1 August 2013
EMA/805826/2012
Committee for Human Medicinal Products (CHMP)
Paediatric Committee (PDCO)

Overview of comments on 'guideline on pharmaceutical development of medicines for paediatric use' (EMA/CHMP/QWP/180157/2011) received during the 2nd public consultation

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

Stakeholder no.	Name of organisation or individual
1	Association of the European Self-Medication Industry (AESGP)
2	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
3	European Federation of Pharmaceutical Industries and Associations (EFPIA)
4	European Paediatric Formulation Initiative (EuPFI)
5	Gary Inwards (individual)
6	Global Alliance for Paediatric Therapeutics
7	IQ Consortium International - DPLG Paediatric Working Group
8	Medicines Evaluation Board (MEB), The Netherlands
9	F. Hoffmann – La Roche Ltd
10	Royal Dutch Pharmacists Association
11	Special Interest Group (SIG) Pediatrics of the Dutch Hospital Pharmacists Association (NVZA)
12	U.S. Paediatric Formulations Initiative

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1. General comments

Stakeholder name	General comment (if any)	Outcome (if applicable)
3	The work on this guideline is important and the rapporteur is thanked for the diligence in working through the many comments received in the first period of public comment. It is appreciated that an allowance for a second period of public comment has been made. Efpia appreciates the opportunity to provide comments to the paragraphs: 1. Section 6.2.1 *Handling of oral solid preparations to facilitate administration* 2. Section 10 *Patients acceptability* including the paragraph *Mixing with food* Some general comments: 1. Section 6.2.1 currently is a rather general text. Industry would benefit from clear statements on what is seen as generally acceptable. 2. Solid oral preparations: Even if an age appropriate formulation is developed, it is assumed that manipulation of the formulation will occur and therefore companies must validate POSSIBLE alternative approaches that may be used. This seems very open ended and subject to numerous assessments of possible options that may occur in the field. The results could lead to extended clinical protocols if paper arguments do not suffice. This is not required in the	Comments noted Second consultation was limited to the sections 6.2.1 and 10. However, general changes which improved wording or the text in general have been accepted. Changes on the scientific content of sections other than those opened for consultation have not been considered. The former section *Manipulation of oral solid preparations to facilitate administration has been* updated and the comment has been accepted. The title of this section has however been changed into Modification of oral solid preparations to facilitate administration The section *mixing with food has been* updated and the comments have been considered. The section *patient acceptability has been* updated and the comment has been considered. Acceptability testing, including palatability, should be embedded in the development program. Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods currently employed, the Agency feels it is not appropriate to impose any method for acceptability testing at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The Agency is currently evaluating what would be an appropriate evidence of patient

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	development of adult dosage forms and may lead to an excessive burden for paediatric formulation development. 3. Mixing with food: EMA has stated that ALL FORMULATIONS are to be evaluated as being mixed with food, because this will be done in practice. The issue is then what example foods to select for assessment. It is impossible to test compatibility with all combinations of food with all alterations of formulations. If this is the norm for paediatric products, industry cannot support this approach. It is proposed to limit testing to a selected age appropriate formulation in combination with an age appropriate type of food, and to justify the ability to mix with this food based on stability and bioavailability arguments. 4. Patient acceptability: Industry is challenged by the requirement to assess patient acceptability and the lack of quantitative tools to confirm that the objective has been met. Not enough guidance is given how to assess patient acceptability. More detailed comments are given in the sections below.	acceptability. This however requires careful considerations and therefore it cannot be implemented to the guideline at this stage. It is foreseen that future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline.
4	EuPFI welcomes the updated guideline, from which it can be seen many of the comments provided as part of the first consultation have been taken on board. The revised guideline is more consistent and has greater clarity than the previous version. However there is some concern over the use of the word	Comment noted The term “handling” has been replaced by the term “modification”.

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	"handling" that was introduced to the guideline to describe "manipulation" or "industry verified manipulation". It is not clear if this term has ever been used anywhere else and if it will universally understood.	
5	**Section 6.1 handling of solid preparations …** Lines 280 – 289 discuss “handling” or manipulation of dosage forms. Any deviation from the formulation used in clinical trials must be justified. If this guideline is to state that it is possible to “handle”, manipulate or modify a medicine then it is absolutely necessary to state how this should be justified. Often a comparative bioequivalence study will be needed. A reluctance to discuss pharmacokinetics is noted, perhaps because this is a quality guideline. It would be extremely useful to get the opinion of PKWP on this guideline (or other PK experts).	Comments noted The section *Modification of oral solid preparations to facilitate administration* has been updated. Further considerations, including impact on bioequivalence, have been included in the revised text. Guidance on PK/PD is outside the scope of this document.
5	**Mixing with food** The comments above apply. Clearer guidance of pharmacokinetics could be given. Lines 736 – 737 state the following: “Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine”. This is the only mention of bioavailability in the section and it is too vague to provide useful guidance.	Comment noted Guidance on the pharmacokinetic and pharmacodynamics aspects of paediatric medicines is excluded from the scope of the guideline. The guideline however indicates that PKPD aspects must be considered where relevant.

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5	**Patient acceptability** Although the definition is acceptable (lines 642 to 655) the rest is very vague, difficult to understand and fails to give any real guidance (lines 656 – 675). The purpose of the document is to give guidance. A clearer more understandable explanation of what is expected in the demonstration of patient acceptability is required. Expertise from outside the drafting group should be consulted.	Comment noted The section *patient acceptability has been* updated and the comment has been considered. Acceptability testing, including palatability, should be embedded in the development program. Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods currently employed, the Agency feels it is not appropriate to impose any method for acceptability testing at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The Agency is currently evaluