these larger tablets are acceptable. The information described is not helpful for the formulation development. It raises questions with regards to the specifications to be set and furthermore the QTPP. Even if training improves the patient acceptability, tablet size may not be evaluated as acceptable during the development, leading to a request to develop another formulation type.	Comment noted. The paragraph is an opening to justify when larger size is acceptable. It is not possible to give further general guidance on that.
254-258	21	It could be made more clear that several small tablets (how many at maximum) is also a measure to improve acceptability versus on larger tablet.	Comment noted. Section 6.2.1 has been revised. The use of multiple small tablets has been discussed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: (addition of sentence at end of paragraph): "Multiple small sized tablets per dose should be taken also into account as a measure to improve the acceptability compared to the administration of one single larger tablet."	Revised text: *"Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
254-258	19	It is unclear in this paragraph as to what is the 'specific regulatory guidance'.	Comment noted.
256-257	19	This statement should be revised to include the effect of foods on bioavailability. Proposed change: Revised sentence to include "providing bioavailability is not affected."	Partially accepted. Mixing with food is addressed in Section 10 where it also is stated that possible effects on the bioavailability should be discussed: Revised text: *"When mixing with food and drinks is proposed the possible effect on biopharmaceutical characteristics of the product should be discussed. Bioavailability*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine."
257-258	10	This statement is beneficial for companies conducting these studies and should be maintained within the final guideline.	Comment noted.
257-258	19	This sentence provides an incomplete picture. While several small sized tablets may facilitate administration in smaller children, a range of strengths is sometimes necessary to reduce the number of tablets for the older patients in order to improve compliance.	Comment noted. Section 6.2.1 has been revised. The use of multiple small tablets has been discussed. Revised text: *"Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as "minitablets"). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s)."*
257-258	23	Comments: • Scored tablets that may be split may also accommodate a	Partially accepted: Section 6.2 has been revised. Scored tablets

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		reduced strength suitable for children. Proposed change: • "In order to avoid a wide range of strengths, a single dose may normally involve several small sized tablets *or tablets with a functional score that may be split for dosing a reduced strength*."	have been addressed. Revised text: "*However, where individually adapted dosing is necessary the number of strengths that are needed to treat patients in the target age group(s) will increase. Alternatives which may provide dosing flexibility for tablets include addition of score lines enabling the administration of a fraction of the full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose (see section 6.2.1).*"
257-258	1	Scored tablets that may be split in 2 equal halves may also accommodate a reduced strength suitable for children. Proposed change: "In order to avoid a wide range of strengths, a single dose may normally involve several small sized tablets *or tablets with a functional score that may be split in 2 equal halves for dosing a reduced strength*."	See above.
257-258	11	What does "In order to avoid a wide range of strengths, a single dose may normally involve several small sized tablets." mean? Proposed change: I am not sure I understand this sentence in the context here.	Comment noted. Section 6.2 has been revised for more clarity. The respective sentence has been deleted. Revised text: See above.
259	30	Is better placed elsewhere.	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: move to General Considerations 6.1	Section 6.2.1 has been revised. The line was kept in this section. However, in the current location, with the new headings introduced, it is considered to fit better.
259-261	19	Acceptability should be confirmed during clinical studies. What about simple rejection; chewing; vomiting? An alternative strategy should be considered for those who cannot manage tablets.	Comment noted. This aspect is discussed in a new subsection on "Handling of oral solid preparations to facilitate administration" in section 6.2.1.
259-261	22	Acceptability should be confirmed during clinical studies. What about simple rejection; chewing; vomiting? An alternative strategy should be considered for those who cannot manage tablets.	See above.
262	10	Might be useful to add a comment about facilitating identification of e.g. different strengths and cross refer to section 9.2	Not accepted: This is not specific to paediatric medicines.
262-264	1	This seems both obvious and a subjective judgement. Proposed change: We apply for deletion of this paragraph.	Comment noted. The text has been revised. This subsection has been deleted but this aspect is addressed in section 6.1. General considerations. Revised text: *"The attractiveness of a paediatric medicine should be carefully balanced between the risk of inadequate patient acceptance and accidental intake, and should be discussed with regards to all aspects*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of the medicine, i.e. the dosage form, the formulation and the primary and any secondary packaging."
263	11	Overly attractive is quite subjective Proposed change: If you want to provide guidance, please clarify.	See above.
263	10	Confectionary comes in many different forms and appearance. Thus "Every effort to differentiate" is a strong statement to use. Proposed change: "Wherever possible tablets should look different to confectionary;"	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
263-264	10	Consider the packaging and device as alternative options to differentiate between medications. Proposed change: Include the recommendations for differentiation in this chapter rather than in section 9.2 and include reference to packaging and device.	Not accepted: This is not specific to paediatric medicines.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
263-264	10	Consider the packaging and device as alternative options to differentiate between medications. Proposed change: Include the recommendations for differentiation in this chapter rather than in section 9.2 and include reference to packaging and device.	Not accepted: This is not specific to paediatric medicines.
263-264	9	Attractive appearance (which includes palatability) of particular formulations is subjective and therefore may be difficult to avoid in different paediatric sub-populations. An alternative view is that these characteristics aid patient compliance. Additionally different strengths of solid oral dosages are differentiated by size/colour/markings to prevent confusion and improve safety. Sugar coatings are often used because the active substance is incompatible with a film-coating process. Proposed change: This section should therefore be revised to include a statement that the above factors may be justifiable under certain circumstances.	Comment noted. The subsection “Appearance” has been deleted and the aspect is mentioned in section 6.1 General considerations and further addressed in section 10 Patient Acceptability: *“Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations: lowering the amount of free active ingredient in solution by choice of a different strength and subsequent change in volume. However, paediatric formulations/preparations must not become too attractive to children (candy like)*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			as this is known to increase the rate of accidental poisoning."

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
263-264	21	Consider the packaging and device as alternative options to differentiate between medications. Proposed change: Include the recommendations for differentiation in this chapter rather than in section 9.2 and include reference to packaging and device.	Not accepted: This is not specific to paediatric medicines.
263-264	26	It should also be recognised that it can be difficult to get children to take medicines, and therefore for oral solid dosage forms it can be a benefit to make them attractive, within sensible limits, for children to take. Child resistant packaging, and placing medicines out of reach and sight of children are the essential safeguards.	Not accepted: Child resistant packaging is not included in the guideline as it equally applies to adult medicines and is subject to national regulation. The subsection “Appearance” has been deleted and the aspect is mentioned in section 6.1 General considerations and further addressed in section 10 Patient Acceptability.: *“Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations: lowering the amount of free active ingredient in solution by choice of a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			different strength and subsequent change in volume. However, paediatric formulations/preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning."
263-264	20	Delete solid. We suggest introducing child resistant packages here, and repeating in section 11.1. Proposed change (if any): Overly attractive oral dosage forms should be avoided. Every effort to differentiate the appearance of oral dosage forms from confectionary should be made, and they should be supplied in child resistant packages/bottles.	Not accepted: Child resistant packaging is not included in the guideline as it equally applies to adult medicines and is subject to national regulation. The text is revised and the subsection "Appearance" has been deleted. The aspect is addressed in section 6.1. General considerations. Revised text: *"The attractiveness of a paediatric medicine should be carefully balanced between the risk of inadequate patient acceptance and accidental intake, and should be discussed with regards to all aspects of the medicine, i.e. the dosage form, the formulation and the primary and any secondary packaging."*
263-264	8	Although I subscribe to the key message of this paragraph, I think it is difficult to judge over this. What are the criteria for distinguishing between 'overly attractive' and 'confectionary'	Not accepted. Message felt important even if the difficulties

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		dosage forms? Proposed change: Delete the paragraph.	mentioned are acknowledged. However, the text is revised and the subsection “appearance” has been deleted. The aspect is addressed in section 6.1. General considerations. Revised text: See above.
263-264	4	**”**Overly attractive oral solid dosage forms should be avoided. Every effort to differentiate the appearance of tablets from confectionary should be made.” Proposed change: This seems to be out of scope of this guidance and more related to a general safety issue common to all medicines.	Comment noted. It is a safety issue common to all medicines but important message. The text is revised and the subsection “appearance” has been deleted. The aspect is addressed in section 6.1. General considerations. Revised text: See above.
265	11	Comment: To not impair the swallowability, the shape of the tablet and its segments should be considered to avoid extra acceptability issue. Proposed change: This should be reflected where appropriate in the document	Comment noted. Section 6.2.1 has been revised. Shape was added as an important aspect for the swallowability.
265	9	Regarding sub-division of tablets it should be specifically stated that where scored tablets are intended to be subdivided, uniformity of weight (and where appropriate content) should be	Not accepted: This is a general requirement to all tablets to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		demonstrated in accordance with the Ph. Eur.	be divided.
265	17	Subdivision of tablets will be necessary to allow for dosing across age ranges. Tablets must therefore be manufactured to allow clean breaks. There is evidence that using a tablet splitter improves accuracy when they are split and therefore suggest that use of tablet splitters should be mentioned in the SmPC. It is also suggested that tablets should be split into a maximum of quarter segments since any division below this leads to increasing inaccuracy of dosing.	Comment noted: Tablets may contain score lines or not and the lines may be suitable for dividing in accurate parts. Where score lines are present it must be clear in the SmPC and PIL if it is suitable for dividing into accurate parts or not. The general test for breakability is based on breaking by hand. There is not to our knowledge evidence that splitters improve accuracy in all cases. It is therefore not possible to promote that in the guideline. This does not preclude an applicant from justifying such a use and thereby being able to include it in the SmPC.
265	25	Subdivision of tablets will be necessary to allow for dosing across age ranges. Tablets must therefore be manufactured to allow clean breaks. Use of tablet splitters should be mentioned in the SPC.	See above.
265	23	Comments to 6.2.1. Sub-division of tablets An underestimated problem of tablets designed for sub-division is the storage of the "remaining part" of the tablet. Two types of problems may occur, a stability problem, since the "remaining part" is no longer protected by the packaging system, and a mixing-up problem when the "remaining part" is kept away from	Comment noted. This is not specific to paediatric medicines.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the original product.	
265-271	7	The use of lines on tablets is not a child-specific issue and should not be adressed in this guideline. If tablets can be divided according SmPC and PIL, the used line is always a scoring line. **Therefore, we see no need for additional regulations and recommend deleting this paragraph.**	Comment noted. Section 6.2.1 has been revised. No additional regulation was introduced. The use of lines on a tablet is considered a valuable tool, particularly in the development of paediatric medicines, to achieve the necessary dosing alternatives.
267	5	Off-label use of the tablet cannot be the responsibility of the Supplier. This text should be removed.	Accepted: The text has been removed and a subsection on “Handling of oral solid preparations to facilitate administration” has been added (see section 6.2.1)
267	11	Comment: either within *or off-label* Proposed change: Remove – use off label cannot be promoted with new paediatric Dosage form which is the reason of this supporting guideline, right?	See above.
267-269	4	*“Therefore, every line on a tablet for paediatric use should result in equal tablet parts according to the criteria of the Ph. Eur. monograph on sub-division of tablets.”* Proposed change: Provide Ph. Eur. chapter and basic requirements - i.e., each half recovers 85-115% of half the label	Not accepted: This comment is not endorsed. Ph. Eur. requirement will not be reprinted in the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		claim.	
268	22	What is the 'specific regulatory guidance'? Proposed change: If there is an intention that the dosage form should be divided, both weight and content uniformity must be demonstrated under 'in use' conditions.	Comment noted. For sub-division of tablets, the Ph. Eur. applies. However, the use of score lines in tablets to obtain fractions of the full tablet dose may not be acceptable in all cases due to the criticality of the dose. For potent medicines (low content of active substance), or for medicines with a narrow therapeutic window, content uniformity also of tablet parts may need to be addressed. The text reflecting score lines has been revised and included in the new subsection "Handling of oral solid preparations to facilitate administration". Revised text (*Handling*): *"Score lines are used to enable the administration of a fraction of a full tablet dose or to facilitate breaking for ease of swallowing. The use of score lines in tablets to obtain fractions of the full tablet dose may not be acceptable in all cases due to the criticality of the dose. The ease of breaking a tablet with score line(s) should be demonstrated."*
268	19	It is unclear in this paragraph as to what is the 'specific regulatory guidance'.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: If there is an intention that the dosage form should be divided, both weight and content uniformity must be demonstrated under 'in use' conditions.	
268-269	12	It is suggested to put the pharmacopeia general monograph reference 0478 at the end of the sentence	Not accepted: The comment is not endorsed. Ph. Eur. requirement will not be reprinted in the guideline.
269	20	It is a widespread practice to divide or crush tablets to facilitate swallowing in children. Proposed change: Thus, it should be made clear in the SmPC and PIL when the scoring line is only meant to facilitate the administration, not to give a part of the dose, ½ or 1/4.	Partially accepted. The text has been revised as part of the subsection on "Handling of oral solid preparations to facilitate administration" (see section 6.2.1) …"
269- 271	10	Is subdivision of a tablet acceptable? Proposed change: Indicate that subdivision of tablets for paediatric use is acceptable, provided breaking the tablet at the breaking line leads to tablet halves fulfilling the Ph. Eur. requirements (each half recovers 85-115% of half the label claim). Provide Ph. Eur. chapter.	Comment noted. The text on subdivision of tablets has been revised and is included in the new subsection "Handling of oral solid preparations to facilitate administration" (see section 6.2.1) Ph. Eur. requirement will not be reprinted in the guideline.
270-271	10	The last sentence in the paragraph is not clear. Proposed change: Insert "…and not to divide the tablet into two	Comment noted. Text has been revised as part of the subsection on "Handling of oral solid preparations to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		halves *for dose adjustment".*	facilitate administration" (see section 6.2.1)
272	5	Crushing tablet is considered (GMP standards) as extemporaneous manufacturing or compounding, it should be deleted from this guideline.	Not accepted: The comment is not endorsed. Crushing of tablets is addressed under the new subsection on "Handling of oral solid preparations to facilitate administration" (see section 6.2.1)
272	17	We agree that it is important to risk-assess using the suggested criteria before a tablet is crushed.	Response to comment not applicable.
272-280	8	Paragraph on crushing tablets is incomplete. Tablets cannot only be crushed, but also broken into pieces, dissolved and dispersed. Modified-release properties are not reflected. Proposed change: 'Manipulation of tablets Unless otherwise justified, manipulation of a uncoated tablet prior to administration...' * the possibility to market the granules or powders for tabletting in a single-dose sachet or capsule that should be opened prior to use or to prepare mini-tablets out of the same granules and powders; .... * the risk for the care-taker who should manipulate the tablets.	Partially accepted: The text has been revised in the new subsection "Handling of oral solid preparations to facilitate administration" (see section 6.2.1).
272-280	10	Should this also include a reference to potentially a "vehicle" being used in the administration e.g. crushing tablets and	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		mixing with milk?	The text has been revised and mixing with food and beverages are addressed in the new subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1) and in section 10.
272-280	1	In this chapter the information on those cases where it is absolutely forbidden to crush tablets is missing. For example: coated tablets and any modified release formulations.	Comment noted. The revised text in subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1) states that *“Where appropriately justified and validated, subdivision or crushing of a tablet prior to administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact”.*
272-280	9	Whilst it is accepted crushing tablets is a common method of administering oral tablet formulations to children, its practice is often controversial, particularly where modified release products are concerned or where crushing is used as a method of providing less than a unit dose. There is no Ph.Eur monograph for crushable tablets. The quality requirements for a tablet designed to be crushed are not specified therefore if the guideline is going to acknowledge this practice then the characteristics of the dosage form should be specified and where possible instructions and restrictions on crushing provided by licence holders. Furthermore, if a tablet formulation	Comment noted. Crushing of tablets is addressed in the new subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		is the only formulation offered, then development pharmaceutics should consider crushing and addition to food or dispersion in liquid. It would be expected that applicants would justify the crushing of tablets with respect to any affect this might have on the products pharmacokinetics (which could influence the safety and efficacy of the product).	
272-280	6	Chapter on Crushing Tablets In this chapter the information on those cases where it is absolutely forbidden to crush tablets is missing. For example: coated tablets or other retards formulations.	Comment noted. The revised text in subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1) states that *“Where appropriately justified and validated, subdivision or crushing of a tablet prior to administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact.”*
273	20	Crushing of a tablet prior to administration should not be the standard procedure to treat children in the indicated target age groups, but may be acceptable. Considerations should at least include: the possibility to market the (tablet) granules in a single dose sachet or a capsule that should be opened prior to use; the impact of crushing on palatability;	Partially accepted: The text has been revised and crushing of tablets is addressed in the subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1)

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		patient acceptance; bio-availability and the risk for the person who should be crushing the tablets.	
273-280	19	It is unclear in this paragraph as to what is the 'specific regulatory guidance'. We question whether the section on “crushing tablets” should be included in a regulatory guidance document considering the negative effects of crushing tablets and that the manipulation of an authorised medicine will normally not be considered acceptable for marketing authorisation. If the inclusion of this section is deemed necessary, it should be stated that any such manipulations must be validated.	Partially accepted: Crushing tablets is addressed under the subsection on “Handling of oral solid preparations to facilitate administration” (see section 6.2.1). Revised text: *“Where appropriately justified and validated, subdivision or crushing of a tablet prior to administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact.”*
275	17	Where products are formulated to allow opening of capsules to access contents prior to administration a suitable range of strengths will be necessary to allow dosing across the indicated age ranges without introducing the risk of errors from attempting to use only a portion of the contents.	Comment noted. Opening of capsules and taking part of the content is not encouraged in the guideline.
275	25	Where products are formulated to allow opening of capsules to access contents prior to administration a suitable range of strengths will be necessary to allow dosing across the indicated age ranges without introducing the risk of errors from attempting to use only a portion of the contents.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
275,276, 280,300-308	30	The formulation as capsules is per se not intended to be opened. From a quality point of view it is not feasible to measure a reproducible amount of either powder of liquid from a capsule as during opening of the capsule an unidentified amount of the content is lost due to spilling and/or adsorption onto the capsule. To address this capsules nowadays have a closure system and cannot be opened. These concerns should be addressed and definitively capsules with a closure system excepted from this approach. Proposed Changes: Skip	Not accepted: The comment is not endorsed. Opening of capsules and taking part of the content is not encouraged in the guideline. However, it is not agreed to remove all references to opening of capsules as it may be a strategy for intake when a child has difficulties to swallow the intact capsule. A revised text regarding opening of capsules is included in the new subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1).
277	10	Suggest to add the following for completeness: Proposed change: - the impact of crushing on palatability; **and dosing accuracy**	Partially accepted: The text has been revised and moved to a new subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1)
277-278	10	• “the impact of crushing on palatability; • patient acceptance;” Proposed change: • the impact of crushing on patient acceptance (e.g. palatability);	Partially accepted: The text has been revised and moved to a new subsection “Handling of oral solid preparations to facilitate administration” (see section 6.2.1): *“In lack of any alternative age appropriate dosage forms, alternative strategies for administering the oral solid preparations should be considered (e.g. dispersing or crushing tablets, mixing with food or drinks). If*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			such an alternative strategy is proposed, the approach should be validated and clear instructions on the handling(s) to be conducted should be given in the SmPC and PIL. Validation of the handling should include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risks for the person who will handle the dosage form (see section 10).”
277-278	4	• *“the impact of crushing on palatability;* • *patient acceptance;”* Proposed change: Are these two bullets the same the information?	Comment noted. See above.
278, 451, 707	11	Comment: Bio-availability Proposed change: bioavailability	Accepted: The text has been revised. Bio-availability was replaced by bioavailability.
279	4	There is a need to ensure that crushing tablets does not impact the absorption process which in turn impacts the availability to the circulation, (‘bio-availability’) Proposed change: Focus on not altering bio-performance, not just bio-availability.	Not accepted: The comment is not endorsed. It is considered that its ultimately the bioavailability that is of interest, and there is little arguments in the comment for using another vocabulary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
280	10	"the risk for the person who should be crushing the tablets." Proposed change: Add: "e.g. the powder is an irritant" so the statement reads: "the risk for the person who should be crushing the tablets **(e.g. the powder is an irritant).**"	Not accepted: The comment is not endorsed. The text is slightly revised and moved to a new subsection "Handling of oral solid preparations to facilitate administration" but without the proposed addition which is only one aspect (see section 6.2.1): Revised text: *"If such an alternative strategy is proposed, the approach should be validated and clear instructions on the handling(s) to be conducted should be given in the SmPC and PIL. Validation of the handling should include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risks for the person who will handle the dosage form (see section 10)."*
280	10	There is no mention of the reproducibility and ease of crushing tablets. Proposed change: Suggest adding the following bullet after line 280: "the reproducibility and ease of crushing tablets per standard pharmacy practices."	Comment noted. A revised text in a new subsection "Handling of oral solid preparations to facilitate administration" discuss in more general terms different kind of manipulations of dosage forms (see 6.2.1).
280	4	"the risk for the person who should be crushing the tablets."	Not accepted: The comment is not endorsed. The text is

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Add: “e.g. the powder is an irritant” so the statement reads: “the risk for the person who should be crushing the tablets **(e.g. the powder is an irritant).**”	slightly revised and moved to a new subsection “Handling of oral solid preparations to facilitate administration” but without the proposed addition which is only one aspect (see section 6.2.1): Revised text: *“If such an alternative strategy is proposed, the approach should be validated and clear instructions on the handling(s) to be conducted should be given in the SmPC and PIL. Validation of the handling should include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risks for the person who will handle the dosage form (see section 10).”*
280	4	There is no mention of the reproducibility and ease of crushing tablets. Proposed change: Suggest adding the following bullet after line 280: “the reproducibility and ease of crushing tablets per standard pharmacy practices.”	Comment noted. A revised text in a new subsection “Handling of oral solid preparations to facilitate administration” discuss in more general terms different kind of manipulations of dosage forms (see 6.2.1).
280	30	Proposed change: addition of a line saying: The risk of loosing activity should be taken into consideration and recommendations made based on data.	Not accepted: The comment is not endorsed. This is covered by the need to address bioavailability which is mentioned in the new subsection on “Handling

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of oral solid preparations to facilitate administration" which has replaced the commented text (see section 6.2.1).
281	11	Dispersible tablets is mentioned but not soluble tablets despite being a Pharmacopeial (Ph. Eur.) category. Similarly effervescent tablets are not mentioned anywhere in the guideline. Proposed change: Add comments on soluble and effervescent tablets: points to consider **Cf WHO Working document QAS/08.257/Rev.3** *Effervescent dosage forms* Effervescent dosage forms are tablets, granules or powders that are dissolved in water prior to administration. The use of these dosage forms usually requires a relatively large volume of water, the intake of which may be problematic for children. It is helpful when an indication of the minimum volume of water is labelled. Furthermore, the label should instruct not to drink the solution before effervescence has subsided in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to moisture and humidity during manufacture, packaging and storage. Drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium,	Comment noted. Subsection moved to section 6.2.2 "Oral liquid preparations" where a new sub-section heading covers effervescent, soluble and dispersible preparations. Revised sub-section: *"Effervescent, soluble and dispersible preparations* *These preparations are intended to be dissolved or dispersed in liquid prior to administration. The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.* *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		which may make them unsuitable for patients with renal insufficiency. I would add here the rather large volumes usually needed can be a problem, especially if there is palatability issue. *Dispersible and soluble tablets* Dispersible and soluble tablets are intended for use in the same way as effervescent tablets. The advantage is that problems with hydrogen carbonate, potassium and sodium are avoided. For the convenience of the users, the formulations shall disintegrate or dissolve within a short time when added to water. Dispersible and soluble tablets are flexible dosage forms, the formulation of which may be suited for several water-soluble APIs, cf section 3a. 3(a) Dosage forms that, in general, are likely to prove most suitable for global use, including for developing countries, and which should be prioritized, are flexible solid dosage forms such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for various APIs. They may not be suitable for medicines requiring a precise dose titration.	*information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing.* *Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."*
281	8	See above (231-232). Proposed change: 'Effervescent, soluble and dispersible tablets'.	Accepted: Subsection moved to section 6.2.2 "Oral liquid preparations" where a new heading covers effervescent, soluble and dispersible

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			preparations. See above for revised sub-section.
281, 286	30	Add to dispersible tablets effervescent and soluble tablets and refer to oral suspensions for details. How children could directly swallow a tablet which is only used to prepare a suspension is not understood. Only in case of a problem with swallowing a dispersible tablet this needs to be addressed. Unintended use should be discouraged.	Comment noted. Subsection moved to section 6.2.2 “Oral liquid preparations” where a new sub-section heading covers effervescent, soluble and dispersible preparations. In this section a new wording is introduced on the potential risks with intake in other ways than the intended. For revised sub-section, see above.
281-290	5	This paragraph is not in line with the volume for below 4 years (20 ml) described in line 333-335. The volume is too high compared to the liquid formulation (5 ml) description for the age group below and over the age of 4 years. Please align both sections.	Comment noted. References to specific volume *vs* age have been deleted both for oral liquid and dispersible preparations and the text revised. Revised text (oral liquid preparations): “*The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking”.* Revised text (sub-section Effervescent, soluble and dispersible preparations): “*The*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content. *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s).”*
281-290	1	As soluble tablets are marketed as well, it is recommended to add an additional paragraph on this type of tablet or change the title and contents of the section on dispersible tablets accordingly. Proposed change: Dispersible/soluble tablets. Add “dissolution” and “dissolved” in connection with “dispersion” and “dispersed”.	Accepted: Sub-section moved to section 6.2.2 “Oral liquid preparations” where a new sub-section heading covers effervescent, soluble and dispersible preparations.
282-285	9	With regard to volumes of liquids for dispersible tablets: a recommendation to state a minimum volume, as stated in the Reflection paper would be more useful as small volumes are better tolerated than large volumes especially if taste masking is poor.	Comment noted. References to specific volume *vs* age have been deleted both for oral liquid and dispersible preparations and the text revised. Revised text (oral liquid preparations): *“The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			preparation may allow better taste masking." Revised text (sub-section Effervescent, soluble and dispersible preparations): *"The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.* *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s)."*
282-285 333-335	21	The proposed maximum volume for oral liquids (5 ml) is restrictive and deviates also from the proposed maximum volume for dispersing tablets (20 ml). We identify difficulties how the proposed maximum volumes for oral liquids can be achieved with lower concentrated solutions. Additional flexibility with the maximum volume to be administered needs to be considered especially if the child is over weight and the dosing is weight based. In this situation, the child still may not be able to swallow a given tablet size and will need the oral liquid. Proposed change (lines 333- 335): "…, the maximum recommended single dosing volume is **20** ml for children aged below 4 years and **50** ml for children aged above 4 years."	Comment noted. See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
282-285	22	Where is the evidence for these volumes? In my experience they are far too big.	Comment noted. See above.
282-285	20	The minimum volume for dispersion should be described and justified in relation to the indicated target age group(s). For well palatable solutions, the volume should not exceed 5 ml including any rinsing where relevant for children below the age of 4, and 10 ml including any rinsing where relevant for children from 4 years. The minimum volume for dispersion should also be stated in the SmPC and PIL.	Comment noted. See above.
282-285	19	Where is the evidence for these volumes? In our experience, these volumes are far too big.	Comment noted. See above.
283	10	Dispersion volumes for dispersible tablets are described as not exceeding 20 ml including rinsings for children below the age of 4, and 50 ml for children from 4 years. This is not consistent with the recommendations in lines 333-335, where for oral solutions and dispersions, the maximum recommended single dose volume is 5 ml for children below 4, and 10 ml for children between 4 and 12 years. It is difficult to understand why it is more tolerate to swallow dispersible tablet in a solvent compared to oral liquid solutions and dispersions. Proposed change: Please provide a consistent recommendation for acceptable dose volumes. These recommendations should, in addition to age, also take into account palatability of the liquid.	Comment noted. See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
283	1	The palatability of a formulation is subjective. Limiting the dosing volume to 20 ml (for children <4 years of age) and 50 ml (for children >4 years of age) is understandable, but this should not be directly linked to the palatability of the formulation. Proposed change: Remove the wording “well palatable” from line 283.	Comment noted. See above.
283-285 333-335	32	The volumes should be scientifically justified. Also the volumes differ between the chapters: “For well palatable solutions, the volume should not exceed 20 ml including any rinsing where relevant for children below the age of 4, and 50 ml including any rinsing where relevant for children from 4 years.” “For oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years.” Proposed change: The numbers should be given as examples instead of absolute limits.	Comment noted. See above.
283-285	18	It is unclear where the recommendation of 20ml and 50 ml has come from.	Comment noted. See above.
283-290	11	For well palatable solutions, the volume should 20ml<4yo	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		50ml>5yo. Based on what? Proposed change: There is a need to base recommendations about dosage forms on clinical evidence.	See above.
285	10	Define/explain SmPC and PIL in the definition list	Not accepted: The comment is not endorsed. SmPC and PIL are established acronyms and therefore not included in the list of definitions. They are however written out when used for the first time in the guideline.
286-290	5	"Parent may wish to administer…the same time, children may not swallow…" It is proposed to remove the first part of the sentence. Although parents may wish to administer medicinal products in a different way, not all possible options can be considered by the Applicant/MAA holder. In fact, ways of administration that involve manipulation of the medicinal product should not be encouraged. In case parents wish to administer a drug product in a different way than described in the SmPC or PIL this is considered to be the responsibility of the parents. Even if behavioural aspect of children can be taken into account to a certain extent – in line with age appropriateness - , behavioural aspects of parents cannot be taken into account. It would be desirable to have standardized wording to be included in the SmPC and PIL.	Not accepted: The comment is not endorsed. Standardized wordings for the SmPC and PIL are not in the remit of this guideline. The text has been revised under sub-sections of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and dispersible preparations'). Revised text (Orodispersible and chewable preparations): *"Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed text: "Children may not directly swallow any given tablet, but decide to keep the tablet in their mouth…"	*If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.* *The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended."* Revised text (Effervescent, soluble and dispersible preparations): *"Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."*
286-290 292-296	10	Dispersible tablets and orodispersible tablets: Sentence suggests that companies should study all types of inappropriate use. This is not feasible.	Comment noted. See above.
286-290 295-296 478-479	10	Although discussing the impact of alternative ways of administration on safety and efficacy of a medicine can be attempted, a scientific evaluation may not be possible since in most cases no BA or clinical data will be available.	Comment noted. The text has been re-worded under sub-sections of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			dispersible preparations'). Revised text (Orodispersible and chewable preparations): *"Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.* *If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.* *The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended."* Revised text (Effervescent, soluble and dispersible preparations): "*Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The text for modified release preparations has been slightly revised. Revised text (Modified Release Preparations): "*For oral solid modified release preparations, the risk of chewing is to be considered when selecting this dosage form for further development. The risk of chewing and its impact on the efficacy and safety of the medicinal product should therefore be discussed and it should not result in a serious risk to patients."*
287-290	10	Sentence starting with "At the same time…" does not refer to dispersible tablets only, but to "any given" tablets. Therefore it should not be placed in a paragraph on dispersible tablets. The following sentence starting with "The impact of these two alternative …" also refers to incorrect use of "any given tablets", which is viewed problematic (see proposed change listed below). Proposed change: Remove the two sentences outlined above. Please see general comments on unintended and incorrect use of medicines.	Comment noted. The text has been revised under sub-sections of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and dispersible preparations'). Revised text (Orodispersible and chewable preparations): *"Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.* *If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			may not be dispersed prior to administration, this should be stated in the SmPC and PIL. *The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended."* Revised text (Effervescent, soluble and dispersible preparations): *"Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."*
289-290 295-296	11	*The impact of these XX alternative administration methods on the safety and efficacy of the medicine should be discussed. The issue should be clarified to the users in the SmPC and PIL.* Proposed change: I think it should be specified in SMPc only if there is a problem (by not using the dosage form how it has licensed for) because it might push patient to use them otherwise if in SMPc, which in turn should be backed up by clinical trials (the reason d'être of the regulation), creating an unnecessary (if not un feasible) burden to applicants and patients enrolled	Comment noted. The text has been revised under sub-sections of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and dispersible preparations'). See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
291	1	As further oral dosage forms designed to be administered directly into the mouth have been developed recently, it does make sense to mention these recent developments here and describe them accordingly. Proposed change: Orodispersible films/tablets and oro lyophilisates.	Comment noted. The sub-heading has been revised to cover all orodispersible and chewable preparations.
291	8	Orodispersible drug formulations may not always be tablets, but also granules/pellets or films. Proposed change: 'Orodispersible formulations'.	See above.
291	19	Consider inclusion of orodispersible film.	See above.
291-298	10	***Orodispersible tablet*** The wording / intention of the text is not clear. While on the one hand the possible use of orodispersible tablets as dispersible tablets is suggested as an option for administration and needs to be discussed, on the other hand it is also requested that the SmPC should clarify whether or not the orodispersible tablet may be used as a dispersible tablet. In the last sentence (lines 297-298), it is requested that direct swallowing should not result in any safety or efficacy problems - in other words, does this mean, that regardless of any limitations given in the SmPC, any orodispersible tablet should	Comment noted. The text has been revised for better clarity. The text has been re-worded under sub-sections of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and dispersible preparations'). Revised text (Orodispersible and chewable preparations): *"Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		also allow (1) the use as a dispersible tablet, and (2) direct swallowing? And what would be the consequence, if the SmPC does not allow use as a dispersible tablet or direct swallowing? <u>Proposed change</u>: Please provide a clarification in the guideline.	*be swallowed without dispersion in the mouth.* *If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.* *The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended."* Revised text <u>(Effervescent, soluble and dispersible preparations)</u>: *"Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."*
291-298	10	Suggest mention the potential need for taste-masking of the active/addition of flavours for ODTs. Also, if taste-masking is required, consider impact on bioavailability.	Comment noted. Palatability as a factor of acceptability of tablets that do not need to be taken intact has been added under general sub-section on tablets. See also discussion in Section 10. Added text (Tablets): *"Where tablets are not*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			intended to be swallowed intact, e.g. (oro)dispersible, or effervescent tablets considerations specific to tablet size and shape are of less importance. However, palatability issues may significantly affect acceptability of this tablet types."
291-298	10	There is no mention of powders, granules or pellets. It would be helpful if a paragraph on these could be added (especially as they are mentioned in the title for this section). Proposed change: Paragraph should also include powders, granules and pellets in subheadings with some details given about methods of administration	Comment noted. The text has been revised. Heading and text now covers all orodispersible (and chewable) preparations.
292	30	Swallowing an orodispersible tablet only causes problems, when resorption in the oral cavitiy is required for faster onset of action or bioavailability Proposed change: Add in line 295 When resorption in the oral cavitiy is required for faster onset of action or to ensure bioavailability, measures need to be taken to avoid swallowing of the intact tablet.	Not accepted. The comment is not endorsed. Orodispersible preparations are by definition intended for oral administration.
297	5	"The direct swallowing of … problems" These risks do not only apply to paediatric medicines, therefore it would be desirable to have standardized wording to be included in the SmPC and PIL.	Partially accepted: Standardized wordings for the SmPC and PIL are not within the remit of this guideline. The text has been revised under sub-sections

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed text: "The effect of direct swallowing of an orodispersible tablet without prior dispersion in the mouth should be evaluated with regards to safety and efficacy"	of 'Orodispersible and chewable preparations' (and 'Effervescent, soluble and dispersible preparations'). Revised text (Orodispersible and chewable preparations): *"Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.* *If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.* *The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended.* *For chewable tablets the risk of chocking should be carefully considered as the child may not be able to chew the tablet correctly."* Revised text (Effervescent, soluble and dispersible preparations): *"Similar to considerations for orodispersible and chewable preparations, the potential risks when*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL."
299	10	Chewable capsules are also available – suggest add to this section.	Comment noted. Chewable capsules are covered by sub-section " Orodispersible and chewable preparations'.
299	20	6.2.2. Capsules Acceptable capsules sizes for the different age groups should be given in the same way as for tablets, see comments for 6.2.1. "Smaller" hard capsules, - how small? This is not precise enough.	Comment noted. Specific references on size vs age for acceptability of tablets or capsules to be taken intact have been deleted. Revised text for capsules: *"As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."*
299 - 308	33	The handling of open soft capsules and the correct dosing of the content seems very difficult for caregivers and patients. If the content of hard capsules are taken with food compatibility test between the powder/granules/pellets and the food should be performed. The suitable food should be listed in the SmPC and	Comment noted. The opening of soft capsules is not generally encouraged. Therefore soft capsules are not mentioned when opening of capsules are

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		PIL.	discussed. This does not prohibit an applicant with a soft capsule designed for to be opened to propose and justify such a dosage form. The text on capsules has been revised.
299-312	9	The paragraph should highlight the flexibility of capsule dosage forms. It may be possible for some children aged six years to take small capsules, but evidence on how to administer the contents as a powder, solution or mixed with food should be provided for those children incapable of taking whole capsule formulations. Oropharyngeal adhesion and choking should be considered when developing paediatric capsule formulations.	Comment noted. The points related to opening of capsules and the need to validate the procedure are addressed under capsules and in the sub-section on 'Handling of solid oral preparations to facilitate administration' (see section 6.2.1). Revised text (Capsules): *"Capsules are usually intended to be taken intact. Where appropriately justified, hard capsules may also be opened and their contents taken as such provided that the feasibility of opening the capsule and removing the contents from the capsules have been demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as stated for oral powders or granules, where relevant. The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group(s) (see subsection "Handling of dosage forms to facilitate administration")."* Added text (Handling): *"Where appropriately*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			justified and validated, subdivision or crushing of a tablet prior to administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact. It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. In addition, capsules may be opened and their contents given as such. Subdivided/crushed tablets or the contents of a capsule may be given with food or drinks (see Section 10). It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. The suitability of the handling(s), including the compatibility with any proposed vehicle, should be demonstrated."
299-312	10	The way section 6.2.2 is written implies that manipulation (opening and emptying) of capsules prior to administration is a general/ common way of use, and swallowing of the intact form is one possible exception or rather seen as an exception. It should be made clear that capsules are usually designed to be swallowed **intact**. This is also foreseen by the Pharmacopeia. Opening and emptying of standard shape soft capsules (oval - designed to be swallowed) should not be suggested as an option. Opening of soft capsules, which have a special design (tear off/twist off part) that allows easier opening may be considered	Comment noted. The opening of soft capsules is not generally encouraged. Therefore soft capsules are not mentioned when opening of capsules are discussed. This does not prohibit an applicant with a soft capsule designed for to be opened to propose and justify such a dosage form. The text on capsules has been revised. A section on "Handling of solid oral preparations to facilitate administration" has been added. A line on"… any risk for the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(consider accuracy of emptying / dosing). However, typical oval-shaped soft capsules are difficult to open / to empty and might require cutting by e.g. a knife and rinsing (of the often non-water miscible, lipidic content). Accordingly, accurate dosing might be difficult to achieve in those cases. Proposed change: "If a soft capsule is to be opened prior to use, its contents should meet the same requirements as oral liquid preparations where relevant. Instructions for removal of the entire amount or small amounts of liquid from a soft capsule and then subsequently administration by the oral route can result in dosing errors and this approach is normally not considered acceptable. **In addition, it is important to assure that the operation/ manipulation from opening capsules does not pose any health hazard when handled by health professionals or care givers, with appropriate information to be included in the Product Information (SmPC, PL)".**	person who will handle the dosage form …" was added to this section.
299-312	11	Capsules dimensions is here conveniently kept out. What does 'smaller' (311) refer to what size? 00 is smaller than 000 – yet big! Disagree re the statement Hard capsules may be taken intact. It seems that or sprinkled onto a an appropriate vehicle is missing (with the usual if appropriately justified of course)– there are such successful peads products! Proposed change: There is a need to base recommendations on	Comment noted. Specific references on size vs age for acceptability of tablets or capsules to be taken intact have been deleted. Sprinkle capsule are covered by text on opening of hard capsules. Revised text for capsules: *"As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		clinical evidence. Add sprinkle capsules!	*be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."* The points related to opening of capsules are addressed under capsules, in part in the sub-section on 'Handing of solid oral preparations to facilitate administration' (see section 6.2.1). Revised text (Capsules): *"Capsules are usually intended to be taken intact. Where appropriately justified, hard capsules may also be opened and their contents taken as such provided that the feasibility of opening the capsule and removing the contents from the capsules have been demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as stated for oral powders or granules, where relevant. The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group(s) (see subsection "Handling of dosage forms to facilitate administration")."* Added text (Handling of oral solid preparations to facilitate administration): *"Where appropriately justified and validated, subdivision or crushing of a tablet prior to*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact. It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. In addition, capsules may be opened and their contents given as such. Subdivided/crushed tablets or the contents of a capsule may be given with food or drinks (see Section 10). It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. The suitability of the handling(s), including the compatibility with any proposed vehicle, should be demonstrated."
300	10	Is opening capsules advocated by the EMA? What data would be required to justify this approach?	Comment noted. The text has been revised. Opening of capsules and taking part of the content is not encouraged in the guideline. References to opening of capsules is included as it may be a strategy for intake when a child has difficulties to swallow the intact capsule. A revised text regarding opening of capsules is included in the new subsection "Handling of oral solid preparations to facilitate administration" (see section 6.2.1).The points related to opening of capsules and the need to validate the procedure are addressed in part under

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			capsules, in part in the sub-section on 'Handing of solid oral preparations to facilitate administration' (see section 6.2.1). Revised text: See above.
300	8	Capsules are not intended to be opened by the child, but the care-taker. Proposed change: '...They may also be opened by the care-taker ...'.	Not accepted. The comment is not endorsed. This does not apply to all age groups.
300-302	5	For improved readability alternative text is suggested: "Hard and soft capsules should be taken intact. In the event that they are opened (only if described in the SmPC and PIL) and their contents taken, the risks should be discussed for all the indicated target age group(s)."	Partially accepted. This is addressed in the revised section "Capsules" and in the new subsection "Handling of oral solid preparations to facilitate administration" (see section 6.2.1) Revised text (Capsules): *"Hard and soft capsules are usually intended to be taken intact. Where appropriately justified, they may also be opened and their contents taken as such provided that the feasibility of opening the capsules has been validated (see subsection "Handling of oral solid preparations to facilitate administration"). The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group(s)."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Added text (Handling of oral solid preparations to facilitate administration): *"Where appropriately justified and validated, opening of a capsule or subdivision or crushing of a tablet prior to administration may also be an alternative strategy for those children that have difficulties to take a tablet or capsule intact. Subdivided/crushed tablets or capsule contents may be given with food or beverages (see Section 10). It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. The suitability of the handling procedure, crushing and/or dispersing/dissolving tablets, including the compatibility with any proposed vehicle, must be demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as stated for oral powders or granules where relevant."*
303-305	5	The division of capsules into solid oral unit dosage forms as given in lines 223 – 225 should include either an explanation on the hybrid formulation type (e.g., hard capsule to be opened to use the contents) or paragraph 303 – 305 should be omitted altogether. Contents of hard capsule (i.e. powder) and soft capsule (i.e. semi-liquid) are usually only developed with the intention that they will not be taken separately. It is unreasonable to require	Comment noted. This has been addressed in the revised section "Capsules" and in the new subsection "Handling of oral solid preparations to facilitate administration". See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		that powder/granules and liquid should meet all various Pharmacopoeias and directives/guidelines at all times i.e. even when the supplier provides appropriate description of the administration procedure not to open the capsules. It should be understood that opening of capsules is considered off-label use (unless otherwise stated in the SmPC or PIL).	
304	8	See above (242-253). Proposed change: '...stated for powders, pellets/granules or small-sized tablets'.	Comment noted. The text has been revised. Pellets are a veterinary dosage form and have been be deleted from this guideline. Small-sized tablets ("mini-tablets") are discussed in section 6.2.1 subsection "Tablets".
306-308	4	*"Instructions for removal of small amounts of liquid from a soft capsule and then subsequently administration by the oral route can result in dosing errors and this approach is normally not considered acceptable."* Proposed change: Please provide rationale or explain concern for this point. Can it be appropriate to aliquot if the content is a solution or 100% drug?	Comment noted. The text has been revised. Opening of soft capsules is not generally encouraged. Therefore soft capsules are not specifically mentioned when opening of capsules are discussed.
309-311	10	"Only if capsules are to be taken intact, the dimensions of the capsule should be justified in relation to the target age group(s), child health conditions, inter patient differences and the risks associated to accidental choking or chewing."	Comment noted. The text has been revised and inter-patient differences deleted. Revised text: *"Where capsules are to be taken*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider adding more guidance to discuss how to determine and deal with “inter-patient differences”.	*intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets.*
309-311	4	*“Only if capsules are to be taken intact, the dimensions of the capsule should be justified in relation to the target age group(s), child health conditions, inter patient differences and the risks associated to accidental choking or chewing.”* Proposed change: Consider adding more guidance to discuss how to determine “inter-patient differences” in drug development.	See above.
309-312	10	There is no recommendation for children younger than 6 years with regards to the use of capsules. There is also no indication whether multiple capsules are acceptable. Proposed change: A single dose may involve multiple capsules.	Comment noted. With regard to the proposal it is considered unnecessary to state that one dose can involve multiple capsules. The text has been revised. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Revised text: *“As for tablets, limited data in the literature are available regarding*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."
309-312	10	The guidance states that capsule dimensions should be justified in relation to the target age group, child health conditions, inter patient differences and risks associated with accidental choking or chewing. It would be helpful to provide guidance on which capsule sizes are acceptable for the different age groups and health conditions. The same applies for the comment in line 312 – 'smaller capsules are only considered acceptable from the age of 6 years' – please provide a definition of 'smaller capsules'. <u>Proposed change</u>: Clarify acceptable capsule sizes in relation to age groups.	Comment noted. The text has been revised. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Revised text: *"As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."*
309-312	21	There is no recommendation for children younger than 6 years with regards to the use of capsules. There is also no indication if multiple capsules are acceptable. A single dose may involve multiple capsules.	Comment noted. With regard to the proposal it is considered unnecessary to state that one dose can involve multiple capsules.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The text has been revised. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Revised text: *"As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."*
309-312	8	I cannot see any difference between the swallowing of intact capsules and tablets. I do not know any scientific evidence for the provided age of 6 years. Proposed change: This paragraph should be adapted to 6.2.1	Comment noted. The text has been revised. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Revised text: *"As for tablets, limited data in the literature are available regarding*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."
311	5	"the smaller hard capsules": please include size specification e.g., size 3, 4 and 5.	Comment noted. The text has been revised. Since there is limited data available in the literature on the influence of the size, shape and number of tablets and capsules on acceptability in different age groups, detailed guidance have been removed from the guideline. A more general requirement for justifications by applicants has been introduced instead. Revised text: *"As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets."*
311-312	10	"Normally, the smaller hard capsules are only considered acceptable from the age of 6 years if to be taken intact." <u>Proposed change</u>: Define "small capsules."	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
311-312	1	Delete sentence “Normally, the smaller hard capsules….” And replace by “Size restrictions as described for tablets in section 6.2.1 apply as well.”	See above.
311-312	22	Where is the evidence that ‘smaller’ capsules are acceptable from 6 years of age? What is a ‘smaller’ capsule?	See above.
311-312	19	Where is the evidence that ‘smaller’ capsules are acceptable from 6 years of age? What is considered as ‘smaller’ capsule?	See above.
311-312	23	Delete sentence “Normally, the smaller hard capsules….” And replace by “Size restrictions as described for tablets in section 6.2.1 apply as well.”	See above.
311-312	4	*“Normally, the smaller hard capsules are only considered acceptable from the age of 6 years if to be taken intact.”* Proposed change: Define “smaller capsules.”	See above.
312	17	We are unable to comment on the statement that hard capsules are only suitable for children over 6 years of age although generally they should be used only in older children due to the hazards mentioned.	Comment noted.
314-335	1	A paragraph should be added about ready-to-use liquids versus reconstitution concepts. Proposed change: Add: "Liquid formulations can be provided as ready-to-use systems, which is generally preferred, or (e.g. in case of poor stability in solution) as a solid for reconstitution to	Partially accepted. A sentence regarding solvents for reconstitution has been added under *General considerations* in section 6.2.2 Oral liquid preparation s (previously 6.2.3).

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		a liquid form. The solid component provided can be powder, granules, a tablet or capsule intended for reconstitution to a liquid form with a solvent specifically developed for paediatric use".	Added sentence: *"For liquid preparations that are prepared by reconstitution from a solid oral dosage form, solvents other than water should be provided as part of the medicinal product."*
315	17	We agree that oral liquids are acceptable from birth but it should be noted that the younger the child the more issues there are likely to be with excipients.	Comment noted. Considerations on the safety of the used excipients have been added. Revised text: *"Preserved liquid preparations will generally be considered acceptable for children from birth provided that the preservatives (and any other excipients) can be considered safe for children in the target age group (see section 9)."*
315	25	6.3.3 Oral Liquids We agree that oral liquids are acceptable from birth but it should be noted that the younger the child the more issues there are likely to be with excipients.	See above.
315	30	Since the header is oral liquid preparations here dispersible tablets may be mentioned. Proposed change: Oral liquid dosage forms and dispersible tablets for use as oral suspensions are normally considered acceptable ...	Comment noted. A new sub-section *Effervescent, soluble and dispersible preparations* has been included under Oral liquid preparations.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
315-319	31	This section is contradictory. Proposed change (if any): Oral liquid dosage forms are normally considered acceptable for children from full term birth. Oral multi-dose liquid dosage forms will normally need to be preserved (see section 9.4), whereas oral solid dosage forms will normally not. This would favour the use of oral solid dosage forms over the use of oral liquid dosage forms in children. Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth, as long as there are no preservative-free alternatives for oral multi-dose liquid dosage forms available on the market.	Comment noted. The text has been revised. Considerations on the safety of the used excipients have been added. Revised text: *"Preserved liquid preparations will generally be considered acceptable for children from birth provided that the preservatives (and any other excipients) can be considered safe for children in the target age group (see section 9)."*
316	8	Only aqueous liquid dosage forms need to be preserved if they are packaged in usual multiple-dose containers (except antimicrobial packaging like Comod or 3K systems). Proposed change: 'Aqueous liquid formulations in multiple-dose containers...'	Accepted: The text has been revised accordingly.
316-319	26	This paragraph could be confusing with respect to preserved liquids. It states that solid dose forms are preferred over liquids (because of presence of preservative in liquids) yet also states that preserved solutions are generally acceptable from birth. The flexibility of dosage offered by liquids is also an important consideration.	Comments noted. The paragraph under 6.2.2 Oral liquid preparations/General considerations has been revised to clarify that preservatives are not the only aspect to be considered. Added sentence: *"However, as for any single development aspect, the use of preservatives*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			should not be the only aspect in deciding on the choice between oral liquid versus oral solid dosage forms." The text on general considerations 6.2 Oral administration covers considerations on flexibility of dosing for different dosage forms.
317	30	This statement is not necessary. Proposed change: replace oral solid dosage form to be used as oral suspensions do not.	Not accepted: It is not clear what is proposed.
318-319	22	Add to 'Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth.' Proposed change: Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth *providing that the relevant excipients are known to be safe in the target age group.*	Accepted: The text has been revised accordingly. Revised text: *"Preserved oral liquid preparations will generally be considered acceptable for children from birth provided that the preservatives (and any other excipients) can be considered safe for children in the target age group(s) (see section 9)."*
318-319	19	'Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth.' - This sentence should be expanded. Proposed changes (if any): Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		children from birth *providing that the relevant excipients are known to be safe in the target age group.*	
318-319	9	The phrase, “Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth”, should be qualified with the statement “provided that the relevant excipients are known to be safe in the target age group”.	See above.
319	11	*Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth*. Proposed change: Add: If the use of the preservatives (and other excipients) is demonstrated as safe (and maybe refer to other section in document)	See above.
320	4	“Oral liquid dosage forms for children should be packaged together with an appropriate dosing device.” Proposed change: Guidance should allow for use of conventional measuring devices such as measuring spoons that are not “dedicated” or “co-packaged” if justified. If appropriate device is commercially available then there should be no obligation for the company to provide the device(s) with the medicinal product – this is essentially an obligation to develop 1 or several specific paediatric SKUs, potentially for very small numbers of patients – commercial viability should be part of the consideration	Partially accepted: The text has been revised to include considerations on the acceptability of commercially available measuring devices. Revised text: *“Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available (see section 11.3). The*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation. This is particularly critical for viscous oral liquids. The SmPC and PIL should include clear instructions on the correct use of the device to ensure that the recommended dose is taken by the child. If commercial devices are to be used, the type of the device (including any adaptor) should be specified in the SmPC and PIL."
320	10	"Oral liquid dosage forms for children should be packaged together with an appropriate dosing device." Proposed change: Guidance should allow for use of conventional measuring devices such as measuring spoons that are not "dedicated" or "co-packaged", if justified. If appropriate device is commercially available then there should be no obligation for the company to provide the device(s) with the medicinal product – this is essentially an obligation to develop 1 or several specific paediatric SKUs, potentially for very small numbers of patients – commercial viability should be part of the consideration	See above.
320-326	9	This section should ensure that the applicant justifies the proposed administration device. Evidence should be provided that this dosing device is able to measure, and where appropriate, deliver a dose with accuracy appropriate for the	Comment noted. The text has been revised to include the need to provide data to support the suitability of the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		medicine concerned". This is in line with the EMA guideline EMEA/CHMP/QWP/178621FE/2004 2004; Guideline on the suitability of the graduation of delivery devices for liquid dosage forms. The physical properties of the liquid should be taken into consideration, particularly if the liquid is viscous.	proposed measuring device for the actual product in question, with emphasis on viscous liquids. Revised text: See above.
320-326	17	We fully support these statements	Comment noted. The text has been revised to clarify when commercially available measuring devices could be considered, while adding points on the need to provide data to support the suitability of the proposed measuring device for the actual product in question, with emphasis on viscous liquids. See above for revised text.
320-326	25	We fully support these statements	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
320-326 327 – 332	21	The first section introduces a dispensing device as should and the expectation of multiple devices to cover a dose range to avoid multiple dosing with a small device to reach higher doses. Next section then highlights the risk with over dosing. This is contradictory as a small device inherently would limit the risk for major overdosing.	Comment noted. The text has been revised. The paragraph specific to the need of multiple devices has been deleted. Considerations for the choice of a suitable measuring device have been clarified in the revised text. Revised text: *"Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available (see section 11.3). The device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation. This is particularly critical for viscous oral liquids. The SmPC and PIL should include clear instructions on the correct use of the device to ensure that the recommended dose is taken by the child. If commercial devices are to be used, the type of the device (including any adaptor) should be specified in the SmPC and PIL.* *The risks of incorrect or accidental under- or*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			overdosing with the measuring device should be discussed and justified in relation to the criticality of the dose for children in the target age group(s) and the potential for dosing errors when measuring the paediatric medicine. Where incorrect dosing is likely to result in a potential serious risk to children, measures such as a dedicated measuring device, application of unit-dose packaging or the selection of another dosage form should be considered."
320-326	10	In terms of guideline structure, this may be confusing to include within this section. Proposed change: We would suggest moving this to section 11.3	Comment noted. The text has been revised. The current text discusses points particular to oral liquid formulations. Reference to section 11.3 has been added. Revised text: See above.
320-326	10	The provision of multiple dosing devices to the patient could result in mis-dosing. The dispenser should ensure that only the correct volume device is provided to the patient. Proposed change: . . . preferably multiple devices with a different dosing content should be **available to the dispenser of** the packed medicine in order to assure the availability of ~~an~~ **the** appropriate device to the patient . . .	Comment noted. The paragraph specific to the need of multiple devices has been deleted. Considerations for the choice of a suitable measuring device have been clarified in the revised text. Revised text: : *"Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available (see section 11.3). The device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation. This is particularly critical for viscous oral liquids. The SmPC and PIL should include clear instructions on the correct use of the device to ensure that the recommended dose is taken by the child. If commercial devices are to be used, the type of the device (including any adaptor) should be specified in the SmPC and PIL."
320-326, 333-335	8	There is no scientific evidence for the provided volumes. A neonate is definitely not capable to swallow 15 ml of liquid (l. 322) and usually not even 5 ml (l. 334). These volumes are not consistent with 346-350 (drops). Proposed change: '...with an appropriate dosing device considering the single dose and the capability of the paediatric patient.' Delete 333-334.	Comments noted. The text has been revised. Specific volume references have been deleted (proposed change as such not implemented). Revised text (General considerations): *"The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			preparation may allow better taste masking."
323 – 326	12	It is suggested that this could be reworded to make it clear that multiple devices may be needed to ensure that accurate dosage can be provided with most suitable devices which may entail more than one device to be included with each paediatric liquid preparation.	Comment noted. The paragraph specific to the need of multiple devices has been deleted. Considerations for the choice of a suitable measuring device have been clarified in the revised text. Revised text (General considerations): : *"Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available (see section 11.3). The device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation. This is particularly critical for viscous oral liquids. The SmPC and PIL should include clear instructions on the correct use of the device to ensure that the recommended dose is taken by the child. If commercial devices are to be used, the type of the device (including any adaptor) should be specified in the SmPC and PIL."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
327-332	10	The meaning of “cups for single use” is not clear. How could the use of single use cups avoid the risk of overdosing? Additionally it can be considered as not economical and ecological to add a high number of cups (e.g. 30 cups for single use if you have a bottle with a 30 days in use period).	Comment noted. The text has been revised. Cups for single use have been deleted. Revised text (general considerations): *“The risks of incorrect or accidental under- or overdosing with the measuring device should be discussed and justified in relation to the criticality of the dose for children in the target age group(s) and the potential for dosing errors when measuring the paediatric medicine. Where incorrect dosing is likely to result in a potential serious risk to children, measures such as a dedicated measuring device, application of unit-dose packaging or the selection of another dosage form should be considered.”*
327-332	33	There is a statement that the applicant should undertake adequate measure in case that an incorrect dosing result in a risk for public health. Which kind of measurement should be presented by the applicant and how should it assess by a quality assessor?	Comment noted. The text has been revised. The revised text (general considerations): *“The risks of incorrect or accidental under- or overdosing with the measuring device should be discussed and justified in relation to the criticality of the dose for children in the target age group(s) and the potential for dosing errors when measuring the paediatric medicine. Where incorrect dosing is likely to result in a potential serious risk to children, measures such as a*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			dedicated measuring device, application of unit-dose packaging or the selection of another dosage form should be considered."
330	10	Replace "public health" by "patients (or children)"; delete "e.g." in the same line.	Accepted: The text has been revised. Revised text: See above.
327-332	21	The meaning of "cups for single use" is not clear. How could the use of single use cups avoid the risk of overdosing? Additionally it can be considered as not economical and ecological to add a high amount of cups (e.g. 30 cups for single use if you have a bottle with 30 days in use period).	Comment noted. The text has been revised. Cups for single use have been deleted. Revised text: See above.
329-330	5	For improved readability alternative text is suggested: "Adequate measures should be undertaken in cases where incorrect dosing could result in a serious risk to the health of the child."	Comment noted. The text has been revised for improved readability. Revised text: See above.
333-334	10	"For oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years." Please provide a clarification for this difference including a comment concerning solutions / suspensions made from powders / granulate for reconstitution. Proposed change: Suggested liquid volumes should be	Comment noted. The text has been revised. As evidence is still lacking in the literature, the references to specific volume vs age have been deleted both for oral liquid (General considerations) and in the re-named sub-section Effervescent, soluble and dispersible preparations. Revised text (General considerations): *"The*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		consistent with volumes described for dispersible tablets. See line 282. Any specific deviation from this should be explained in guidance to help manufacturers.	*volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking."* Revised text (sub-section Effervescent, soluble and dispersible preparations): "*These preparations are intended to be dissolved or dispersed in liquid prior to administration. The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.* *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing."*
333-334	4	*"For oral liquid solutions and dispersions, the maximum*	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years." Proposed change: Suggested liquid volumes should be consistent with volumes described for dispersible tablets. See line 282. Any specific variation from this should be explained in guidance to help manufacturers.	
333 – 334	1	Volumes should be consistent with volumes mentioned in lines 283-284. Max. dosing volumes should be increased to 20 ml for children aged below 4 yrs and 50 ml for children aged between 4 and 12 years	See above.
333 – 334	23	Volumes should be consistent with volumes mentioned in lines 283-284; alternatively please explain the differing volumes Max. dosing volumes should be increased to 20 mL for children aged below 4 years and 50 mL for children aged between 4 and 12 years	See above.
333-335	10	Our experience indicates that 8-12 year olds can fairly easily be administered 15 mL volumes, so the 10 mL in 8-12 yr olds may be too restrictive.	See above.
333-335	9	As per the Reflection paper (EMEA/CHMP/PEG/194810/2005), this section should reflect maximum and minimum dose volumes as targets. Applicants should justify the volume with	Comment noted. The text has been revised. As evidence is still lacking in the literature, the references to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		respect to palatability, patient acceptability and accuracy of measurement. 5ml therefore is an ideal volume rather than maximum.	specific volume vs age have been deleted both for oral liquid (General considerations) and in the re-named sub-section Effervescent, soluble and dispersible preparations. Dosing volume is also covered as part of acceptability considerations in section 10. Accuracy of volume is discussed in the context of measuring devices. Revised text (General considerations): *"The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking."*
333-335	5	Maximum recommended dosing volume for age 13-18 is not described. Please align with line 281 – 290. Proposal for additional text: "Maximum dosing for adolescents aged 13 – 18 is xxx ml"	Comment noted. The text has been revised. As evidence is still lacking in the literature, the references to specific volume vs age have been deleted both for oral liquid (General considerations) and in the re-named sub-section Effervescent, soluble and dispersible preparations. Revised text (General considerations): *"The volume of the dose of an oral liquid preparation may have an impact on the patient*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking." Revised text (sub-section Effervescent, soluble and dispersible preparations): "*These preparations are intended to be dissolved or dispersed in liquid prior to administration. The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.* *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing."*
333-335	26	The draft guideline states that for oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5ml for children aged below 4 years and 10ml for children	Comment noted. The text has been revised. As evidence is still lacking in the literature, the references to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		aged between 4 and 12 years. We question the need for a recommended maximum here. The important factor is palatability. Meeting these administration volumes may result in a formula which would be rejected on grounds of taste. There could be circumstances where it would be preferable to provide a more palatable formulation requiring larger dose volumes. In lines 284 and 284 for dispersable tablets, volumes not exceeding 20ml for children under 4, and 50mls for children over 4 years are proposed as acceptable. Therefore it is not justified to recommend very limited dose volumes for oral liquids. Proposed change (if any): Delete maximum recommended single dosing volumes.	specific volume vs age have been deleted both for oral liquid (General considerations) and in the re-named sub-section Effervescent, soluble and dispersible preparations. Revised text (General considerations): *"The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking."* Revised text (sub-section Effervescent, soluble and dispersible preparations): "*These preparations are intended to be dissolved or dispersed in liquid prior to administration. The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.* *The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing." Dosing volume is further covered as part of acceptability considerations in section 10.
333-335	11	*For oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5 ml for children aged below **4 years** and 10 ml for children aged between 4 and 12 years. The minimum dosing volume will be determined by the accuracy of the dosing device*. Usually the cut off consensus so far was **5years** of age – any evidence to 4yo? Proposed change: There is a need to base recommendations on clinical evidence.	See above.
334 – 335	5	For improved readability alternative text is suggested: "The accuracy of the dosing device should be appropriate for the minimum dosing volume."	Comment noted. The text has been revised to cover accuracy of dosing. Revised text: *"The device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
336	17	Solutions should always be preferred to suspensions, but we understand that consistency is important for palatability and thus demonstration of acceptability to swallow is ideal.	Comment noted. The ability to swallow and dose volume is part of considerations for acceptability and palatability - this is covered in section 10. Although preferable in view of homogeneously distributed active substance in the liquid, a solution may e.g. require the use of excipients that make it less preferable compared to a suspension (or an alternative dosage form).
336	25	Solutions should always be preferred to suspensions	Comment noted. Although preferable in view of homogeneously distributed active substance in the liquid, a solution may e.g. require the use of excipients that make it less preferable compared to a suspension (or an alternative dosage form). Risks for dosing errors related to inherent properties/problems of suspensions are highlighted in the sub-section.
336-344	19	The information is valid but it should be emphasised that “easy re-suspension with moderate shaking” should be a key requirement for an oral suspension.	Accepted: The text has been revised. Revised text: *“Where sedimentation cannot be avoided, easy re-suspension with moderate shaking is recommended to reduce the risk of insufficient shaking and dosing errors arising*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			from inhomogeneous distribution of the active substance."
340-344	10	It is not considered utile to discuss the possible consequences of incorrect use of an oral suspension where shaking prior to use is mandatory. Development of suspensions without any kind of sedimentation / segregation over storage time might not be impossible. Proposed change: (suggested new wording): It has to be ensured that the need for proper shaking prior to use is clearly described in the patient leaflet and on the label in such a way that the formulation is shaken correctly. Warnings might be given, that in case given instructions (shaking) are not followed, serious under-, or over-dosing may result. Sentence "Adequate measures…." (lines 341-342) should be deleted.	Comment noted. The text has been revised. The worst-case scenario/incorrect shaking may equally apply to suspensions that are shaken when they should not. Text has been added and the sub-section revised for better clarity. Revised text (sub-section Oral suspensions): *"Where sedimentation cannot be avoided, easy re-suspension with moderate shaking is recommended to reduce the risk of insufficient shaking and dosing errors arising from inhomogeneous distribution of the active substance.* *The risks of under-dosing and over-dosing to the child if not shaking the container properly or not shaking it at all should be discussed. Clear instructions on correctly taking the dose should be included in the SmPC and PIL, including warnings if incorrect shaking may lead to over- or under-dosing. Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to the child's health. Such measures may involve the application of single*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			unit dose packaging or selection of a different dosage form."
341	30	From a quality point of view it is not feasible to investigate in a reproducible way the impact on the applied dose of not shaking the container properly. Proposed Changes: delete 'not shaking the container properly'	Not accepted. The text has been revised. The applicant will need to justify the range of conditions investigated. Revised text: *"The risks of under-dosing and over-dosing to the child if not shaking the container properly or not shaking it at all should be discussed. Clear instructions on correctly withdrawing the dose should be included in the SmPC and PIL, including warnings if incorrect shaking may lead to over- or under-dosing."*
341	5	Excessive shaking results sometimes in a worse situation than not shaking as foaming or bubbling may occur. Not all suspensions need to be shaken. Please replace text by' i.e. not shaking the container properly or not shaking it at all in case clear instructions for shaking are provided in the SmpC and PIL.'	Comments noted. The text has been revised. Foaming has been added to attributes to be considered when developing suspensions. Revised text: *"Critical product quality attributes to be considered for oral suspensions include physico-chemical characteristics of the suspension such as viscosity, potential for foaming, air entrapment, sedimentation and sticking of the suspended active substance to the primary container and to the measuring*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			device. Where sedimentation cannot be avoided, easy re-suspension with moderate shaking is recommended to reduce the risk of insufficient shaking and dosing errors due to inhomogeneous distribution of the active substance. *The risks of under-dosing and over-dosing to the child if not shaking the container properly or not shaking it at all should be discussed. Clear instructions on correctly withdrawing the dose should be included in the SmPC and PIL, including warnings if incorrect shaking may lead to over- or under-dosing. Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to the child's health. Such measures may involve the application of unit dose packaging or selection of a different dosage form."*
341-344	9	Oral suspensions are often packaged in individual dosage sachets for the reason of convenience and marketing e.g. liquid paediatric paracetamol sachets.	Comment noted. The text has been revised. Revised text: *"Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to the child's health. Such measures may involve the application of unit dose packaging or selection*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of a different dosage form."
342	5	For improved readability alternative text is suggested: "…will result in a serious risk to the health of the children."	Partially accepted. The text has been revised. Revised text: See above.
345	10	"*Drops"* Proposed change: Consider to reword "Oral Drops" to distinguish from eye drops, ear drops.	Accepted: The text has been revised accordingly using the standard term 'oral drops'. The sub-section is now *Oral drops* (under 6.2.2)
345	11	Drops are defined (Ph. Eur) as solution, suspension and emulsion Proposed change: Add 'suspension and emulsion' L348	Comment noted. The text has been revised. The word liquid is used instead of solution. Revised text: *"The volume dispensed (i.e. drop size) will be determined by the design and physical characteristics of the dropper, the physical-chemical properties of the liquid and how the dropper is handled."*
345	4	"Drops" Proposed change: Consider to reword "Oral Drops" to distinguish from eye drops, ear drops.	Accepted: The text has been revised accordingly using the standard term 'oral drops'. The sub-section is now *Oral drops* (under 6.2.2)
346-348	22	Specific guidance is required on the 'in use' testing of medicines administered as drops because of the large effect on drop size	Comment noted. The text has been revised. The necessity for

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		of the operator and instruction.	correct handling of the dropper is highlighted in the revised text. Revised text: *"The volume dispensed (i.e. drop size) will be determined by the design and physical characteristics of the dropper, the physical-chemical properties of the liquid and how the dropper is handled. Clear instructions should be included in the SmPC and PIL on the correct use of the dropper."*
346-348	19	Specific guidance is required on the 'in use' testing of medicines administered as drops because of the large effect that operator and administration instruction have on the drop size.	See above.
346-350	21	The maximum number of drops seems very restrictive. Is there any rationale to limit the maximum number of drops?	Comment noted. The section has been revised to clarify the relevant considerations to the number of drops. Reworded text: *"Oral drops can provide a useful means to administer medicinal products in low doses or small volumes. The risk of counting the incorrect number of drops, and the accuracy and precision of the volume dispensed should be justified in relation to the criticality of the dose. In order to avoid counting errors, alternative measuring devices should be considered where the dose*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			comprises more than 10 drops. Unless otherwise justified, oral drops will only be considered acceptable for paediatric medicines containing active substances with a wide therapeutic window."
348-350	10	The sentence: "The maximum number of drops per single intake should be stated and should normally not exceed 10 drops (i.e. about 0.5 ml)" is problematic since the intake of commonly used childrens' paracetamol syrups) often exceeds 0.5 ml (especially for somewhat older children. Proposed change: "The maximum number of drops per single intake should be stated. As a reference, 10 drops corresponds to about 0.5 ml"	Comment noted. The section has been revised to clarify the relevant considerations to the number of drops. Revised text: See above.
348-350	4	The sentence: *"The maximum number of drops per single intake should be stated and should normally not exceed 10 drops (i.e. about 0.5 ml)"* is problematic since the intake of commonly used childrens' paracetamol syrups, for example often exceeds 0.5 ml (especially for somewhat older children). Proposed change: "The maximum number of drops per single intake should be stated. As a reference, 10 drops corresponds to about 0.5 ml"	See above.
349-350	8	20 drops should be also manageable (in terms of counting and applicability, see comments above).	Comment noted. The section has been revised to clarify the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: 'not exceed 20 drops (i.e. about 1.0 ml).'	relevant considerations to the number of drops. Revised text: See above.
349-350	11	10 drops ~0.5ml. Why not 5 drops? (People are less likely to make a mistake f they count only with one hand!) and ~0.25ml should still be Ok with an oral syringe of 1ml Proposed change: There is a need to base recommendations on clinical evidence	Comment noted. The section has been revised to clarify the relevant considerations to the number of drops. Revised text: See above.
354	11	Size and shape implies solid dosage form (tablets, patches…). What about non solid dosage forms? (sprays? Liquid?) The only PUMA is a buccal liquid! Proposed change: Add	Comment noted. The text has been revised, covering both liquid and solid oromucosal preparations. Revised text: *"The correct use and acceptability of oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time. The adhesive properties of oromucosal preparations should be discussed in relation to the local area where they should be applied. In order to avoid the risk of swallowing mouthwashes or dental gels, these medicines dosage forms need to be applied in young children using a cotton bud, sponge or similar applicator."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
354-355	8	Use pharmacopoeial terms. Size and shape are not the only critical properties, but also mucoadhesion, taste etc. Proposed change: '6.2.4 Oromucosal preparations The properties of oromucosal preparations...'	See above.
355-356	9	Tablets and lyophilised wafers are quite small and therefore specific preparations for the paediatric population may not be required.	Comment noted. Even though a dosage form can be regarded as age appropriate, additional considerations may apply e.g. with regards to dosing needs. Wafers are covered by the sub-sections included under oral administration, although not specified as such.
355-358	10	Suggest to pay special attention to palatability for the oromucosal route of administration	Comment noted. Aspects of palatability are discussed as part of acceptability in section 10.
355-383	10	For each section, guideline should recommend specific sizes, shapes and/or volumes in the different age groups for the various dosage forms covered e.g. inhalers, enemas etc. (as was done with tablets).	Comment noted. The guidance provides a general approach in line with what is given for tablets, where a more general requirement for justifications by applicants has been introduced due to limited data available in the literature on the influence

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of the size, shape and number of tablets on acceptability in different age groups.
358	5	For improved readability alternative text is suggested: "…similar device in younger children"	Comment noted. The text has been revised. 'Attribute' has been changed to 'applicator'.
358	1	"Younger children" is not specific. We believe that what is meant here is children not able to spit out the solution either because of their age of because of a disease. Proposed change: "… in younger children <u>not able to spit out the solution</u>."	Comment noted. The text has been revised. Text has been added to highlight the age dependent ability to correctly use oromucosal preparations. 'Young children' have not been specified as such. Revised text: *"The correct use and acceptability of oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time. The adhesive properties of oromucosal preparations should be discussed in relation to the local area where they should be applied. In order to avoid the risk of swallowing mouthwashes or dental gels, these dosage forms need to be applied in young children using a cotton bud, sponge or similar applicator."*
358	10	Please provide clarity in terms of what is meant by "younger" children.	Not accepted: The text has been revised. Text has been

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Suggest to remove ”younger” or specify as for example “pre-school children” or “X years old”	added to highlight the age dependent ability to correctly use oromucosal preparations. ‘Young children’ have not been specified as such. Revised text: See above.
358	10	‘attribute’ is not a suitable term Proposed change:. . .or similar ~~attribute~~ **device** in younger children.	Comment noted. The text has been revised. ‘Attribute’ has been changed to ‘applicator’.
358	12	“Applicator” rather than “attribute”. It is not appropriate to recommend mouthwashes and certainly not gargles in younger children as these are not suitable dosage forms for the young	Partially accepted. The text has been revised. ‘Attribute’ has been changed to ‘applicator’. Although not specifically addressing mouthwashes/gargles, text has been added to highlight the age dependent ability to correctly use oromucosal preparations. Revised text: *“The correct use and acceptability of oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time.”*
358	23	It is unclear to what age group “younger children” refers. Proposed change: Please specify “younger” children.	Comment noted. The text has been revised. Text has been added to highlight the age dependent ability to correctly use oromucosal preparations. ‘Young

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			children' have not been specified as such. Revised text: See above.
358	19	The word "attribute" is not appropriate in the context of this sentence. Proposed change (if any): "applicators" or "items"	Accepted: The text has been revised accordingly. 'Attribute' has been changed to 'applicator'.
358	11	Comment: Attribute Proposed change: Change to device or dosing aid/applicator	See above.
358	22	'attribute, is the wrong word. Proposed change: item?	See above.
Section 6.3	25	Systemic absorption will be a major issue for young children and should be considered fully	Comment noted. The risk for systemic effects is already mentioned.
359	8	Use pharmacopoeial terms. Proposed change: '6.2.5 Nasal preparations	Accepted: The section has been revised. Terminology based on Standard Terms has been introduced.
359-367	9	The complexity of the nasal device should also be considered. The type of preservative used should be considered in particular as there are safety concerns regarding the use of benzalkonium chloride in aqueous preparations.	Comment noted. The text has been revised. Sentence added: *"The use of any preservative should be justified as outlined in Section 9."* Complexity

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			of the nasal device was not introduced.
360-367	31	Preservatives are not addressed in this section, in spite of the well characterized toxic effects of preservatives on the nasal mucosa. The Federal Institute for Drugs and Medical Devices (BfArM, Germany) has published a graduated plan procedure ("Stufenplanverfahren") regarding the nasal use of benzalkonium chloride-containing medicinal products in 2003, already. Proposed change (if any): Nasal medicines will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment a particular medicine should be discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. Also, the patient acceptability in view of palatability and sensation of the medicine on actuation should be discussed and justified. For nasal medicines with a local action, the risks of systemic (adverse) effects due to both correct and incorrect application should be discussed. Devices for nasal administration should be adapted to the size of the nostrils/nasal cavity for the intended target age group(s). Specific container systems for the preservative-free application of nasal medicinal products are available on the market. Thus (potentially toxic) preserved formulations of medicines for nasal	Comment noted. The text has been revised. Revised text: See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		administration will not be considered acceptable for children except in justified circumstances.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
365-367	10	Comment: This would mean adaptation of dose volume, spray pattern etc and could become very complicated to impossible as there is no technical solution to provide a variable nasal dose currently. Proposed change (line 366-367): "**Efforts should be made** to adapt devices for nasal administration to the size of the nostrils/nasal cavity for the intended target age groups(s). **If the adaptation is technical not feasible this may be considered acceptable.**"	Comment noted. The text has been revised. Revised text: *"Devices for nasal administration should be suitable for the size of the nostrils/nasal cavity, including the delivered volume, for the target age group(s)."*
365-367	17	Systemic absorption will be a major issue for young children and should be considered fully.	Comment noted. Text has not been revised as the GL text contains considerations on the risk of systemic effects.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
365-367	21	This would mean adaptation of dose volume, spray pattern etc and could become very complicated to impossible as there is no technical solution to provide a variable nasal dose currently. Proposed change (line 366-367): "**Efforts should be made** to adapt devices for nasal administration to the size of the nostrils/nasal cavity for the intended target age groups(s). **If the adaptation is technical not feasible this should be considered as acceptable.**"	Comment noted. The text has been revised. Revised text: *"Devices for nasal administration should be suitable for the size of the nostrils/nasal cavity, including the delivered volume, for the target age group(s)."*
366	10	" Incorrect application should be discussed": It is not considered feasible to discuss *all possible* ways of incorrect application. Proposed change: Clarify expectations or delete.	Accepted: The text has been revised. "due to both correct and incorrect application" was deleted.
366	8	Nasal preparations with desired systemic drug delivery should be separately mentioned as they display some additional risks. Proposed change: Insert in line 366 'For nasal preparations with intended systemic action, safe and complete drug delivery from the device to the children's nose is crucial and should be paid particular attention to with demonstrated evidence of safety wherever possible.	Not accepted: The comment is not endorsed. The point is linked to the safety of the delivery route, and is as such part of the clinical development. The text has been revised. Revised text: *"Nasal preparations will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment with a particular paediatric medicine should be*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. The use of any preservative should be justified as outlined in section 9. Also, the patient acceptability should be discussed in relation to the palatability and sensation of the medicinal product on actuation. *For nasal preparations with a local action, the risks of systemic (adverse) effects should be discussed. Devices for nasal administration should be suitable for the size of the nostrils/nasal cavity, including the delivered volume, for the target age group(s).”*
367	10	This is very brief. No mention of preservative, acceptable dose volume etc. Proposed change: Suggest add comment around volume of fluid per actuation – this should not be so large that the dose runs out of the nostril. Also, for some nasal delivery devices, a degree of co-ordination is required (e.g. spray pumps) and so these may be less suitable for very young children/infants/toddlers.	Comment noted. The text has been revised to introduce points on excipients and the administration volume. Revised text: See above.
Section 6.4	21	The use of pressurized metered dose inhalers at birth may not be feasible. The actuation of the device (care giver) still needs to be coordinated with an inhaled breath, which is difficult for an	Comment noted. Orally inhaled medicines need to be justified with respect to age-appropriateness (first

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		infant. The use of a nebulized solution may be a better solution.	paragraph), which includes the suitability of the device.
368	10	The use of pressurized metered dose inhalers at birth may not be feasible. The actuation of the device (by the care giver) still needs to be coordinated with an inhaled breath, which is difficult for an infant. The use of a nebulized solution may be a better solution.	See above.
368	11	Should reference to organisation such as The Global Initiative for Asthma (GINA) be made here?	Not accepted: The comment is not endorsed. References to organisations are not part of the GL.
368	19	Addition of packaging information on nebuliser solutions to this section Proposed change (if any): Add *Nebuliser solutions should be packaged as the smallest volume to be administered unless an appropriate dosing device is included.*	Not accepted: The comment is not endorsed. Suitability of package size is addressed in Section 11.
368-376	9	Other guidelines discuss the issue of inhalation products for children in detail and should be referenced in this section. Technique and accessibility of the device are important considerations, particularly if the device is not autoactivated and requires some sort of co-ordination to deliver the drug from the device. The ability of the child/carer to use the device will be of paramount importance to the successful administration of drug to the site of action. Design of primary and secondary packaging	Comment noted. The aspects brought up are part of the justification requested in the first paragraph.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		of the inhaler should take into considerations the limitations of factors such as patient size and co-ordination when developing age-appropriate products.	
369- 370	10	Are there recommendations for the specific length of time different age groups should be put on a nebuliser for a to be given dose of medication?	Comment noted. No recommendations have been given. To be justified on a case by case basis.
370	22	'specific regulatory advice' required. Proposed change: Add *Nebuliser solutions should be packaged as the smallest volume to be administered unless an appropriate dosing device is included.*	Not accepted: The proposed change is not endorsed. Suitability of package size is addressed in Section 11.
371	10	Specify age from which pMDIs are acceptable without a spacer – mention that co-ordination is required. Proposed change: Usually above 6 years old. What about breath actuated inhalers?	Not accepted: The proposed change is not endorsed. In the absence of data this has to be justified by the applicant. The text has been revised to include a general sentence. Revised text: *"Companies should justify the suitability of the proposed equipment for use in the target age group(s)."*
371-372	1	Specification of the age of children who can use pMDIs without a spacer should be added. Unless for breath actuated pMDIs 2-3 years seems too young due to the hand-mouth-coordination.	Not accepted: The proposed change is not endorsed. Message rather similar to current wording and data not

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: "*Considering the different available options for applying orally inhaled medicines, pressurised metered dose inhalers and nebulisers - in combination with a specific spacer system and / or a facemask – are generally deemed acceptable for children from birth. For children younger than 2-3 years a spacer system with a facemask is recommended.* Older children may use the inhaler with or without a spacer."	available in support of more precise ages. The text has been revised to include a general sentence. Revised text: *"Companies should justify the suitability of the proposed equipment for use in the target age group(s)."*
373	1	Dry powder inhalers – *except for active systems which may also be suitable for younger children* – can usually only be applied by elder children because it is the child patient which makes his or her dose by the inspiratory flow."	Comment noted. The text has been revised. Revised text: *"Unless appropriately constructed, dry powder inhalers can ~~usually~~ only be applied by older children because it is the child patient which makes his or her dose by the inspiratory flow."*
373	23	Dry powder inhalers – *except for active systems which may also be suitable for younger children* – can usually only be applied by elder children because it is the child patient which makes his or her dose by the inspiratory flow."	See above.
374	10	"For high potency medicines, …". Unclear whether this refers to just high potency medicines formulated in dry powder inhalers or high potency medicines formulated in any inhalation device. <u>Proposed change</u>: If it is for high potency medicines formulated	Comment noted. The text has been revised. The message is not specific to paediatric formulation. The sentence has been deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		in any inhalation device, then suggest to include as a separate paragraph	
374-376	1	This is not specific to paediatric development Proposed change: Delete sentence “For high potency medicines …” ().	Accepted: The text has been revised. The sentence has been deleted.
375	10	“….an end of life lock-out system and measures to prevent inadvertent multiple dosing…..” would make all pMDI’s unsuitable. Also what is meant by “measures to prevent inadvertent multiple dosing” is vague. Proposed change: Wouldn’t dose-counter and some feedback mechanism be adequate? Please clarify what is meant by measures to prevent inadvertent multiple dosing. An example would be valuable.	Accepted: The text has been revised. The message is not specific to paediatric formulation. The sentence has been deleted.
377	11	Shape of the suppository shaped to the size of the child…? Evidence based?	Comment noted. The text has been revised Revised text: *“The size (length and diameter) of the suppository should take into account the age and size of the child.”*
379-381	10	"Unless suppositories have been especially designed to deliver smaller amounts of the full dose, they should not be cut in order to provide a smaller dose."	Not accepted: The comment is not endorsed. However, where suppositories have been designed and validated for cutting in order to provide a

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Add "Suppositories may be subdivided provided that specific instructions are included in the SmPC and the PIL."	smaller dose, the SmPC and PL should include instructions on this.
379 – 381	5	In line with the earlier statement on dividing lines in tablets it is proposed to add a sentence " It is very likely that care givers will cut suppositories for dose reduction. Supplier should include instructions in the SmPC or PIL not to cut suppositories unless this can be justified and appropriately executed by care-givers"	Not accepted: The text proposal is not endorsed. However, where suppositories have been designed and validated for cutting in order to provide a smaller dose, the SmPC and PL should include instructions on this.
380	9	The guideline would benefit from further information regarding the rationale for not cutting suppositories. There should be some additional information on excipient vehicles suitable for paediatric administration of rectal dosage forms. For example, polyethylene glycol may lead to irritation of the rectal mucosa.	Partially accepted: The text has been revised. The rationale for not cutting suppositories has been added. Excipients issues are covered in section 9, patient acceptability in section 10. Revised text: *"Unless suppositories have been specially designed to deliver smaller amounts of the full dose, they should not be cut in order to provide a smaller dose, due to the high risk of dosing errors related to inhomogeneous distribution of the active substance and difficulties in reproducible cutting."*
381	10	Why is this different to tablet splitting? Same requirements?	Comment noted. The text has been revised. The guideline text discusses cutting suppositories that have not

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			been designed to be cut, which does not preclude development of suppositories intended to be cut, provided the cutting procedure has been validated to chow accurate dosing, without any likely effects on patient acceptability. Revised text: See above.
383	10	Clarify Proposed change: The length of the ~~canule~~ **rectal tube** of the enema . . .	Accepted: The text has been revised accordingly.
383-386	25	6.5 Rectal administration We agree strongly with this statement	Comment noted.
387	11	Cutaneous Proposed change: Change to topical? Dermal?	Comment noted. The heading has been changed to 'Cutaneous and transdermal preparations' in order to use standard terms and to cover preparations intended for both local and systemic effects.
391	11	What about physical occlusion?	Comment noted. The text has been revised to mention only occlusion as a general term, encompassing any type of occlusion (e.g. by coatings, the vehicle, or by physical occlusion).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Revised text: *"Where relevant, the impact of occlusion, fever or thermal heating on skin permeability and the risk of overdosing should be discussed."*
391-392	9	This section should be based on the information provided in the Reflection Paper EMEA/CHMP/PEG/194810/2005: "Thermoregulation and transepidermal water loss might be influenced drastically depending on the vehicle used, especially neonates" (page 15/45).	Partially accepted: The text has been revised to highlight the types of developmental changes to be considered. The impact of occlusion, e.g. of vehicle, on skin permeability is included in the text. Revised text: *"Developmental changes in barrier function of the skin, such as dermis thickness, hydration and perfusion of the epidermis and the changing ratio of body surface area to weight, should be taken into consideration when developing cutaneous and transdermal preparations for children.* *The use of excipients known to sensitize the skin (e.g. some surfactants and adhesives) should be carefully considered and justified. The need or restriction to use water-impermeable or other types of materials as a coating to the cutaneous medicinal product should be clarified. Where relevant, the impact of occlusion, fever or thermal heating on skin permeability and the risk of overdosing should*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			be discussed."
394, 398	11	Would Medicated plasters go for PIPs?	Comment noted. The guideline applies to development of all paediatric medicines irrespective of PIP status.
396	21	Typo – the word "should" needs to be removed.	Accepted: The text has been revised accordingly. The word "should" has been deleted.
396	5	Correction needed: "…Easily reached by the child are preferred"	See above.
398	22	Change 'Patches and plasters are preferably developed for use as a single dose/strength.' Proposed change: ' *Patches and plasters are preferably developed for use without the need for manipulation to achieve a smaller dose'*	Accepted: The text has been revised accordingly. Revised text: *"Patches and plasters are preferably developed for use without the need for cutting to achieve a smaller dose, i.e. developed in a sufficient range of age-appropriate sizes or strengths."*
398	18	'Patches and plasters are preferably developed for use as a single dose/strength" requires re-wording. Proposed change: ' *Patches and plasters are preferably developed for use without the need for manipulation to achieve a smaller dose'*	See above.
398-401	9	Manufacturers should be encouraged to produce age-	Partially accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		appropriate patches that do not require cutting. The practice of cutting patches may have adverse consequences with respect to drug delivery. There are patches where the active is in a matrix which can be cut however there are other designs of patch where the active is in a reservoir. Active from a reservoir may release very rapidly if cut. If an opiate-containing reservoir patch were to be cut, this may result in overdose. Cutting should only be considered in exceptional circumstances. The guideline could benefit from further discussion on the different release mechanisms from patches if cutting is to be recommended. The guideline would benefit from making reference to the thinner dermis of the neonate and avoidance of certain penetration enhancers (Dimethyl Sulfoxide for example). Additionally there may be contact skin reactions caused by the adhesive used to adhere the patch to paediatric skin. If the guideline is to recommend cutting patches, then the means to justify this practice should be discussed. The Ph.Eur "Dissolution Test for Transdermal Patches" should perhaps demonstrate that the rate of release is unaffected. Justification for the ease of use, and accuracy of cutting should be provided. The stability of the half that is not used immediately should be investigated (if the intension is to use it at a later date). The finished product specification should include a measure of the accuracy of the cutting line.	The text has been revised. Additional text on cutting of patches and plasters was added. Revised text: *"Patches and plasters are preferably developed for use without the need for cutting to achieve a smaller dose, i.e. developed in a sufficient range of age-appropriate sizes or strengths. However, some types of patches (e.g. matrix types) may be developed to provide for a range of doses/strengths by cutting. Cutting will only be considered acceptable if clearly marked cutting lines are present and if dose uniformity and consistency of delivery properties have been appropriately demonstrated.* *Information whether the patch can (or cannot) be cut to provide a smaller dose needs to be included in the product information, with clear instructions how lower doses can be obtained by cutting along to the marked lines. Instructions should also be provided for safely discarding the (cut) patch, or the potential to use the remaining parts of the patch after cutting."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Consideration should be given to the amount of drug remaining in the transdermal device after use. Misuse of a used device may have particular safety implications for the paediatric patient population. For example some opiate patches contain an excess of active, most of which is present after use in the discarded patch.	
402-412	9	It may be preferable to provide separate sections on preparations for the eye and ear. The guideline should provide some additional explanation to clarify whether the toxicity of the ophthalmic preservatives is systemic or local.	Comment noted. The text has been revised to reflect that the concern is for local toxicity. No separate sections on eye and ear preparations were introduced. Revised text: *"In order to avoid the use of preservatives with potential local toxicity to the cornea and/or mucous membranes, single dose preparations or multi-dose preparations in a dedicated multi-dose container that does not require its contents to be preserved i.e. preservative free containers should be considered for children, especially neonates. This is especially important if long term use may be necessary."*
405	11	*…, however…* Proposed change: *. However,*	Accepted: The text has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
411-412	5	It would be desirable to have standard wording for inclusion in SmPC and PIL with information to be given to the parent/care giver as to hold container and child in order to correctly administer the medicine	Not accepted: Standard wording for the SmP and PIL are outside the scope of this GL.
Section 6.8	32	The considerations for infusions should be added (see also EMA workshop 07 November 2006, Doc. Ref: EMEA/484678/2006)	Comment noted. The text has been revised. Some specific concerns as to infusions developed for neonates have been added. Revised text: *"Neonates may only accept very small volumes of medication in order to avoid volume overload and to allow sufficient room for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosage rates are not feasible by using standard pump equipment. These aspects should be considered in particular to medicines intended to be administered as a continuous infusion. In addition, specific concerns related to incompatibility with co-administered medication in the infusion line, osmolarity, inappropriate diluents, and potential for over- or under-dosing due to lag-volume effects in iv fluid lines should be investigated during the development."*
413	18	Issues on central lines and peripheral lines should be included in	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		this section. Proposed change (if any): For intravenous formulations requiring frequent dosing intended for use in chronic conditions, the use of the central venous route should be discussed and appropriate information should be included in the SmPC.	The text has been revised. The route of intravenous administration (peripheral or central) has been added to the list of considerations. Revised text: *"The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified towards the characteristics of the parenteral preparation, the age and weight of the child, the maximum number of injections per day and the duration per treatment. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment periods."*
413	18	Consideration should be given to the rate of administration of intravenous infusions and the requirement of infusion devices. The practicality of administering small volume should be considered and dilutions can be avoided by providing appropriate concentrations of the parenteral medicine.	Comment noted. The paragraph has been revised. The rate of administration has been integrated. Revised text: See above. For neonates, considerations on the concentration of infusions have been added. Revised text: *"Neonates may only accept very*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			small volumes of medication in order to avoid volume overload and to allow sufficient room for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosage rates are not feasible by using standard pump equipment. These aspects should be considered in particular to medicines intended to be administered as a continuous infusion. In addition, specific concerns related to incompatibility with co-administered medication in the infusion line, osmolarity, inappropriate diluents, and potential for over- or under-dosing due to lag-volume effects in iv fluid lines should be investigated during the development. "
413	23	Is there literature on the amount of endotoxines that is tolerated by neonates, children, adolescents compared to adults? Proposed change: Include a hint on the possible need for endotoxin testing even for small injection volumes.	Not accepted: This comment is not endorsed. The existing guidance for endotoxins is found in the Ph. Eur. and the issue is not considered paediatric specific.
413	5	Please consider to add a table to this sections to describe the maximum allowable volume to be dosed I.V., I.M. and S.C. per age group	Comment noted. It is not foreseen to have a table with precise volumes (by analogy with the tablet sizes).
415-416	9	The guidance would benefit from separate information vaccine	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		formulations, in particular the use of excipients such as egg albumin. Vaccine formulation issues might also include aggregation of certain types of vaccine, interaction with silicon and latex from stoppers or pre-filled syringes and allergy to egg albumin and other potential excipients/contaminants. Latex derivatives in needle sheaths should be mentioned as a factor to be considered where a product will be provided with an integrated or separate needle device. Silicone derived alternatives should be used where appropriate.	Not implemented since these issues were not considered paediatric specific.
419-423	21	In section 6.8 it seems that only single use containers are considered. What about multiple use containers? Especially in the light of the use of preservatives this should be discussed. A specific discussion could be considered for section 11.3.	Comment noted. This section covers both type of containers (single and multiple use). Hence, there is no need to revise section 6.8. For further information on preservatives refer to section 9.
419-423	11	Other formulation factors are missing: viscosity, pH, buffering capacity, osmolarity Proposed change: add	Accepted: The text has been revised accordingly. Revised text: *"The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified towards the characteristics of the parenteral preparation, the age and weight of the child, the maximum*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			number of injections per day and the duration per treatment."
419-423	5	"The site of the injection ….Where appropriate, needle free injectors should be considered, especially for medicines requiring frequent or long treatment periods." Needle free injection is not popular and not well established yet. Proposed text: "…number of injections per day and the duration of treatment. Where appropriate, needle free injectors may be considered, especially for medicines requiring frequent or long treatment periods."	Accepted: The text has been revised accordingly. Revised text: *"Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment periods."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
421-423	21	Injections with needle free injectors have been reported painful. We would recommend to include also other alternative injection devices for medicines requiring frequent or long treatment periods. Proposed change: “Where appropriate, needle free injectors **could** be considered, …”	Accepted: The text has been revised accordingly. Revised text: See above.
421-423	8	To my best knowledge there is no scientific evidence for claiming needle-free injectors being superior to conventional needles, neither for short- nor for long-term treatment. In contrast, pain is sometimes bigger with needle-free injections as they impact a broader skin area. Proposed change: ‘Where appropriate, needle-free injectors may be considered.’	Accepted: The text has been revised accordingly. Revised text: See above.
422	11	Needle free injector should be considered for frequent/long treatment period Proposed change: There is a need to base recommendations on clinical evidence	Comment noted. The text has been revised. Revised text: See above. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment periods.
423	18	The use or potential use of micro-needles should be mentioned.	Accepted: The text has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Revised text: See above.
424-425	5	It is assumed that dilutions will be made only by a specialist e.g. a Pharmacist. This is a different situation in comparison to the other dosage forms, where care-givers are involved. A parenteral drug product can only be diluted under aseptic or sterile conditions. In case the physician has the desire to make serial dilutions not described in the PIL or SmPC this cannot be the responsibility of the Applicant/MAA holder. Proposed text: “Serial dilutions performed by appropriate personnel e.g., Pharmacists (in order to achieve the required dose) are only acceptable if dose adjustment is required and if diluting instructions are given in the PIL or SmPC.”	Not accepted: Comment not considered paediatric specific. Dilution of parenteral products should always be done by healthcare professionals.
424-426	16	We agree that serial dilutions must be avoided	Comment noted.
424-426	25	6.8 Parenteral administration Serial dilutions must be avoided.	Comment noted. The GL states that serial dilutions are not acceptable.
426-430	18	Additional information should be added to the paragraph. Proposed change (if any): Charts should be provided for guidance to convert calculated dose to a dose volume for administration. Also, package volume should not allow administration of 10 times the intended dose (to avoid 10 fold errors).	Not accepted: The proposed change is not endorsed. It is left to the applicant to present such charts in the product information. Concerning dosing errors and package volume, this is covered in section 11.2 Container size.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
426-430	32	Volumes should only be given if scientifically justified or should be clearly marked as examples.	Comment noted. The text has been revised. Revised text: *"The volume should be justified according to the age of the children. Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml however for neonates and small infants lower volumes are warranted."*
426-430	22	Need to say something about conversion of the accurately calculated dose and conversion to dose volume. Charts should be provided for guidance. Also, package volume should not allow administration of 10 times the intended dose (to avoid 10 fold errors).	Not accepted: The proposed change is not endorsed. It is left to the applicant to present such charts in the product information. Concerning dosing errors and package volume, this is covered in section 11.2 Container size.
427-429	9	Syringes are not always supplied with parenteral products, but their selection should be appropriate to the volumes of liquid being prepared and administered.	Comment noted. This issue is reflected in section 11.3.
428-430	4	The guideline refers to 1ml syringe and smallest possible injection volume of 0.1mL. However, smaller volume syringes (0.5mL) with graduations less than 0.1mL are commercially available and hence injection volumes of less than 0.1mL can be justified. Proposed change: delete sentence: *"For the currently available*	Accepted: The text has been revised accordingly. Revised text: *"The minimum dosing volume of a medicine will depend on the accuracy of the relevant measuring device. Where relevant, the size of the syringe and the graduation that permits accurate administration should*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		1-ml syringes, the smallest volume for parenteral administration is set at 0.1mL." This sentence is superfluous to lines 426-428 and implies that lowest feasible volume is 0.1ml.	*therefore be described as well. The volume should be justified according to the age of the children. Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml however for neonates and small infants lower volumes are warranted."*
429	20	Unless otherwise justified, subcutaneous and intramuscular injection volumes should not exceed 1 ml. This is much for a neonate. Age groups should be specified.	Comment noted. The text has been revised to reflect this comment. Revised text: *"The minimum dosing volume of a medicine will depend on the accuracy of the relevant measuring device. Where relevant, the size of the syringe and the graduation that permits accurate administration should therefore be described as well. The volume should be justified according to the age of the children. Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml however for neonates and small infants lower volumes are warranted."*
435-438	11	Fluid restriction, concomitant administration (other drugs, blood products, TPN and fluid maintenance) especially is Neonates included in PIP should be clearly presented in relation with volumes, compatibility and primary packaging (cf toxic aluminium leaching!)	Comment noted. The text has been revised. Revised text: *"Neonates may only accept very small volumes of medication in order to avoid volume overload and to allow sufficient room*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosage rates are not feasible by using standard pump equipment. These aspects should be considered in particular to medicines intended to be administered as a continuous infusion. In addition, specific concerns related to incompatibility with co-administered medication in the infusion line, osmolarity, inappropriate diluents, and potential for over- or under-dosing due to lag-volume effects in iv fluid lines should be investigated during the development."
435-438	21	Volumes of medication vary with patient age and weight. Could further information on the relation between patient age and/or weight and maximal injection volumes be added?	Comment noted. The text has been revised. Revised text: *"The volume should be justified according to the age of the children. Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml however for neonates and small infants lower volumes are warranted."*
443	18	For parenteral products which are intended for use in an out-patient setting, consideration should be given to the safe disposal of the administration device, especially in paediatric setting.	Not accepted: The proposed change is not endorsed. The comment was not considered since this was not paediatric specific.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Single use injection devices for injection and reconstitution, as well as devices with a re-use prevention feature or needle-less systems should be developed.	
444	16	Where medicines are likely to be administered via feeding tubes, administration devices compatible with connections on feeding tubes should be provided.	Comment noted. Not implemented in the text as such a request is not seen as feasible. Section 6.2.3. covers considerations on feeding tube administration (previously 6.9), while administration devices are covered in section 11.
446-447	4	*"...the particle size, viscosity, dosing volume and compatibility of the oral medicine with the tube material should be discussed and justified."* Proposed change: Provide definition for "compatibility". Does this mean chemical compatibility or potential tube blockage?	Accepted: The text has been revised to reflect that both chemical compatibility and physical blockage of the tube should be considered. Revised text in section 6.2.3 (previously 6.9): *"The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be considered during pharmaceutical development."*
451-453	5	The impact of administration of pre-suspended or dissolved oral medicines should be higher than the impact of the tube, and its effect assessed. Effect of tube can be discussed by dose	Not accepted: The proposed text is not endorsed. The sub-section 6.2.3 (previously 6.9) specifically

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		recovery. Proposed text: "The impact of suspending or dissolving an oral medicine prior to the administration through a feeding tube and the effect of the tube on recovery should be discussed." "The aforementioned requirements only apply for medicines where the SmPC ad PIL state that the medicine can be administered through a feeding tube."	addresses issues related the impact of the feeding tube. The new sub-section on 'Handling of oral solid preparations to facilitate administration' includes the requirement to validate the dosing accuracy after any proposed handling procedure, which applies also for administration through feeding tubes.
453-454	4	*"The aforementioned requirements also apply for medicines where the SmPC and PIL state that the medicine may be administered through a feeding tube."* Proposed change: This guidance should discuss safeguards when drugs should not be put through tubes, e.g. enteric drug delivery dependent on GI pH levels.	Comment noted. The text has been revised. Revised text in subsection 6.2.3 (previously 6.9): *"Where administration through feeding tubes is highly likely, the SmPC and PIL should provide information if the medicinal product can (or cannot) be administered through a feeding tube, including instructions on the correct procedures."* In section 8, age related differences in gastric pH and potential implications for e.g. enteric coated products are discussed.
455 - 461	33	The most fixed dose combinations are waived during the PIP procedure.	Response to comment not applicable.
457-458	18	Can consider using HIV and TB as examples.	Accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The text has been revised. Revised text: *"Fixed dose combinations are often developed as an alternative substitution therapy for patients already treated with the individual components, especially for chronic diseases <u>such as HIV or tuberculosis."</u>*
458	22	Use HIV and TB as examples.	See above.
462	10	Alternative dosing regimens, for example weekly dosing are also considered of potential added value. It would be beneficial to introduce this concept, and its acceptability, as an option and provide direction for developing such an approach.	Accepted: The text has been revised. The specific example of weekly dosing was not included in the revised text as it is addressed by the general preference of maximum twice daily dosing.
463-465	5	Pharmacokinetic considerations and the clinical indication of the medicinal product should be considered when choosing dosing frequency. Proposed text: "The choice of dosing frequency should be justified in terms of the characteristics of the active substance, the intended clinical effect…., the pharmacokinetic profile, the indication and patient therapeutic adherence."	Accepted: The text has been amended, "pharmacokinetic profile" and "indication" were incorporated in the revised text.
464	10	Clinical effect is not directly linked to type of dosage form but is firstly determined by the active compound properties (half-life,	Accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		receptor binding). Proposed change: Delete: "(immediate versus prolonged release)".	The text has been revised "(immediate versus prolonged release)" was deleted
465	19	Adherence is mentioned a number of times in the document but in some places the terminology 'compliance' is used. The document should be consistent in the use of terminology. Also there could usefully be a short separate section on adherence, including issues relating to parents.	Comment noted.
465	21	The guidance states that convenience/adherence should be taken into account. There is very limited data and understanding available related to adherence. A separate guidance on adherence would be helpful to enable the pharmaceutical company to make judgements about adherence. For adherence studies there is currently no established scientific practice and limited well developed technical solutions.	Comment noted.
465-466	10	Suggest to emphasize developing drugs formulations which will allow once or twice daily administration as some day care institutions are not allowed to give medication and small children cannot take the responsibility for own medication.	Accepted: The text has been revised.
468-470	10	Move text to chapter 8.	Accepted: The text has been moved to Section 8
463-470	32	Comment: More frequent dosing might be acceptable for short term.	Accepted: The text has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Clearly distinguish between short and long term use of medicines.	
471	10	Extended release formulations are also of interest. Please provide consideration on acceptability and guidance for development.	Comment noted.
472-473	9	The particle size of product in modified release preparations is not related to the target age range. The wording of lines 472 - 473 is confusing and seems to propose that it is. Does this sentence refer to Multiple Unit Pellet Systems (MUPS)? These sentences should be clarified.	Accepted: The text has been revised.
473	10	“Multiparticulate Systems”: Please provide definition of term / describe relevant dosage form(s).	Comment noted.
477-479	5	This also applies to adults. Please remove paragraph.	Not accepted: The risk of accidental chewing is considered higher in children.
477-479	10	If the risk of chewing is considered a risk affecting suitability of dosage form, what is expected as acceptable approach to mitigate the risk to an acceptable level? It would be also be helpful to know any criteria for risk assessment in terms of chewing.	Comment noted.
477-479	21	If the risk of chewing is considered as risk affecting suitability of dosage form, what is expected as acceptable approach to mitigate the risk to an acceptable level? It would be also helpful	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		to know any criteria for risk assessment in terms of chewing.	
(244) 478	15	With regards to oral preparations, mention is made in section 6.2.1 (line 244) and section 8 (line 478) of the "risk of chewing" a tablet. Line 247 onwards discusses the ability of a child to swallow a tablet, and appropriate tablet size, however we don't see any mention of a chewable tablet preparation, which may be of benefit for younger children who cannot swallow tablets whole.	Accepted: Chewable preparations have been addressed in Section 6.2.1.
479	10	Proposed change: Replace “public health” by “patients”	Accepted: The text has been revised; “public health” is replaced by “patients”.
479	12	results in a serious risk to the “child” health rather than “public” health is suggested	Accepted: The text has been revised; “public health” is replaced by “patients”.
480-483	9	Comment: Certain formulations such as Multiple Unit Pellet Systems (MUPS) can be dispersed in low pH food (e.g. apple sauce) or liquid immediately prior to administration. The applicants should be encouraged to provide these type of administration data where available. Proposed change (if any): Please revise accordingly.	Accepted: Additional considerations on dispersing (administering) medicines with food and drinks has been included in the revised guideline (Sections 6 and 10).
480-484	10	Include reference to literature for preclinical and clinical safety	Not accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		considerations.	No literature references are included in the guidelines.
480-484	5	More guidance with regards to these aspects would be welcomed by industry as no specifications are currently available to determine e.g., pH conditions for dissolution testing. Please include evidence supported data with regard to this statement.	Comment noted. There is not difference in the development of an in vitro test (for QC testing) between adults and children. In vitro testing is addressed by other guidelines. The text "*These aspects should also be considered when designing in vitro testing during pharmaceutical development*" has been deleted.
483-484	11	Is it really the place to comment on: These aspects should also be considered when designing in vitro testing during pharmaceutical development. Suggestion - Proposed change / suggested text (if any): Remove?	See above.
483-484	9	The last sentence requests that the stated physiological conditions should be considered when developing the *in vitro* release test. There is a concern that this will not necessarily ensure that optimal test conditions and could be in conflict with other regulatory guidance. It should be noted that i*n vitro* testing is not capable of taking into account variability of gastric emptying and transit time. These factors are important but their variability can not be	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		taken into account by *in vitro* testing with dissolution apparatus. The dissolution conditions for modified release preparations need not be biorelevant, if justified. It is incorrect to state that dissolution media should be tailored to the gastric pH's of various age groups. The note for guidance on quality of modified release products: A oral dosage forms B: transdermal dosage forms section I (quality) CPMP/QWP/604/96, states the following: "*The prolonged release formulation should therefore be tested in vitro under various conditions (media, pH (normally pH range 1-6.8, in cases where it is necessary 1-8), apparatus agitation etc.). Testing conditions providing the most suitable discrimination should be chosen".* Gastric pH need not be considered when designing *in vitro* testing. Dissolution mediums with physiological pHs are not always used to establish IVIVC. The dissolution conditions used to establish IVIVC should be shown to be predictive of product performance. The dissolution condition need not necessarily be physiological. The dissolution test may only be a quality control test (i.e. no IVIVC established) designed to demonstrate that production batches release active in a similar manner to the clinical trials batches for which safety and efficacy was established. The last sentence (Lines 483-484) should be reworded or	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		deleted. It may be unnecessary, given other available guidance and should not conflict with other guidance. Proposed change (if any): The last sentence in lines 483-484 should be reworded or deleted.	
485-580	19	Most of the information in this section should be in the annex. More 'specific regulatory guidance' is required in this section.	Comment noted. The text has been further revised and additional guidance on use of various excipients has been included in the text.
485-584	8	I appreciate the chapter on excipients and the provided flow chart. However, I would expand the term 'excipient' (intentionally added components) to the more general term 'ingredients'. For safety reasons it does not make any difference whether a component of the medication is added intentionally or by degradation, incomplete evaporation (residual solvents), leaching, etc. Proposed change: Change 'excipient' to 'ingredient' or 'component'.	Not accepted: The regulatory term which should be used is "excipients". Impurities, degradation products or residual solvents, etc. are already addressed by other existing guidelines.
486	23	Comments to 9.1. General considerations: The use of alcohol should be addressed, since it may be a useful excipient for liquid dosage forms. What amounts of alcohol for the different target age groups are acceptable is a subject of	Comment noted. Alcohol as a specific excipient has not been addressed in the guideline. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		ongoing discussion.	the suitability of an excipient in a paediatric medicine. nformation on specific excipients will be provided in the Guideline on Excipients which is currently under revision.
486	30	This section could be shortened and in more detail addressed in a separate guideline. (such as CHMP/QWP/396951/2006 where paediatrics are addressed in the introduction)	Comment noted. The text has been revised.
486-584	24	Better inform healthcare professionals about the adverse effects of excipients. Set up a working group within the European Medicines Agency (EMA) concerned specifically with excipients, similar to the Herbal Medicinal Products Committee (HMPC). It would be responsible for centralising adverse effect data on excipients and for evaluating them, drafting monographs for each excipient, issuing clear recommendations on their use, publishing public assessment reports on the EMA website, including summaries of adverse effect data for each age group, and compiling lists of excipients that are eligible or ineligible for use in each age group.	Comment noted. The ongoing revision of the Guideline on Excipients will result in improved information about excipients. As part of the review process it is planned to provide regular updates on excipients in form of Q&A documents or reflection papers.
487-488	9	The introduction to excipient guidance should state that some excipients are not considered inert or inactive and there are specific instances where excipients have demonstrated toxicity in particular paediatric sub-populations, e.g. the preservative benzyl alcohol, solvents such as ethanol and propylene glycol. Inclusion of these excipients in a formulation should be carefully considered and thoroughly justified and alternative excipients discussed and discounted.	Partially accepted: The text has been revised both in introduction and in later parts.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
493	1	We suggest to add palatability as another aspect to be considered in excipient selection for oral intake.	Accepted: The text has been revised accordingly.
494	10	It is unclear what is meant by “pharmaceutical technologic characteristics”. Proposed change: Change to “functional attributes”.	Partially accepted: Bullet points have been revised, “p*harmaceutical technologic characteristics*” has been replaced by “*the function of the excipient in the formulation and potential alternatives*”.
494-496	20	Delete single in line 496, - se line 503. ADIs are on daily basis. Short term and long term should be defined. Proposed change (if any): ADI (Acceptable daily intake) for the excipient and the target age groups capacity for clearance of the excipient. Safety evaluations in other EU guidelines like the Food legislation and the Scientific committee of consumer safety. … the safety profile of the excipient for children all over the indicated target age groups on basis of daily exposure (and not the concentration or strength of the medicine)	Not accepted: ADIs values have not been established for all excipients. As a general approach the safety profile should be assessed based on exposure, either single or daily, depending on the relevant setting. Information sources mentioned in the comment are already mentioned in the subsequent sections.
494-501	10	It is proposed to complete the list of aspects by: • the route of administration	Partially accepted: Bullet points have been revised to include

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• /indication (including life threatening disease (could be added behind “the characteristics of the disease”)	severity of the condition to be treated. The route of administration is not included in the list but it is discussed within Section 9.
495	10	Comment: Style Proposed change: The safety profile of the excipient for all children over the entire indicated target age groups on the basis of single…..	Comment noted. The text has been revised
495-496	5	For improved readability alternative text is suggested: “The safety profile of excipients for children across all the indicated target age groups on the basis of single and daily exposure”	Comment noted. The text has been revised.
496	10	Substitute “daily exposure” by “maximum daily excipient intake and exposure” to be more precise and for avoidance of any misunderstanding.	Comment noted. The text has been revised.
498-499, 501	11	Comment / Rationale: the criticality of the condition to be treated and the characteristics of the disease = same, no? Suggestion - Proposed change / suggested text (if any) Clarify the point above Add Rote of administration in safety profile (L495)	Comments noted. The text has been revised.
499	10	A clarification of what “the characteristics of the disease” means with respect to the excipients selected for the formulation would be helpful.	Comment noted. The bullet point has been deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
501 (and 571)	4	**Comment:** *"...allergies and sensitization."* & *"In-house information as non-published scientific evidence."* **Proposed change (if any):** Include limited use of animal derived materials when possible.	Not accepted: The issue has already been covered by the existing text at a more general level.
501	4	Consider adding the following excipient considerations. **Proposed change (if any):** • Pain of injection • Injection site reaction	Partially accepted: The paragraph has been revised.
502-515	22	Rather a long paragraph and it is difficult to see what is the 'specific regulatory guidance'.	Comment noted. The paragraph has been revised.
502-515	18	The paragraph appears rather long and it is unclear as to what is the 'specific regulatory guidance'.	See above.
502-520	10	The guidance provided in this paragraph is not as clear as in other parts of the draft guideline. This is a really important paragraph as at present there seems to be some perspective that all excipients must be avoided / minimised in products for children. Proposed change: Efpia proposes that this section be simplified considerably to better express the key points. We take these key points to be that "A proposed paediatric product should be developed to avoid unnecessary safety risks arising from excipient selection / inclusion". A very simple statement to this	Partially accepted: The paragraph has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		effect may suffice.	
504-507	5	Remove this statement as it could lead to questioning of the quality of authorized medicines.	Accepted: The text has been deleted.
511-512	10	*"In other words, applicants should not come…."* Proposed change: Delete sentence or reword as a more constructive statement.	Accepted: The sentence has been deleted.
511-512	5	More guidance would be welcome as to what the expectations are. Consideration could be given to reviewing this statement as well, as the intention is not clear.	Comment noted: The text has been revised.
513-515	30	Please clarify, that the rationale for development including a discussion of possible benefits and risks of possible alternatives is only required, in case excipients with an identified risk are used. In addition with suggest to skip the wording "of a number" and "feasible" for the following reasons: "of a number" the level of expectation is unclear to the applicant. "Feasible" a discussion of possible alternatives is useful and in the interest of the patient, however, to assess if these alternatives are feasible would require development work and testing, which is both untypical and unreasonable.	Accepted: The text has been revised.
514-515	10	*It is unclear what, the value this statement adds. "*This principle is already established in the Concept Paper for this guideline." Proposed change: Delete statement	Accepted: The sentence has been deleted as it was considered redundant.
516	10	This paragraph states that the safety of some excipients "may	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		be subject to debate" without providing any specific clarity on what excipients are meant here. Proposed change: Please provide additional specifics here or advice on where key references may be found. (The annex on excipient safety referred to in line 577 is a good idea and should be pursued in parallel with the development of this guideline.)	This guideline will not give details or references to particular excipients. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate.
516-518	18	This sentence is ambiguous and grammatically incorrect. Proposed change (if any): There are emerging evidence suggesting that the safety of some excipients that are commonly used in licensed paediatric medicines may be above the recommended daily intake or unsuitable in some target age groups. However, these information would require further research ……	Comment noted. The paragraph has been revised.
517	11	Comment: Word missing Suggestion - Proposed change / suggested text (if any) Acceptable daily intake?	See above.
519	10	Choice of excipients should be based on a documented risk /benefit assessment. Recommend using clearer language rather than the description "questionable excipients". Proposed change: "Until then, pharmaceutical companies are recommended to avoid ~~**questionable**~~ excipients **with**	Partially accepted: The text has been revised. The term "questionable excipient" has been removed from the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		potential safety concerns in new paediatric medicines."	
519	21	Please provide a list of questionable excipients	Not accepted: In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine.
519	22	What are 'questionable' excipients?	Comment noted. The term "questionable excipient" has been removed from the guideline.
519	18	What are "questionable" excipients? This is likely to be open to interpretation.	Comment noted. Reference to "questionable excipients" has been removed.
519	5	It is proposed that a table is included indicating the questionable excipients. It is proposed that questionable is defined in a way that the grounds for the questionable status are clear. Clear guidance would be welcome as to what excipients are to be avoided and in what circumstances. The mechanism for new evidence to be evaluated and the conclusions reached should be indicated in the guideline, as well as the way to make this	Not accepted: Reference to "questionable excipients" has been removed. In view of the ongoing revision of the Guideline on Excipients inclusion of a table with questionable excipients was not considered appropriate. The Guideline explains a general (high level) approach which needs to be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		information public.	followed in order to demonstrate the suitability of an excipient in a paediatric medicine. Further guidance on how to evaluate the acceptability of excipients has been added.
521-528	22	What is the 'specific regulatory guidance'?	Comment noted. The paragraph contains general comments on use of the novel excipients and flags aspects which should be considered when these excipients are used in medicines for children.
521-528	23	It is unclear if this section refers to "novel excipients" - excipients used for the first time in a drug product or by a new route of administration, or if it refers to excipients used for the first time for paediatric use. In case excipients used for the first time in a drug product or by a new route of administration are meant they should be called "novel excipients". **Proposed change**: Add an explanation that excipients used for the first time for paediatric use are not considered novel excipients.	Accepted: The text has been revised. The meaning of the term "novel excipient" has been explained.
521-528	1	It is unclear if this section refers to "novel excipients" - excipients used for the first time in a drug product or by a new route of administration, or if it refers to excipients used for the first time for paediatric use. In case excipients used for the first time in a drug product or by a new route of administration are meant they should be called "novel excipients".	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Add an explanation that excipients used for the first time for paediatric use are not considered novel excipients.	
521-528	18	It is unclear as to what is the 'specific regulatory guidance'.	Comment noted. The paragraph contains general comments on use of the novel excipients and flags aspects which should be considered when these excipients are used in medicines for children.
527	17	Where evidence is lacking research should be commissioned to evaluate safety of excipients. Although post marketing surveillance is important and should be carried out is it ethical to rely on this to establish a safety profile in children rather than have data available before marketing?	Response to comment not applicable.
527	25	Where evidence is lacking research should be commissioned to evaluate safety of excipients. Although post marketing surveillance is important and should be carried out is it ethical to rely on this to establish a safety profile in children rather than have data available before marketing?	Response to comment not applicable.
527-528	23	"If used, the safety profile of any new excipient should be closely monitored post marketing.": Is it expected that a post-approval commitment be formally submitted to address the need to monitor the safety profile of any new excipient? Proposed change: Please clarify.	Comment noted. The request to monitor new excipients in the post-authorisation phase has been removed.
527-528	1	"If used, the safety profile of any new excipient should be	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		closely monitored post marketing.": Is it expected that a post-approval commitment be formally submitted to address the need to monitor the safety profile of any new excipient? **Proposed change:** Please clarify.	
528	11	Only the safety of the final product (including the API) can be monitored post marketing. Therefore, evaluation of excipient safety related questions can only be done in context with general pharmacovigilance activities. Differentiation of any findings with respect to API or excipient as the cause for any intolerance might not always be possible. Proposed change: Delete last sentence, since safety monitoring of new products is already covered by the PSUR (post marketing safety report).	Accepted: The sentence has been deleted.
528	9	This is not a relevant to a pharmaceutical development guideline and should perhaps form part of the Risk Management Plan. The concept of post-marketing safety monitoring of an excipient is particularly difficult. It would be difficult to distinguish between adverse events caused by the active substance and those caused by the excipient unless the adverse events were markedly distinguishable from the active and disease itself. Therefore pre-approval safety characterisation (particularly non-clinical data) of an excipient is more important and relevant.	Accepted: The text has been revised.
530-531	5	For improved readability alternative text is suggested: "… allergic children, it is recommended to avoid use of	Comment noted. The text has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		excipients that are known for their … “	
531-532	10	Allergic reactions in children to specific ingredients in foods or medicines may be very rare events and cannot be fully excluded. For example, sodium benzoate is widely used as a preservative in paediatric liquid oral formulations, but is known to cause allergic reactions in some children. As a consequence of the statement in lines 531-532, development of oral liquid preparations containing preservatives should be avoided (is discouraged) and appropriate solid dosage forms without preservatives should be developed instead. Rather then banning the use of preservatives, a risk based approach should be advocated.	Comment noted. The statement is not banning the use of preservatives, but calls for precautionary approach. The text has been further revised.
535	10	Include references to specific Commission, ICH and CHMP guidelines.	Not accepted: Only a general statement that guideline should be read in conjunction with all other relevant directives and regulations, and relevant Commission, and CHMP guidelines, Q&A documents and other documents as linked to or published on the EMA website has been kept. The list of regulatory documents has been deleted form the guideline.
538	10	In the Information sources to be consulted, the composition of currently authorised medicines for children is listed. Is it possible to find a list from the EMA website containing all	Comment noted. There is no dedicated list containing all approved excipients in the paediatric medicines. Qualitative information about

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"approved" excipients in these approved products for children?	product's composition may be found in the PI, the quantitative composition is usually not available publicly. The text has been revised.
538	5	It is proposed that a database will be set up providing a list of excipients in the currently authorized paediatric medicines.	Not accepted: At present, no such list is foreseen. It has been acknowledged that this information might not always be available or easy to access. Text has been revised, 'if available' was added.
539	17	It is essential that full consideration is given to the likely exposure to excipients across the expected age and dose ranges.	Comment noted. The comment has already been reflected in the existing text.
539	25	It is essential that full consideration is given to the likely exposure to excipients across the expected age and dose ranges.	Comment noted. The comment has already been reflected in the existing text.
539-542	13	How does a formulator get access to the excipient quantities used in existing paediatric medicines? I see this as the only way of accurately determining "maximum daily excipient intake" in existing medicines.	Comment noted. The quantitative composition of excipients may not always be publicly available, the text has been revised and 'if available' was added.
541-542	10	*The text* "in all or a sample of the licensed medicines" *causes confusion and does not seem to add value to the prior statement*	Accepted: The text has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Delete the text " in all or a sample of the licensed medicines"	
542	18	Requires a statement about maximum daily excipient intake and exposure with account taken of potential age related differences in clearance of excipients, in particular in premature neonates and neonates in general.	Comment noted. The comment has already been reflected in the existing text.
545 and 565	23	We understand food legislation is applicable as well for children. It may be worthwhile to specify that food information is of limited use for infants and toddlers. Proposed change: Please clarify.	Comment noted. The background information for the food legislation does not necessarily specifically relate to paediatric data, so these sources should be handled with care. Text partly revised.
545 and 565	1	We understand food legislation is applicable as well for children. It may be worthwhile to specify that food information is of limited use for infants and toddlers. Proposed change: Please clarify.	See above.
546	22	What does 'rather wide' mean? As read I take it to mean that lower limits are required for medicines compared to foods. How should this be dealt with?	Comment noted. The text has been revised.
546	18	What does "rather wide" mean? We consider this is intended to say lower limits are required for medicines compared to foods. Further 'specific regulatory guidance' is required in this section.	Comment noted. The text has been revised.
576	10	An annex providing an oversight of the most current information	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		regarding excipients would be extremely helpful. What is the timeframe for the annex? Comment: Does the EMA intend to work with industry to develop the contents of the annex? Efpia would recommend that they do?	In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine.
576	13	In our opinion the idea of an annex is good, in principle, if it contains references or reference locations that can be used to risk assess the use of a particular excipient in a formulation. However, we believe that if the purpose of the annex is to create a positive and negative list of excipients this will actually hamper paediatric formulation development by restricting innovation and cost control.	Comment noted. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine.
577-580	5	It is helpful to indicate when this annex will be issued and what the contents will be. There may be excipients available with enough safety data not requiring any further justification as they may be generally accepted as safe for use in paediatric medicines.	Comment noted. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine.
577	10	Please provide more information on the content of the intended annex from the agency. Will this annex be some kind of a	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		positive and negative list? The following information would be highly appreciated in an annex as already published in the article from Prof. Jörg Breitkreutz & Joachim Boos: "**Paediatric and geriatric drug delivery",** 2007 (see attached pdf file): Name of the excipient, route of administration (e.g. oral or parenteral), adverse reaction.	
578	22	Most of the information in this section should be in the annex. What is required here is the 'specific regulatory guidance'.	Comment noted. In view of the ongoing revision of the Guideline on Excipients inclusion of an annex to the Guideline was not considered appropriate. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine.
581	9	The decision tree needs revision, restructuring and the individual steps need validating. At each of the evaluation points there is no opportunity to say 'No'.	Accepted: The decision tree has been revised.
581	9	The decision tree needs revision, restructuring and the individual steps need validating. At each of the evaluation points there is no opportunity to say 'No'.	See above.
581	13	Decision tree – there is no path forward if the answer to the first question "is there a CHMP opinion available?" is "No"	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
581	13	In the Decision tree are the sources for “precedence of use” in rank order of importance/validity, or is this a random order?	Comment noted. The decision tree has been revised. The hierarchy of the information sources has been further clarified in the guideline.
581	4	**Comment:** Decision Tree **Proposed change (if any):** Decision tree not actionable with the use of vague and subjective terms such as *“is it relevant,”* “*up to date”* and *“applicable to age group.”* Consider not providing a decision tree but only a list of bullets as items to consider if these terms cannot be better specified.	Comment noted. The decision tree has been amended. Further explanation was included in the General considerations sections within Section 9.
581	10	This figure is useful but needs to be larger in size to allow it to be read. From what one can read presently, we wonder why a decision should be ‘within 5 years’ and we also wonder how this table will work in a year’s time (will it then be ‘within 6 years’ or a rolling 5 years ? why is a rolling 5 years relevant ?). Why does an excipient need to be present in a number of previous paediatrics medicines - rather than just in one?)	Comment noted. The decision tree has been revised, comments partly taken into consideration. Reference to the 5 years period has been deleted.
581	10	The flow diagram does not provide an option if the answer is “no” to any of the main questions (in the hexagonal boxes). What strategy should be followed if one or multiple are answered ‘NO’. It is not completely obvious if it means stop or go for the different options. Proposed change: Complete flow diagram. Add the “No”s to the hexagonal large boxes. Route of administration should also be	Accepted: The decision tree has been revised.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		considered.	
581	10	For better understanding of the flowchart it would be helpful to include a “NO” line from the questions in the hexagonals.	See above.
581	10	Decision tree not actionable with the use of vague and subjective terms such as “is it relevant,” “up to date” and “applicable to age group.” Proposed change: Specify in text what exactly is meant by “relevant,” “up to date” and “applicable to age group.”	Comment noted. The decision tree has been amended. Further explanation was included in the General considerations sections within Section 9.
581	10	Would previous usage in clinical studies count as “current paediatric medicines”? Clarification needed.	Comment noted. Medicinal products used in clinical studies are not considered to be authorised medicinal products.
581	10	At the end of the Figure 1 decision tree, it is proposed to add an alternative option to the text “Conduct animal studies”, as below: Proposed change: “Conduct animal studies **or develop an alternate dosage form or route of administration where such excipients are not needed**”.	Partially accepted: The text has been revised accordingly: “Additional data needed (e.g. juvenile animal studies, PK data, clinical studies), alternatively reformulate”.
581	10	There may be cases that an excipient does not have a CHMP opinion available and there are no Commission/CHMP/ICH guidelines available, but the excipient is approved in current pediatric medicines. According to the flowchart the following requirements need to be adhered to in this case: 1) it must be approved in a product with a comparable or higher	Comment noted. The diagram was intended to be all inclusive as described. Conclusion should be based on an overall assessment of available information.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		daily exposure AND 2) it must be administered in a more risky or comparable route AND 3) it must be administered during a comparable or longer duration AND 4) it must be for a more serious or comparable indication AND 5) there must be no new data relevant to safety that have not been considered. Was the flow diagram intended to be all-inclusive as drawn or does the	
581-582	23	Comment: Decision tree, END means also proceed or go with the use of the excipient? Proposed change: If yes, suggest to add some wording on that Comment: Is the excipient approved in a number of current paediatric medicines? Proposed change: Please specify a number Comment: The concentration of an excipient in a marketed product is usually not known by the applicant unless it is a product of this company. Proposed change: Delete the box with the daily exposure Proposed change: In Figure 1 (decision tree for the use of excipients) an option for “No” at the main decision points should be added.	Partially accepted: The decision tree has been revised. The term “END” has been further clarified and the option “No” has been included in the flow diagram. The quantitative composition of excipients may not always be publicly available, the text has been revised and ‘if available’ was added. Deletion of the box with daily exposure was not endorsed.
581-582	1	Comment: In the decision tree, does END also mean proceed or	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		go with the use of the excipient? Proposed change: If yes, suggest to add some wording on that Comment: Is the excipient approved in a number of current paediatric medicines? Proposed change:Please specify a number Comment: The concentration of an excipient in a marketed product is usually not known by the applicant unless it is a product of this company. Proposed change: Delete the box with the daily exposure Proposed change: In Figure 1 (decision tree for the use of excipients) an option for “No” at the main decision points should be added.	
582	9	Line 582 is missing. The missing text should be added as it impacts on the sense of Lines 583 and 584.	Accepted: Lines 583-584 were explanatory note to the figure. Sentence has been clarified.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
582	21	There may be cases that an excipient does not have a CHMP opinion available and there are no Commission/CHMP/ICH guidelines available but the excipient is approved in current pediatric medicines. According to the flow chart the following requirements need to be adhered to in this case: 1) it must be approved in a product with a comparable or higher daily exposure AND 2) it must be administered in a more risky or comparable route AND 3) it must be administered during a comparable or longer duration AND 4) it must be for a more serious or comparable indication AND 5) there must be no new data relevant to safety that have not been considered. Was the flow diagram intended to be all-inclusive as drawn?	Comment noted. The diagram was intended to be all inclusive as described. Conclusion should be based on an overall assessment of available information.
582	21	For better understanding of the flowchart it would be helpful to include a “No” line from the questions in the hexagonals.	Accepted: The decision tree has been revised.
583-584	10	“end i.e. no further need to justify the use of the particular excipient in the paediatric medicine (when the excipient or the medicinal product meets the conditions stated)” Proposed change: “END i.e. no need to further justify the use of the particular excipient in the paediatric medicine”	Accepted: The term “END” has been further clarified.
583-584	4	*“end i.e. no further need to justify the use of the particular excipient in the paediatric medicine (when the excipient or the medicinal product meets the conditions stated)”* Proposed change (if any): Consider adding clarity surrounding the term, “end”.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
585-599	12	Colouring Agents – this text might benefit from a slight reorder in that the overriding message is that paediatric medicines should not normally be coloured. Therefore the use of the specific approved colouring agent should be balanced against the potential risks of adding the colouring agent in terms of allergenic potential etc. Therefore, in line 598 – 599 it should really read that the lack of a colouring agent should be explained rather than justified because as currently written it seem to contradict what it said in 598-599.	Comment noted. The text has been revised, to clarify that colouring agents may be used in medicines for children. It has been explained that that the use of any specific colouring agent in a paediatric medicine should be discussed and justified.
586-589 (and 547-548)	10	Colouring agents: In section 9.1 it is stated that "all…colorants described in the Food Legislation and acceptable for the paediatric population are normally considered acceptable for use in oral paediatric medicines…." However, in section 9.2 it is stated: "…paediatric medicines should normally not be coloured". Please provide a clarification of "normally" in these 2 texts.	Comment noted. The text has been revised, to clarify that colouring agents may be used in medicines for children. It has been explained that that the use of any specific colouring agent in a paediatric medicine should be discussed and justified.
586-589	10	*" …paediatric medicines should normally not be coloured"* Comment: This general statement for paediatric medicines (all age groups) is deemed disproportionate, considering the amounts of coloured foods (e.g., candies/sweets) children of a certain age consume. Some medicines also need to be differentiated from others, e.g. adult formulations or formulations for different age groups, and there are only limited alternatives. The use of different shapes requiring different tablet tooling is not always feasible for technical reasons. The colour could be less harmful than the wrong dose, therefore it is	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		not considered justified to use “normally”. Efpia agrees that use of colours should be justified on a case by case basis. Proposed change: Either delete sentence since the statement in lines 592-594 is much more meaningful or replace by statement such as “Paediatric medicines should normally not be coloured unless there is no other alternative to differentiate between medicines and to avoid accidental dosing errors. Whether it makes sense that paediatric medicines are coloured should be decided on a case by case basis, taking into account the various age groups for which different unit dosage forms have to be given as well as the existing adult formulations.”	
587-589	10	The sentence which states that patients have a choice of foods but not of medicines, is unnecessary since this argument holds to most excipients, and not only to colouring agents. Proposed change: Remove the sentence.	Accepted: The text has been revised accordingly.
589	13	Use of colour is discussed as something to avoid but also something that may be justified to avoid accidental dosing errors, especially in multi-particulates that cannot be printed or embossed. Line 589 could be altered slightly to reflect the positive role colour can provide. Proposed change (if any): As a consequence, paediatric medicines should not be coloured solely for aesthetic reasons.	Comment noted. The text has been revised.
589	1	Conflict with the information given on page 16 related to colorants deemed acceptable for paediatric solid oral dosage	Accepted: The text has been revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		forms. **Proposed change:** Delete the paragraph. Keep the flexibility. Colours are useful to differentiate between different paediatric medicines and this should be kept flexible. The parallel with food is neither appropriate nor relevant here given the minimum amount that is ingested with the medicine.	
589	9	Medicines may need to be coloured for the purposes of improving appearance, palatability and compliance. They may be coloured to distinguish strengths of product. Like other excipients included in the formulation, the use and choice of a particular colourant or colourants should be justified. Justifications should be relevant to the particular paediatric sub-population.	Comment noted. The text has been revised.
590-592	10	*"The use of any specific colouring agent in a paediatric medicine should be discussed and justified in terms of allergenic potential, minimal toxicological implications in the target age groups, child patient and caregiver's acceptability…"* Comment: A paediatric formulation is not a consumer product but for use in patients. Therefore, it is not considered justified to include acceptance by the caregiver regarding colouring. Proposed change: Delete "caregiver's"	Accepted: The text has been revised and "caregiver's" was deleted.
590-597	21	What is the PDCO point of view regarding pigments for coloring? Are the pigments for coloring considered as better coloring agent alternatives?	Not accepted: At present there is no clear evidence that pigments are better/safer than other colouring

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: "…as better alternatives are commonly available, **i.e. coloring pigments.**"	agents.
590-597	10	What is the PDCO point of view regarding pigments for coloring? Are the pigments for coloring considered as better coloring agent alternatives? Proposed change: "…as better alternatives are commonly available, **i.e. coloring pigments.**"	See above.
599	5	It is unclear what is meant by "... in the light of all measures undertaken ... ". Please specify.	Comment noted. The text has been revised. It has been further explained that that the use of any specific colouring agent in a paediatric medicine should be discussed and justified.
601-608	9	This section should be expanded to include guidance on palatability and taste tolerance. It should also acknowledge the difficulties caused by subjectivity, the potential inappropriateness of conducting taste trials in paediatric populations and cultural and geographic differences in what constitutes a palatable medicine. The texture and feel of oral flavoured medicines should be mentioned.	Partially accepted: Inclusion of a discussion about palatability aspects within section 9.3 was not considered appropriate. However, more detailed discussion on acceptability, including palatability, has been included within Section 10.
601-608	10	*"the rationale […] justified according section 9.1. and 9.5"* Comment: Reference to section 9.1. is not required, as this is part of the same chapter (this applies to all chapters in section 9).	Not accepted: The use of colouring agents, unlike other excipients, is governed by a specific directive. The use of flavouring agents should be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		It is also not clear, why the justification for flavours should be done according to criteria in section 9.5. concerning sweeteners. Moreover, flavouring agents are covered by EU food legislation. Proposed change: Similar to colorants, appropriate reference should be made to the existing EU regulatory framework.	discussed in relation to their use in food.
603	10	Comment: typo Proposed change: Add in "to" in sentence justified according to section…	Comment noted. The paragraph has been revised, reference "to" sections 9.1 and 9.5 were removed.
604	10	It is unclear why natural flavours are preferred over synthetic flavours (if these have a precedent use in paediatric medicines).	Comment noted. The statement "Natural or chemical equivalents of natural flavours should be used if possible." has been removed.
605	10	Clarify the difference between a chemical equivalent of a natural flavour and a synthetic flavour (both could be made synthetically).	See above.
605	10	The acceptability of a flavour, be it natural or artificial, should be linked to data. Natural flavours may have varied profiles due to seasonal nature and may not be preferred. Proposed change: 'The use of flavours should be justified by the company, including the choice of natural *versus* synthetic flavours. ~~Natural or chemical equivalents of natural flavours should be used if possible.~~'	Partially accepted: The text has been revised. The statement "Natural or chemical equivalents of natural flavours should be used if possible." has been removed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
606	10	It can be difficult to provide the composition of natural or synthetic flavours. Some third party companies do not provide the compositions of flavours or only under a secrecy agreement. (Here we suffer from having no DMF procedure for excipients). Due to the complexity of the composition of flavours it may also be difficult to evaluate their potential impurities. Would such provision of information be needed for a natural flavour? Would it be needed for a flavour precedented in approved paediatric medicines? Proposed change: *"The qualitative composition of flavours should be provided. See* EMEA/CHMP/QWP/396951/2006*. In addition, safety concerns should be discussed. Where possible t~~T~~hese concerns should include potential impurities (i.e. residual solvents) and the risk of allergies and sensitization."*	Comment noted. The text has been revised.
605-606	10	Please clarify "chemical equivalents of natural flavours". Is the guidance referring to nature-identical flavouring substances? Proposed change: "Natural or **nature-identical** flavour substances should be used if possible."	Comment noted. The statement "Natural or chemical equivalents of natural flavours should be used if possible." has been removed.
605-606	21	Please clarify "chemical equivalents of natural flavours". Is the guidance referring to nature-identical flavouring substances? Proposed change: "Natural or **nature-identical** flavour substances should be used if possible."	See above.
605-606	23	The quantitative composition of a flavour can only be provided for an individual substance. For flavours consisting of mixtures, quantitative composition of a flavour is proprietary knowledge of	Comment noted. The paragraph has been revised. It has been

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the flavour supplier and not known by the applicant. As long as there is no DMF procedure for excipients in Europe there is no mechanism to provide this information Proposed change: Remove “quantitative” from the sentence.	clarified that the qualitative an quantitative composition of any components of the flavouring agent that are known to have a recognised action or effect should be provided. This is already required by existing guidelines (SmPC).
605-606	1	The quantitative composition of a flavour can only be provided for an individual substance. For flavours consisting of mixtures, quantitative composition of a flavour is proprietary knowledge of the flavour supplier and not known by the applicant. As long as there is no DMF procedure for excipients in Europe there is no mechanism to provide this information. Proposed change: Remove “quantitative” from the sentence.	See above.
606	8	It is impossible for providing the quantitative composition of flavours for the pharmaceutical companies. The composition of a flavour is usually confidential and the intellectual properties are usually restricted to the chemical provider. The quantitative composition is usually not required for safety evaluation, but the qualitative composition for sure. Proposed change: ‘...qualitative composition...’	See above.
607-608	5	It seems unsuitable to assess the impurities in the flavours themselves. It is proposed to assess the impurities as a part of drug product specifications. Proposed text:	Comment noted. The text has been revised .

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"The safety concerns on the residual solvents should be considered. The other impurities should be evaluated in the finished product specification."	
609	5	Please incorporate some discussion regarding the margin of amounts in addition to the minimum effective amount.	Comment noted. The text has been revised.
609-620	9	Specific preservatives should be mentioned here, for example the parabens and benzyl alcohol. Unpreserved, sterile products may be a viable alternative for certain medicines in certain circumstances. It may also be helpful to acknowledge that it is recognised that suitable alternative preservatives may not be always be available or compatible with the active ingredients and under these types of circumstance, less attractive alternatives may become justifiable.	Not accepted: The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. Specific excipients are not discussed in this guideline.
610	10	'Preservatives have a potential to cause toxicological problems,…' – This is a very general statement – preservatives vary greatly in their potential to cause adverse effects, depending on type of preservative, concentration, route of administration, age group, etc. It would be helpful to provide more specific information and examples. Proposed change: Please provide more specific information on preservatives. It would be helpful if specific preservatives were listed here as is done for sugars and sweeteners in lines 625-628. Alternatively, include a reference to where further information could be found.	Comment noted. The text has been revised. Further guidance on the use of preservatives has been added. The Guideline explains a general (high level) approach which needs to be followed in order to demonstrate the suitability of an excipient in a paediatric medicine. Specific excipients are not discussed in this guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
610-620	31	In this section, it should be more clearly emphasized that total avoidance of preservatives has to be the aim of the pharmaceutical development of medicines for paediatric use. Proposed change (if any): Preservatives have a potential to cause toxicological problems, especially in young children. The need to preserve the paediatric medicine and the choice of the preservative system at the lowest concentration feasible should be justified in terms of risk to benefit balance. The risk to benefit balance should at least take account of the facts as described underneath. It is emphasized that the general chapter on excipients also applies to preservatives. The appropriateness of the preservative system for the indicated target age groups should be discussed. It may become necessary to use more than one preservative in certain circumstances. The individual and combined toxicity of the preservatives should be considered. When the lowest concentration feasible to achieve appropriate microbiological preservation is close to the level that would not be acceptable from a safety prospective, applicants should consider alternative dosage forms. Pharmaceutical companies are encouraged to consider novel strategies that allow the preservative-free formulation of paediatric medicines.	Partially accepted: A balanced approach regarding the use of preservatives is needed. Text has been revised to encourage strategies to allow preservative free formulations.
614	18	Some confusion here as to what is being considered as	Comment noted

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		excipients	The text has been revised.
617-620	10	The notion of concentration “close to the level that would not be acceptable from a safety perspective” is too vague and should be clarified. Usually the preservative ranges are narrow by nature. Either the ranges in the literature are considered acceptable or they are deemed inacceptable. Efpia suggests that the recommendation to consider other dosage forms would apply to situations where the lowest concentration to achieve microbiological preservation is beyond the acceptable safety level. Proposed change: *“When the lowest concentration feasible to achieve appropriate microbiological preservation is ~~close to the level~~ beyond the level that would not be acceptable from a safety prospective, applicants should consider alternative dosage forms.”*	Comment noted. The text has been revised.
621-643	9	The choice of sweetener, like the choice of flavouring, should not be made in isolation but should be justified based on the taste of the active substance.	Comment noted. These aspects are already discussed in the text. Also are further addressed in the revised text of Section 10.
621-643	10	To add as a new paragraph: Excipients for improvement or masking of the taste: Alternative methods for masking bad taste should be added. Reason: By using these methods the amount and / or number of excipients may be reduced for example by multifunctional	Comment noted. No new paragraph has been added however relevant elements have been included and discussed in revised text of Section 10.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		excipients. Proposed change (if any): add as new paragraph: *"Lowering of concentration of free molecules of the drug substance (for example by coating of the particles of a suspension, building of molecule complexes) or diminishing of contact time with the receptors by examples: use of lipophilic vehicles, increase in viscosity etc."*	
621	17	Where cariogenic sugars are used the product should carry a warning/advice to clean teeth after each dose. The side effects of non cariogenic sugars eg sorbitol should not be underestimated.	Comment noted. Potential side effects non cariogenic sugars have already been mentioned in the initial text. The use of cariogenic sugars is also addressed in the section.
621	22	Much of this section is not specific to children and reads like a textbook for pharmaceutical development.	Comments noted. The text has been revised.
622-628	11	I am not sure if the classification provided is the right one Typically the following is used Nutritive (Provides energy to body) – Sugar (sucrose, dextrose, fructose, lactose) – Corn syrup – High fructose corn syrup – Sugar alcohols (polyols)	Comment noted. The text has been revised, classification of sugars has been deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		☐ Non-Nutritive – High-intensity sweeteners Then polyols and intense sweeteners have the further characteristic to be non cariogenic. Polyols pause problem of digestive tolerance for some of them. I would kep cariogenicity and digestive disturbance for the list of considerations but would not base my classification on that. Also there are some natural intense sweetener(even if not necessarily used in pharma products); they are not all synthetic. Suggestion - Proposed change / suggested text (if any): In terms of formulation, they could be viewed as bulk agent or not (High-intensity sweeteners) as it will dictate their quantity in the formulation and the related risk assessment to be made.	
622-643	18	Much of this section is not specific to children and appears to have been lifted from a textbook for pharmaceutical development. More 'specific regulatory guidance' is required in this section.	Comment noted. The text has been revised.
622-643	25	Where cariogenic sugars are used the product should carry a warning/advice to clean teeth after each dose. The side effects of non cariogenic sugars eg sorbitol should not be underestimated	Comment noted. Potential side effects non cariogenic sugars have already been mentioned in the initial text. The use of cariogenic sugars is also addressed in the section.
624-628	10	Three categories of sweetening agents are presented (cariogenic, non-cariogenic and synthetic) – for completeness,	Comment noted.

<table>
<tr><th>Line number(s) of the relevant text</th><th>Stakeholder number</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>we suggest to include natural sweeteners as well. It may be easier to present the categories in the form of a table:<table><tr><td></td><td>Cariogenic</td><td>Natural</td></tr><tr><td>Natural</td><td>glucose, sucrose, fructose</td><td>Artificial</td></tr></table></td><td>The text has been revised. The classification of sweeteners has been removed.</td></tr>
<tr><td>628</td><td>21</td><td>Sucralose is suggested to be listed as additional sweetening agent.

Proposed change: “synthetic sweetening agents (e.g. aspartame, acesulfame, potassium [Ace K], saccharin, <u>sucralose</u>”</td><td>Comment noted.

The text has been revised. The list of sugars has been deleted.</td></tr>
<tr><td>628</td><td>23</td><td>• As sucralose is a commonly used synthetic sweetener please add it to the list.

Proposed change (if any):

add Sucralose as part of e.g addition</td><td>See above.</td></tr>
<tr><td>628</td><td>1</td><td>As sucralose is a commonly used synthetic sweetener please add it to the list.

Proposed change: Add Sucralose as part of e.g. addition.</td><td>See above.</td></tr>
<tr><td>629-643</td><td>10</td><td>Co-morbidity is another factor to be taken into account when deciding whether or not to use sugar (e.g. diabetes).</td><td>Accepted:

The text has been revised and suitability in</td></tr>
</table>

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: However, the following considerations should normally also be taken into account when choosing a formulation and justified. • effect of sugar content on teeth • …. *co-morbidity that would preclude the use of sugar (e.g. diabetes)*	relation to other conditions included.
636-637	9	There is some concern about the robustness of medicines using sugars (with no additional preservative) and this is not something we would want to see in a guideline in case it encourages the use of high sugar preserved products. Consideration should be given to removing this statement.	Accepted: The text has been revised. The bullet point was deleted.
636	18	Wording such as “more or less” is not appropriate for a regulatory guidance. A more definitive statement should be used.	Comment noted. The text has been revised. The term has been removed.
636	22	‘more or less’ is a strange statement to have in regulatory guidance. Are they self-preserving or not?	Accepted: The term has been removed.
642	10	“Compatibility” with other ingredients – this is part of the overall stability evaluation of any formulation and not a specific issue related to paediatric formulations or to flavours. Proposed change: remove this point.	Comments noted. The point has been removed and the text further revised.
643	10	Some sweeteners are known to affect gastric transit which	Comments noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		affects bioavailability. Proposed change: This could justify a separate bullet that effect of sweeteners on gastric transit should also be considered.	The paragraph has been revised. The guideline asks to consider the potential laxative effect of polyols (e.g. sorbitol, mannitol) and flags the fact that the osmotic properties of polyols may also affect bioavailability.
643	10	*"Any effect of the sweetening agent(s) on the absorption of the medicine in the sick child"* Comment: A clarification of the following points is necessary: - What is the rationale for this point? - Does this relate to non-cariogenic sugars? - Why are especially sick children mentioned?	Comment noted. The text has been revised and the reference to "sick child" has been removed. Only general discussion on potential effect of polyols on bioavailability is mentioned in the revised text.
643	10	There is no mention of the impact of disease state. Proposed change: Consider adding impact of disease state to the bullet list after line 643, i.e. high levels of natural sugars may not be appropriate for any age group with severely impaired renal systems.	Accepted: The text has been revised and suitability in relation to other conditions included.
643	13	There is a long discussion about the use of sucrose as a sweetener, however sucrose can also be used as a substrate for drug layering. Used in this manner the sucrose is unlikely to come into direct contact with the teeth, the amount of sugar used will also be limited minimising the risk of dental caries. I believe that, within this section, provision should be made for	Not accepted: Section 9.5 is dedicated to substances which are used as sweetening agents. The use of sucrose as substrate for drug layering is not addressed in this section, however and the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the use of sucrose as a drug layering substrate rather than solely as a sweetening agent.	guideline text does not discourage such use.
643	4	There is no mention of the impact of disease state. Proposed change (if any): Consider adding impact of disease state to the bullet list after line 643, i.e. high levels of natural sugars may not be appropriate for any age group with severely impaired renal systems.	Accepted: The text has been revised and suitability in relation to other conditions included.
643	5	It is assumed that an impact evaluation of the effect of sweetener on the absorption of a medicine in a sick child is very difficult. During safety and efficacy studies the drug product is evaluated. Please provide an example procedure how to evaluate excipient effects in sick children.	Comment noted. The text has been revised and the reference to “sick child” has been removed. Only general discussion on potential effect of polyols on bioavailability is mentioned in the revised text.
644-724	9	As there appears to be three separate topics discussed: Patient Acceptability, Palatability and Mixing with food, it may be helpful to divide this large block of text into these sections to improve readability and make referral easier. Specific guidance on exactly what types of studies would be expected in a Marketing Authorisation Application for a paediatric medicine could be provided. It may be helpful to provide further information on the type of data required to demonstrate palatability, patient acceptability, ease of use and accuracy of dosing.	Accepted. Two sub-headings (i.e. Palatability, Mixing with Food) have been added to break-up this long piece of text and make it more readable. Partially accepted: The comments are partially endorsed and the text has been amended. Exact guidance can not be given, although expectations with respect this issue are indicated in the revised text.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
644	7	*Patient Acceptability:* The Patient Acceptability is mainly determined by the route of administration and dosage form. Both of them are usually well known in general. There is no need to evaluate patient acceptability as an integral part of all pharmaceutical development studies, which makes them more complicated and more extensive. We recommend restricting this evaluation to medicines which use new/critical routes of administration and/or dosage forms.	Not accepted: Generic medicine should be equivalent (or better) in acceptability to the innovator. The statement on acceptability applies to both new and generic medicines.
644	22	This section reads like a textbook for pharmaceutical development.	Partially accepted: Comment noted.
644	19	Much of this section appears to have been lifted from a textbook for pharmaceutical development. More 'specific regulatory guidance' is required in this section.	Partially accepted: Comment noted.
644	23	Comments to 10. Patient Acceptability: Full agreement that patient acceptability should be an integral part of the pharmaceutical development. Questions for palatability should be integral part of clinical efficacy/safety studies.	Accepted: The following text has been added: "Patient acceptability of the medicinal product should be studied in children themselves as part of any clinical study involving the proposed product."
651-652	18	Unclear meaning of this final sentence in paragraph.	Accepted: For paediatric medicines, the user may comprise both the child and its adult caregiver.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The sentence is unclear and might be interpreted to mean that the parent uses the medicine. The following sentence has been used instead at start of this chapter. “Patient acceptance can be defined as the overall ability and willingness of the patient to use a medicinal product as intended and its care giver to administer the medicine as intended”.
653 and 661	18	Paragraphs starting at line 653 and at 661 have considerable repetition	Accepted: The text line 661 has been deleted: “For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient acceptability is also encouraged to be tested during paediatric clinical trials if any”. The text line 653 remains “Evaluation of the patient acceptability of a paediatric medicine should be an integral part of the pharmaceutical development studies”.
654 – 660	5	There is too much emphasis on acceptability, no guidance is included as to what acceptability levels are expected, and what overall will be considered as adequate acceptability levels. It is suggested to include this in the guideline or change priority	Accepted: Acceptability levels are mentioned.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		setting. (See also comment on lines 207 -221).	
654 – 656	5	It seems unnecessary to differentiate between medicines failing under the scope of the Paediatric Regulation or those outside the scope: The standards for paediatric medicines should be the same. Proposed text: "Evaluation of the patient acceptability of a medicine should be an integral part of the pharmaceutical development studies. ~~For medicines falling under the scope of the Paediatric Regulation, p~~ Patient acceptability of the medicine may preferably be studied in children themselves"	Accepted: The text "for medicines that fall under the scope of the Paediatric Regulation" has been deleted.
655-656	2	Patient acceptability of the medicine should be studied in children themselves as part of the clinical trial and not only as "preferably" in our opinion. Proposed change (if any): "preferably" to be suppressed, "unless to be duly justified" to be added at the end of this key sentence.	Accepted: The text has been revised to "Patient acceptability of the medicinal product should be studied in children themselves as part of any clinical study involving the proposed product"
659	2	Adult data is necessary to be taken into account Proposed change (if any): ", taken into account that adult data is the first necessary step for improvement of palatability in medicines intended for paediatric use" to be added at the end of the sentence	Not accepted: Acceptability of the dosage form is usually assessed in children. Reference to adult data is made in regard to palatability.
660	10	Comment: Style	Partially accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: ..are due to poor or a lack of patient acceptance	Although valid this sentence has been deleted. ("It should be thoroughly investigated if drop outs and poor compliance during clinical trials are due to bad patient acceptability").
661-667	23	It is not clear why this guidance states that adequate patient acceptability is encouraged for medicines that do ***not*** fall under the scope of the Paediatric Regulation. Is this section intended to address the fact that if an adult formulation is to be used as a paediatric formulation, the palatability of the adult formulation must (at a minimum) be assessed in adults, while the actual study of palatability in children may be addressed as a post-approval commitment? Proposed change: Clarification; this text seems somewhat contradictory to the scope of this draft guideline (lines 124-126).	Accepted: The text "for medicines that fall under the scope of the Paediatric Regulation" has been deleted.
661-667	1	It is not clear why this guidance states that adequate patient acceptability is encouraged for medicines that do ***not*** fall under the scope of the Paediatric Regulation. We believe this is an error. Proposed change: This text seems somewhat contradictory to the scope of this draft guideline (lines 124-126). Please delete.	Accepted: The text "for medicines that fall under the scope of the Paediatric Regulation" has been deleted.
661	28	*"For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient acceptability is also to be tested during paediatric clinical trials."* Comment: A clarification is deemed necessary on what is meant	Accepted: The text "for medicines that fall under the scope of the Paediatric Regulation" has been

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		by “medicines which do not fall under the scope of the paediatric regulation” – such medicines out of scope should not be addressed in this guideline. In case the statement refers to the PUMA process as laid down in regulations (EC) No 1902/2006 and 1901/2006, it should be reworded accordingly.	deleted.
661	10	This paragraph is considered unclear. The term ‘patient acceptability’ is defined above as involving several factors, BUT the specific focus on ‘palatability’ in line 663 leads to question whether the guidance on lines 665 to 667 relates to all aspects of patient acceptability or only relates to childrens' palatability acceptance. Proposed change: Please revise this paragraph for improved clarity.	Accepted: Chapter 10, patient acceptability now has a separate sub-paragraph for palatability -
661-666	5	It seems unnecessary to differentiate between medicines failing under the scope of the Paediatric Regulation or those outside the scope. The standards for paediatric medicines should be the same. Proposed text: ~~For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient acceptability is also encouraged to be tested during paediatric clinical trials if any. If not, adequate~~ “Palatability could be demonstrated ~~otherwise~~ e.g. by data from literature, studies in dedicated adult panels or feedback from patients who have been using the same or a similar product. In	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		absence of actual data in children, applicants are encouraged to confirm the adequate patient acceptability post…"	
662	2	Acceptability studies in children should be done whenever possible Proposed change (if any): "strongly" after "*encouraged*" and ", due to major impact on adherence / compliance" at the end of the sentence	Accepted: The text has been revised to "Patient acceptability of the medicinal product should be studied in children themselves as part of any clinical study involving the proposed product"
668-693	The United Kingdom 9	Cross-reference to the guideline section on palatability should be made.	Not accepted: This comment is not understood as line 668 is in the palatability section.
668-678	5	Since there is good correlation from palatability studies in adults and acceptability in children, it should be made clear that studies performed in adults provide adequate confirmation. Furthermore, the guideline seems to fail to recognise that a main element of patient acceptance of any medicine is the necessity to take it in order to obtain a curative effect, improve health or prevent worsening of the condition. Please rephrase or remove statement.	Partially accepted: Reference to adult palatability studies is made in the text "Information on the palatability of the active substance should consequently be acquired at an early stage in the development of a medicinal product, e.g. from dedicated adult panels and literature". Children don't always recognise curative effect but recognition of adult studies is a good point.
668-678	10	*Palatability testing* An opinion regarding testing of palatability in healthy children (when the drug is considered safe) and concerning the option of	Not accepted: Specific guidance on the design of a palatability study is not be given in the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		palatability studies with a swirl and spit out approach should be given in the guideline (as mentioned in EMA 2008 ethics guidance).	guideline.
671	2	Complementary concept Proposed change (if any): ", on the tongue" to be added at the end of the sentence	Not accepted: The text is "Palatability is defined as the overall appreciation of an (often oral) medicinal product towards its smell, taste, aftertaste and texture (i.e. feeling in the mouth)" which is thought acceptable.
671-672	2	To push for innovative solution in difficult situations Proposed change (if any): "it" and "Of note, some active ingredients (in particular with bitter or acid taste) are known to have a bad palatability and difficult to be masked by traditional techniques and an innovative age-appropriate formulation is necessary for their acceptance in children."	Not accepted: This statement is considered to vague to be appropriate.
674-675	22	What evidence is there of the accuracy and comparability of the electronic tongues (various devices of differing technology) with taste panels or child patients?	Accepted: Reference to electronic tongue has been removed.
674-675	9	What evidence is there of the accuracy and comparability of the electronic tongues (or various devices of differing technology) with taste panels or child patients?	See above
674-675	2	Necessary specifications Proposed change (if any): "and children panels when necessary"	Not accepted: Examples of "dedicated adult panels and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		after “adult panels”, “(for bitter taste).” to be added at the end of the sentence	literature” has been sighted. The absence of reference to children’s panels does not exclude them.
674	5	There is no sufficient data or supportive evidence available to date that palatability data generated with an electronic tongue are representative for the in vivo situation. It is therefore recommended to remove remarks to the use of an electronic tongue with regards to palatability testing. It can be included with regards to salt selection screening during development.	Accepted: Reference to electronic tongue has been removed.
675-678	4	*“The palatability of the active substance should contribute to the choice of the selected finished dosage form(s) and route(s) of administration. Unless otherwise justified, the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or beverages).”* Proposed change (if any): This statement is too restrictive and may not always be necessary to ensure safety and effectiveness. Reduce to a “recommendation” rather than mandate. Lines 694-699 support the conclusion that co-administration with food can be acceptable.	Not accepted: The text has not been amended. The “unless otherwise justified” allows some flexibility.
675-678	10	“The palatability of the active substance should contribute to the choice of the selected finished dosage form(s) and route(s) of administration. Unless otherwise justified, the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or beverages).” Proposed change: This statement is too restrictive and may not	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		always be necessary to ensure safety and effectiveness. Reduce to a “recommendation” rather than mandate. Lines 694-699 support the conclusion that co-administration with food can be acceptable.	
676	2	Important to be considered also Proposed change (if any): “and its excipients”	Not accepted: This was considered a minor change that was not implemented as excipients were discussed elsewhere in the section.
676-678	21	The co-administration of multiparticulates with semi solid food is known to improve swallowability in younger children. Proposed change (addition of sentence after paragraph line 678): “Mixing with semi-solid food to further improve the swallowability and assist the administration is acceptable.”	Accepted: The following text has been added (under section mixing with food): “Mixing recommendations can also be applied as a further means to improve the patient acceptability and the ease of swallowing of an otherwise already palatable medicinal product.”
676-678	10	The co-administration of multiparticulates with semi-solid food is known to improve swallowability in younger children. Proposed change (addition of sentence after paragraph line 678): “Mixing with semi-solid food to further improve the swallowability and assist the administration is acceptable.”	See above.
679	10	This paragraph brings the first mention of the concept of the target quality product profile. This concept should be introduced much earlier in the guideline.	Partially Accepted: This text has been deleted but mention of this concept is included earlier on in the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
679-685	10	Patient acceptability of taste should be accompanied with a validated measure. There is acceptable palatability which may differ from liking the medication.	Not accepted: Although a validated measure would be the ideal in practice this property seems far too subjective to achieve a validated measure.
680	5	Definition on what constitutes a “generally acceptable taste” should be provided.	Not accepted: As it is very hard to define a generally acceptable taste, no amendment has been undertaken.
681	10	The draft text notes that normally development of a product with a neutral taste should be considered. This seems rather challenging / optimistic … shouldn’t patient acceptability be the key consideration provided adequate safety exists for the flavour used? A flavoured product may be a factor that maintains patient compliance across time.	Not accepted: No amendment suggested as both options (neutral and acceptable taste) are stated in the guideline.
681-683	2	No taste could be an option Proposed change (if any): “no or” after “*neutral taste*” and “on” to be added before “*repeated*”	Not accepted: No taste is an option but this is covered by neutral taste. No amendment suggested.
690	2	Useful example and more exact word Proposed change (if any): “(i.e. beta cyclodextrines)” after “*complexing agent*” and “active ingredient” instead of “*drug*”	Accepted: The text “use of a cyclodextrine” has been added. “Drug” has been replaced as proposed.
690	10	We were rather surprised to see the guideline encourage the addition of complexing agents to address flavour issues rather than the use of taste maskers / flavourants given the potential	Not accepted: Complexing agents were only one means suggested. Other ways of masking taste were

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		for safety concern with excipients discussed in earlier sections. Proposed change: Change emphasis to recognise that use of flavours may be more simple and effective than more complex formulation approaches.	also mentioned.
691	4	The section *starting "The measures that can be undertaken to improve the palatability (...)"* Proposed change (if any): Consider rewording: "*Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent or for liquid preparations: lowering the amount of free drug in solution by choice of a different strength and subsequent change in volume".* Followed by: *"However, paediatric dosage forms must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning."*	Accepted: The text has been revised as follows: "Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations: lowering the amount of free active ingredient in solution by choice of a different strength and subsequent change in volume. However, paediatric formulations/preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning".
691	10	The section starting "The measures that can be undertaken to	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		improve the palatability (...) Proposed change: Consider rewording: "Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent or for liquid preparations: a lowering of the amount of free drug in solution by choice of a different strength and subsequent change in volume" followed by: "However, paediatric dosage forms must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning."	
691- 693	10	This makes a reference to a "candy like" dosage form. How is this judged, e.g. by a palatability test?	Partially accepted: As no alternative term was proposed and the term "candy" is a well understood term, the term remains.
692	5	Guidance should be given as to what is expected from the evaluation of degree of children's attractiveness for a developed formulation. Please include proposal.	Not accepted: Not possible to measure degree of attractiveness and must be judged on a case by case basis.
694-699	25	Where the product is to be mixed with foodstuffs those foodstuffs tested and recommended should be acceptable for	Partially accepted: Reference to "common foods" is made. The

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the target age ranges.	following is stated “Therefore, the effect of mixing the medicinal product with certain type(s) of common foods or drinks for children should be discussed and/or studied for every paediatric medicine.”
694-699	17	Where the product is to be mixed with foodstuffs those foodstuffs tested and recommended should be acceptable for the target age ranges.	See above.
694–712	10	The guideline proposes to test mixing including palatability and also bioavailability. This can lead to infinite studies given the broad range of ‘common food or beverages’. Also there are different types of beverage / food for children for different cultures which will complicate the whole studies. Guidance on which foods and beverages should be studied would be helpful.	Partially accepted: There is mention of “Common foods” and the following text has been added: “Nevertheless the SmPC and PIL should give clear instructions on what foods and drinks have been demonstrated to be appropriate for the medicinal product to be mixed with.”
697-698	2	Comment: Clarity Proposed change (if any): “or” to be deleted, “also” to be added.	Accepted: Grammatical but worthy of amendment. It is unusual to start a sentence with “Or”.
701	5	“it should be discussed which foods mask the original taste best” Proposed text: “it should be discussed which foods mask the original taste effectively”	Accepted: Agreed “best” not a guideline word. This phrase has been avoided.
701	10	It is unreasonable to suggest foods should be screened to ascertain which foods mask the task best. It would seem	Accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		reasonable only to provide information on which common foods can be used to adequately mask the taste of the medicine. Proposed change: Please remove the suggestion that all foods should be screened.	It is not suggested that all foods should be screened. The following text has been added: "It is understood that food and drinks are usually not standardized products and that the whole range of variability cannot be covered by patient's acceptability and compatibility studies. Nevertheless the SmPC and PIL should give clear instructions on what foods and drinks have been demonstrated to be appropriate for the medicinal product to be mixed with."
704	2	Necessary to specify, often lacking information Proposed change (if any): "and the modalities of administration clearly stated (mixing ,storage-time and temperature..)." to be added at the end of the sentence	Accepted: Storage and temperature now mentioned in this section.
704	10	It was surprising to read that instruction should be given that mixing with food would be a 'necessity'. It is not clear that this need be the case. The mixing of the medicine with food could be optional provided the natural taste of the product can be administered. Proposed change: Remove implication that mixing with food will be a necessity.	Not accepted: The proposal remains that all medicines should be studied with regard to mixing with food. The following text gives the reason "Moreover, the lack of recommendations on mixing with foods or drinks will not assure that caregivers will not employ this method in order to administer the medicine. Therefore, the effect of mixing the medicinal product with certain type(s) of common foods or drinks for children should be discussed and/or studied for every

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			paediatric medicine.”
707	11	Comment: Typo: “...of...” should be “...or...”	Accepted: Typo amended. This text has been significantly amended.
707	32	There are several topics where it is unclear if data would be required for a justification and what kind of data might be useful. One example is the compatibility with food where it is mentioned that food or beverages might affect the bioavailability and/or therapeutic action (line 707ff) and that the effect of food should be discussed and/or studied. Proposed change: Scientific justifications and clear detailed guidance should be provided for any proposed requirement of additional studies.	Accepted: The following text has been added: “Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine.”
707-712	10	It is surprising to see that the effect of mixing of a product with different foods and drinks should be discussed or studied, even if there is no recommendation on the label to carry out mixing. It is not clear which foods/drinks should be studied – different foods/drinks may have very different effects on stability and bioavailability of the mixture. If there is no recommendation on the product label to mix with food/drink, the patient/caregiver should not do so.	Accepted: It is agreed that assessment of compatibility is only necessary with what the SmPC indicates. The following text has been added; “The SmPC and PIL should always contain clear information if the product can or cannot be mixed with foods or drinks. If mixing with foods or drinks is not recommended the SmPC and PIL should clearly state that the mixing of the medicinal product with food or drinks has not been studied and is the responsibility of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			the user".
707-712	19	We applaud the CHMP for considering situations whereby paediatric medicines are administered by other means than intended, as it reflects the pragmatic approach from carers to administer medicines to uncooperative children. However, the consequences of the statement must be considered; does it imply that all oral dosage forms must be assessed for compatibility with foods and liquids? And if so, which food and liquid should be considered?	See above.
707-712	22	I am personally very happy to see this statement because it reflects the pragmatic approach from carers to administer medicines to uncooperative children. However, the consequences of the statement must be considered - does it not mean that all oral dosage forms must be assessed for compatibility with foods and liquids? Which foods and liquids?	See above.
709-712	10	*"Moreover, the lack of recommendations on mixing with food* ***or (comment: not "of")*** *beverages will not assure that caregivers will not employ this method in order to administer the medicine. Therefore, the effect of mixing the medicinal product with different types of common food or beverages for children should be discussed and /or studied in the ~~development pharmaceutics~~ pharmaceutical development section of the dossier…"* Comment: In case a palatable and acceptable formulation is acceptable without mixing with food, no instructions for mixing	Accepted: Stability and bioavailability issues are now differentiated. The following text on stability has been added: *"Unless otherwise justified, information on the stability of the product in the recommended foods should be provided. This information should include information on any restrictions*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		with food should be required. In case mixing with food is recommended / required, then the required stability testing makes sense. In case a drug has a significant food effect (impact of food on oral bioavailability) and mixing with food or administration after/ in combination with meals is not recommended for this reason, then the respective instructions should be given in the label (and need to be followed). In such cases, it is not considered useful to test the stability or the impact on bioavailability of the drug product for a combination with food as part of Pharmaceutical Development. Data regarding food effects are usually obtained in clinical safety studies in adults and may need to be confirmed in relative BA studies in paediatric groups. Proposed change: Reword this paragraph and clearly differentiate between bioavailability considerations and stability considerations with respect to mixing with foods. Since common food or beverages vary globally, rendering comprehensive studies potentially unrealistic and unfeasible. Another proposal is to clarify in text an alternative approach to this issue, i.e. via a scientific risk assessment e.g. *what properties of certain food or beverages could drive incompatibility, e.g., pH? reducing sugars? potential interaction?* rather than screening for 'common food or beverages' as suggested.	*on the temperature of the food stuffs".* The following text on bioavailability has been added: *"When mixing with food and drinks is proposed the possible effect on biopharmaceutical characteristics of the product should be discussed. Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine".*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
709-712 (and 713-714)	32	Timeframes for mixing instructions are contradictory: 709-712:"Therefore, the effect of mixing the medicinal product with different types of common food or beverages for children should be discussed and/or studied in the development pharmaceutics targeting at in in-use shelf-life of 30 minutes." 713-14:"Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately i.e. within 5 minutes." Proposed change: In-use shelf-life should be studied for the individual medicines if applicable.	Accepted: Reference to specific times has been removed. The following text has been added: "Unless otherwise justified, information on the stability of the product in the recommended foods should be provided".
710-712	1	These procedures cannot be standardized. Commercially available food is usually not standardized. Therefore it seems unfeasible to conduct these studies Proposed change: Delete "and/or studied" from the sentence. Add: "It is understood that food and beverages are usually not standardized products and that the whole range of variability cannot be covered by studies."	Partially accepted: It is recognised that food is variable in its composition. The following text has been added: "It is understood that food and drinks are usually not standardized products and that the whole range of variability cannot be covered by patient's acceptability and compatibility studies. Nevertheless the SmPC and PIL should give clear instructions on what foods and drinks have been demonstrated to be appropriate for the medicinal product to be mixed with."
710-712	23	Comment: • These procedures cannot be standardized.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• Commercially available food is usually not standardized. • Therefore it seems unfeasible to conduct these studies Proposed change: • Delete “and/or studied” from the sentence. • Add: “It is understood that food and beverages are usually not standardized products and that the whole range of variability cannot be fully covered by studies.”	
711	2	Comment: limit detailed Proposed change (if any): “with a maximum”	Partially accepted: Reference to specific times has been removed. The following text has been added: “and needs to be taken within clearly specified time after mixing”.
711	5	Which items should be evaluated in the case of in-use stability? From analytical point of view, it will be difficult to analyze precisely in such matrix (drug with food). Furthermore not all drug products will be stable for 30 min. Proposed text: “In case it is stated in the PIL or SmPC that the drug product can be mixed with food or liquids prior to administration a positive remark on which food type to be used should be stated in SmPC and PIL. The effect of the mixing with the food product should be discussed/studied with regard to allowable foods, mixing time and in-use stability. The maximum allowable in use stability after mixing should be stated in the	Partially accepted: Reference to specific times has been removed. The following text has been added: “and needs to be taken within clearly specified time after mixing”. The following text has been added with regard to types of foods: “If mixing with foods and drinks is recommended, the type(s) of foods and drinks should be clearly indicated including any

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		SmPC and PIL."	temperature conditions where relevant."
711	10	Where did 30 minutes come from? Is shelf-life of 30 minutes adequate? If active is mixed with milk, there is a possibility that food is consumed over a period up to 1 hr, particularly for sick children. What about the challenge of incomplete ingestion of the food? Proposed change: Suggest to refer to the in-use shelf-life: ……targeting at the in-use shelf-life (often approx. 30 minutes).	Accepted: Reference to specific times has been removed. The following text has been added: "Unless otherwise justified, information on the stability of the product in the recommended foods should be provided".
711	10	Where did 30 minutes come from? Is shelf-life of 30 minutes adequate? If active is mixed with milk, there is a possibility that food is consumed over a period up to 1 hr, particularly for sick children. What about the challenge of incomplete ingestion of the food? Proposed change: Suggest to refer to the in-use shelf-life: ……targeting at the in-use shelf-life (often approx. 30 minutes).	See above.
711	11	"...at in..." should be replaced by "...an..."	Accepted: Typo corrected but this text has been significantly amended.
711-712	10	Please clarify the "study" aspect in this sentence. Should sponsors conduct studies *in vitro* (stability studies) or *in vivo* (clinical studies)?	Accepted: Stability and bioavailability issues are now differentiated.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			The following text on stability has been added: "Unless otherwise justified, information on the stability of the product in the recommended foods should be provided. This information should include information on any restrictions on the temperature of the food stuffs". The following text on bioavailability has been added: "When mixing with food and drinks is proposed the possible effect on biopharmaceutical characteristics of the product should be discussed. Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine".
711-712	10	Please clarify the "study" aspect in this sentence. Should sponsors conduct studies *in vitro* (stability studies) or *in vivo* (clinical studies)?	See above.
711-714	8	There is a contradiction between 711 ('in-use shelf-life of 30 minutes') and 714 ('within 5 minutes'). This may prevent reasonable new developments, and is usually demonstrated by in-use stability studies. Proposed change: Avoid detailed times, but use term 'appropriate time' or 'evidence-based time until administration'.	Accepted: Reference to specific times has been removed. The following text has been added: "Unless otherwise justified, information on the stability of the product in the recommended foods should be provided".
711-716	9	This section should be clarified. Why establish an in-use shelf life of 30 minutes and then recommend that medicine mixed	Accepted:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		with food is taken within 5 minutes?	Reference to specific times has been removed. The following text has been added: “Unless otherwise justified, information on the stability of the product in the recommended foods should be provided”.
712	2	Necessary to specify, crucial information to study in drugs intended for children Proposed change (if any): “The applicant should clarify and study if necessary the impact on pharmacokinetic-pharmacodynamic characteristics of the medicine” sentence to be added.	Accepted: The following text has been added: “Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine”.
713-715	4	*“Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately i.e. within 5 minutes. Positive mixing instructions with common food or beverages are recommended.”* Proposed change (if any): Suggest that mixing instruction should be based on pharmaceutical development data.	Partially Accepted. Reference to specific times has been removed. The following text has been added: “Unless otherwise justified, information on the stability of the product in the recommended foods should be provided”.
713-716	1	The recommendation to take or administer, respectively, with food mixed medicine within 5 minutes is not comprehensible on the grounds that in-use shelf life studies of 30 minutes for mixed medicines are strongly recommended. If such studies prove that stability of medicines with specific beverages and food is ensured, why restrict the use of mixed medicines to only 5 minutes after preparation of the mix? Proposed change: “Caregivers should be instructed in the SmPC	Partially accepted: Reference to specific times has been removed. The following text has been added: “Unless otherwise justified, information on the stability of the product in the recommended foods should be provided”.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		and PIL that any mixed medicine should be taken immediately, i.e. within *30 minutes provided that no other, specific information on the in-use shelf-life of any mixed medicine is available."*	
713-716	23	The recommendation to take or administer, respectively, with food mixed medicine within 5 minutes is not comprehensible on the grounds that in-use shelf life studies of 30 minutes for mixed medicines are strongly recommended. If such studies prove that stability of medicines with specific beverages and food is ensured, why restrict the use of mixed medicines to only 5 minutes after preparation of the mix? Proposed change: "Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately, i.e. within *30 minutes provided that no other, specific information on the in-use shelf-life of any mixed medicine is available."*	See above.
713-716	10	Limiting the contact time with food to 5 minutes seems unduly restrictive, and could be impractical. On the basis of a 30 minutes shelf life being demonstrated at Line 711, a limit time of 15 minutes for the routine time would be more appropriate. Suggest that mixing instruction should be based on pharmaceutical development data. Proposed change: Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately i.e. within ~~5~~ **15** minutes. Positive mixing instructions with common food or beverages are recommended. Appropriate	Accepted: Reference to specific times has been removed. The following text has been added: "Unless otherwise justified, information on the stability of the product in the recommended foods should be provided".

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		warnings should be added in cases where the medicine can not be mixed with certain food or beverages for even ~~5~~ **15** minutes or shorter. If a sponsor conducts stability studies with certain foods and shows that the admixture is stable for longer under certain conditions (i.e., refrigeration), the guideline should allow for such information to be included in the patient instructions in lieu of the recommendation stated herein.	
723-724	5	It is unclear what is expected for evaluation of "differences between countries". Please make a more elaborate statement.	Accepted: Reference to different countries has been removed.
725-726	9	Section 11 would benefit from information concerning child resistant containers.	Comment noted. Child resistant containers (CRC) is not sufficiently paediatric specific. It is considered that CRC were often necessary on adult medicines where accidental poisoning of children can occur such as iron and paracetamol tablets. This issue is addressed in section 11.1 to some extent. The following is stated *"The container closure system should differentiate the medicinal product from confectionary and toys to reduce the attractiveness of the product to children"*.
Section 11	33	In the general considerations a recommendation to use child	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		resistance primary packaging might be useful.	
727	19	This section should include packaging consideration in terms of safety for caregivers. For example, tablets/capsules should be packaged only in blister or strip packs for oncology medicines, in order to minimise skin contact by the caregivers.	Not accepted: This is not considered specific to paediatric medicines.
730-732	21	What is meant by “dedicated container cap” in the context of removal of content from the container? Clarity on this term is requested.	Comment noted. The text has been revised. Further clarification has been included in Section 11.1. The following is stated: *“Other containers will require a "syringe adaptor", which is an integrated bung in the neck of the bottle into which the oral syringe fits. The syringe adaptor allows the entire contents of the bottle to be successfully removed form the bottle”.*
732	11	Not sure what is meant by the “dedicated container cap” Syringe nozzle cap?	See above.
737	19	We agree that novel packaging may improve child acceptance but there should be emphasis on differentiating the packaging from confectionary or toys. We are aware of the statement in line 264 under oral administration but this is equally applicable to all container closure system or dosing devices.	Accepted: The text has been revised. In addition to “novel containers” the following is stated: *“The container closure system should differentiate the medicinal product from confectionary and toys to reduce the attractiveness of the product to children”.*
743	5	“2) accidental dosing error”	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Please explain what is meant by this in the context of this paragraph?	Accidental dosing errors may occur when medicines are used. For example, inappropriately large injection vials may pose a risk of the wrong dose being drawn up. From a safety perspective the use of small vials may reduce the potential for dosing errors. The term “accidental dosing error” has been retained and is believed to be self explanatory.
744	4	*“...4) environmental waste...”* Proposed change (if any): Environmental waste appears out of scope of a guidance on pharmaceutical development...	Comment noted. The text has been revised. The phrase regarding “Environmental waste” has been removed.
744	5	“4) environmental waste” Please explain what is meant by this in the context of this paragraph?	See above.
744	10	It is stated that the contents of the container should be justified 'in terms of environmental waste'. Please clarify to what extent this should be investigated.	See above.
744	19	It would aid clarity if the meaning of “environmental waste” can be further explained in the context of the sentence. Is it referring to wastage of medicinal product? If so, the issue of wastage would have been minimised when taking into account the dosing recommendations.	See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
745-747	18	5) the risk of unapproved multiple usage of a product for single use for reasons of e.g. cost reduction. For liquid preparations for single use, the contents of the container should normally be less than 10-fold of the lowest recommended dose. Comment: It would be helpful to state the evidence or logic for this guidance	Comment noted. The text has been revised. Reference to multiple use for cost reasons has been removed as cost is out of the scope of a quality guideline. Reference has been made to the risk of 10-fold over dosing. There are examples of medication errors where too large a dose has been withdrawn from injection vials intended for adult use.
746	10	We were surprised to read, given the guidance given in lines 742 to 745, that the “contents of a container (for single use) should normally be less than 10-fold of the lowest recommended dose”. This would seem to give the potential for significant mis-administration. Maybe one should not put such focus on only container volume, but manage risk here with a reasonable combination of product volume, device volume and dosing instruction (as well as considering the circumstances of use of the medicine – i.e. risks may be different in-patient versus out-patient.)	See above.
749-751	5	Although oral liquids such as solutions and suspensions were considered the most age appropriate dosage form for children they are not addressed here. It is proposed to dedicate a paragraph to containers used for oral liquids.	Comment noted. The paragraph has been revised. Reference to oral liquids and suspensions removed form this section.
749-751	10	Apparent inconsistency between ‘containers for single use’ and ‘a dedicated administration device’.	Comment noted. The text has been revised. Reference to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Powders, pellets and granules for oral use should **preferably** be packed in containers for single use. They can be packed in larger volumes in sachets, but also in smaller volumes in capsules. ~~Alternatively,~~ **Where multiple use packs are appropriate,** a dedicated "~~measuring and~~ administration device" ~~can be acceptable~~ **may be provided**.	"containers for single use" and "a dedicated administration device" have been removed form this section.
753	10	Suggest state that small vial sizes are preferred in order to reduce potential dosing errors and waste.	Comment noted. The text has been revised. During the review process this paragraph was removed.
757-783	9	Section 11.3 should specifically state that applicants are required to provide a dosing device with their product. Where a medicine requires measurement before administration it is expected that a specific dosing device will be provided with the medicinal product. Evidence should be provided that this dosing device is able to measure, and where appropriate, deliver a dose with accuracy appropriate for the medicine concerned. This is in line with the EMA guideline EMEA/CHMP/QWP/178621FE/2004 2004; Guideline on the suitability of the graduation of delivery devices for liquid dosage forms.	Accepted: The text has been revised accordingly. It has been further clarified that for products where adequate accuracy can be demonstrated with commonly available measuring devices then supplying a dosing device is not an obligation.
757-783	9	Dosing devices should be CE marked, and conform to the Medicines Device Directive, Council Directive 93/42/EEC, as amended.	Comment noted. No specific reference was made to the Medical Devices Directive. This is not a child specific requirement and reference to this guideline is covered by the statement *"... this guideline*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			should be read in conjunction with all other relevant directives and regulations, …" in chapter 3 of the GL.
757-783	10	The section on dosing devices should be divided into subheaders to clearly differentiate when the guideline is addressing devices for oral *versus* parenteral administration. For example, at line 770 the discussion turns to syringes and needles, but lines 774 – 779 seem to refer to devices for oral administration as it seems inconceivable that there would be a recommendation to provide a syringe and needle that require a cleaning instruction. 'Oral syringes must not be able to accept needles' is in contrast to line 772 'not to flush syringe and needle' Proposed change: Clearly separate devices for parenteral versus oral administration.	Comment noted. Section has been revised for clarity. No specific sub-headings for parenteral versus oral administration were introduced.
757	10	Devices described in the text are generally Medical Device by Medical Device Directive definition. A reference to this directive is recommended.	Comment noted. No specific reference was made to the Medical Devices Directive. This is not a child specific requirement and reference to this guideline is covered by the statement *"… this guideline should be read in conjunction with all other relevant directives and regulations, …"* in chapter 3 of the GL.
758-783	10	Special attention to availability of suitable, small dose selection and injection devices in applicable diseases should be added.	Comment noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
760	10	It is unclear what measures could be taken to reduce the risk that the cap not be co-administered into the mouth of the patient. Proposed change: Remove expectation for some measure to manage this (low) risk.	Accepted: The text has been revised. Reference to co-administration of syringe cap has been deleted.
760-761	5	It is unclear how to estimate possibilities or risk for co-administration of cap. Please include an explanation	See above.
760-761	19	Are there not EU standards for oral syringes that should be cited?	Comment noted. No specific reference was made to EU standards for oral syringes. Reference to EU standards is covered by the statement *"… this guideline should be read in conjunction with all other relevant directives and regulations, …"* in chapter 3 of the GL.
760-761	22	Are there not EU standards for oral syringes that should be cited? There has been (? still is) a BS for oral syringes.	See above.
762	10	We were surprised to see that the minimum volume that may be administered need be determined based on the accuracy of the device. Should it not only be necessary to show that the doses to be provided can be delivered with adequate accuracy. After all if a dose volume is the lowest that is approved why should dose accuracy below this limit from the device need to be explored / need to be delivered ?	Comment noted. The text has been revised. The respective line has been deleted. The accuracy of the measuring device to deliver the required dose should be demonstrated.
762-763	5	It is unclear which level of assurance is required for dosing	Comment noted.

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		accuracy. For evaluation of dosing accuracy using an administration device, the guideline should indicate whether AV (acceptance value) as per the Content Uniformity testing per dosing described in Ph.Eur. is required, or whether the minimum dosing volume test suffices. It is proposed that the test method is indicated.	The test method has not been indicated. The criticality of the dose response curve and the accuracy of dosing should be discussed.
764-769	19	This is unclear. In general dosing devices should measure volume and be generic in nature. They should not measure /mg' or 'doses' unless justified and measures taken to prevent those devices being used with other products (of different strength).	Comment noted. The text has been revised. General reference to graduations being based on dosing recommendations has been deleted.
764-765	9	It may be considered inappropriate for devices to be marked in anything other than millilitres (mls). Parents may retain a mixture of dosage devices which could result in the wrong dose of another medicine being administered. It is suggested that it is specifically stated that graduations should be mls. The dosage instructions should also reflect these units.	See above.
764-769	22	This is unclear. In general dosing devices should measure volume and be generic in nature. They should not measure /mg' or 'doses' unless justified and measures taken to prevent those devices being used with other products (of different strength).	See above.
765	11	“The contents of the dosing...” should be replaced by “The size of the dosing...”	Partially accepted: The text has been revised. The term “nominal volume” of the dosing device is used.
767	2	In exceptional cases, there may be a need to pack multiple	Comment noted.

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		dosing devices with the product in order to allow the health care professional to dispense the appropriate device.	The text has been revised. Reference to multiple dosing devices has been deleted.
770	5	It is unclear what “flushing” means. Therefore it is not understandable what causes the overdosing issue of flushing. Please include flushing in the glossary/definitions section.	Comment noted. The text has been revised. Further explanation has been provided regarding flushing and how the dead space in syringes can affect accuracy.
774-775	26	What is the justification for considering that the multiple use of a dosing device in order to provide the recommended dose is not acceptable. Can it be clarified as to whether the concern is dose accuracy, or hygiene.	Comment noted. The text has been revised. The respective line has been deleted.
774 – 775	11	Not sure what this sentence is getting at. If repeat dosing is OK (2nd sentence) then presumably it shouldn’t matter if the repeat is immediate or on different dosing occasions, as long as cleaning is still done? Proposal to delete following sentence: The multiple use of a dosing device in order to provide a single, recommended dose is normally not considered acceptable e.g. a single 7.5 ml dose should not be given by a 5.0 ml syringe.	See above.
774-779	19	This is inadequate. See above. There are examples of named devices being used with other products and error resulting.	Comment noted. The text has been revised. It has been further clarified that the product’s name should be displayed on a measuring device which is specifically designed to deliver the correct

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			doses of a particular product, e.g. a cup to measure a particular number of granules. This is to avoid mixing devices for different medicinal products, when commonly available devices cannot or should not be used.
774-779	22	No. This is inadequate. See above. There are examples of named devices being used with other products and error resulting (France?).	See above.
777	10	The addition of product name on a syringe may cause supply problems, e.g. to hospitals and also there is the risk that a patient may use it for another product, despite warnings. I would be better to advocate the use of clear markings in ml on the syringe.	See above.
780-781	26	Measuring spoons can be acceptable for volumes below 5ml, provided they meet Ph. Eur. “Uniformity of mass of delivered dose” requirements”. Proposed change (if any): Delete “or volumes below 5ml”	Accepted: The text has been revised. The phrase “volumes below 5 ml” was deleted. This section has been rephrased so that the accuracy of dosing devices are discussed when used in combination with narrow therapeutic window medicines.
780-783	17	Use of a syringe for smaller doses is preferable to a measuring spoon due to the accuracy of measurement. It is best practice to use a syringe for measuring doses below 5ml.	Comment noted. The text has been revised. It is stated that the dosing device should be age appropriate and the accuracy of the dosing device should be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			demonstrated.
780-783	25	11.3 DOSING DEVICE Therapeutic window should be the major factor determining dosing device. 2.5ml volumes for many medicines can be safely measured using graduated spoons.	Comment noted. The text has been revised. The need for special considerations for measuring devices for paediatric medicines with a narrow therapeutic window has been addressed.
781-783	4	*"Otherwise, spoons and cups will only be considered acceptable if all of the relevant dosing intervals can be conducted with the device with an acceptable dose accuracy and reproducibility."* Proposed change (if any): The guidance should allow for use of conventional measuring devices such as measuring spoons that are not "dedicated" or "co-packaged" if justified. (See also comment on Lines 230-231.)	Accepted: The text has been revised. It has been further clarified that for products where adequate accuracy can be demonstrated with commonly available measuring devices then supplying a dosing device is not an obligation.
781-783	10	"Otherwise, spoons and cups will only be considered acceptable if all of the relevant dosing intervals can be conducted with the device with an acceptable dose accuracy and reproducibility." Proposed change: Guidance should allow for use of conventional measuring devices such as measuring spoons that are not "dedicated" or "co-packaged" if justified. (See also comment on Lines 230-231.)	See above.
784	18	The need to use IV tubing and administration apparatus of small internal diameter for neonates should be a requirement.	Comment noted. Although probably a valid request, the guideline would be straying into the region of clinical practice rather than pharmaceutical

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			development.
785-792	10	The requirement for suitable needles for use in injection devices should be added	See above.
793-799	10	*Section 12 – User Information (Summary of Product Characteristics and Patient Information Leaflet):* "Pharmaceutical industries should provide clear user instructions that favour the correct and full administration of the medicine. …. User instructions should be sufficiently robust towards unwilling children, **especially where full adherence is critical for therapeutic outcomes."** *Consider deleting the bolded phrase (above). User instructions should always aim for full adherence because, presumably, the safety and effectiveness of the product were based on the doses, intervals, and routes of administration, including mixing with food or beverages, to which patients adhered in the clinical program. Given the numerous caveats in this guideline calling for justification for just about every aspect of the paediatric dosage form, it is incongruous to suggest that full adherence to the labelled administration instructions is not necessary for all products, especially with unwilling children.* Proposed change: Delete "especially where full adherence is critical for therapeutic outcomes" from line 799.	Not accepted The unwillingness of children to accept a medicine may be due to several causes, including, but not limited, to the design of the medicine. As a consequence, it is not always possible to overcome the lack of child medication acceptance by product optimization. In cases where the unwillingness of the child cannot be respected by e.g. skipping a dose or administering the medicine at a later point in time, it is essential to keep the burden to the child as little as possible. Adequate user instructions are hereto essential.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
795	11	"...that favour the correct..." should be replaced by "...that clearly describe the correct..."	Not accepted Product information should always clearly describe the correct and full administration of a product. However it can not be guaranteed that the product will be used as requited. Therefore it is important to include additional information (warnings) about consequences of incorrect use, hence the term "favour".
797	10	Typographical Proposed change: ~~scenario's~~ **scenarios**	Accepted The text has been revised accordingly
798-799	5	"User instructions should be sufficiently robust towards unwilling children" .It is unclear what is intended by the phrasing "sufficiently robust". It seems difficult to cover all potential situations concerning children's unwillingness. Please include more specific remarks.	Comment noted. See the aforementioned explanation regarding unwilling children. The term "sufficiently robust" is not to be interpreted as a tick–box criterion, but rather as the best reasonably possible risk mitigation measure allowing parents/health care professionals to administer the medicine.
798-799	18	'robust towards unwilling children' needs clarification.	Comment noted. The comment is not clear.
799	10	It is not possible to guarantee dosing instructions for unwilling children. Better to emphasise that they should be clear and	See above

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		simple/easy to understand. Consider the inclusion of diagrams where necessary. Proposed change: Suggest to remove	
801-828	9	Consideration should be given to providing this glossary of terms at the beginning of the guidance document.	Not accepted. It is a standard practice to include a glossary at the end of a guideline.
803	10	*Missing word in the definition of "age-appropriate medicines"* Proposed change: Medicines***, the*** pharmaceutical design of which is tailored for use in the intended age group.	Accepted The text has been revised accordingly
803	11	"Medicines pharmaceutical design of which is tailored for use in the intended age group" should be replaced by "Medicines for which the pharmaceutical product design is tailored for use in a specific paediatric age group"	Comment noted. The definition of "Age-appropriate paediatric medicine" has been further revised.
805-807	10	Inclusion of formulations used in preclinical development studies within the definition of "preliminary formulations" is likely to introduce some confusion. Any formulation other than the "to-be-marketed" formulation, which is employed in development studies is preliminary. Therefore, the adjective "early" is unnecessarily restrictive. Tying the definition to situations where development of the final "to-be-marketed-formulation" would be the rate limiting step in conducting early studies does not reflect the paradigm for paediatric drug development. Clinical trials generally need to be conducted, not only to define essential	Comment noted It is agreed that "to-be-marketed" formulation can also be used as a preliminary formulation. However in majority cases preliminary formulations are relatively simple formulations which are further developed. The statement that preliminary formulations are relatively simple, does not exclude the possibility to use "to-be-marketed" formulation.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		characteristics that the final paediatric formulation must include, but also to determine whether the drug demonstrates sufficient safety and effectiveness to warrant development of a marketable product. Consequently, "preliminary formulations" are employed in paediatric development programs for a variety of reasons, until a final formulation is available. Proposed Change: *Preliminary formulations are ~~relatively simple and easy to prepare~~ used in ~~clinical~~ development studies before* ***~~developing the final~~ finalisation of the*** *appropriate paediatric medicinal product.*	
809-814	19	We fundamentally disagree. The last sentence describes compounding or extemporaneous/magistral dispensing. EuPFI has a paper in preparation exploring such terminology and provides suggestions for standardisation.	Comment noted. The definition of manipulation has been removed from the guideline.
809-814	22	I fundamentally disagree. The last sentence describes compounding or extemporaneous/magistral dispensing. EuPFI has a paper in preparation exploring such terminology and provides suggestions for standardisation.	See above
810	10	Typographical Proposed change: ~~deliberately~~ **deliberate**	Comment noted. However the definition of manipulation has been removed from the guideline.
813	1	It is unclear if a parenteral or oral solution is meant as a syringe for oral use is mentioned.	Comment noted. However the definition of manipulation has

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Please clarify if an oral solution or parenteral solution is meant.	been removed from the guideline.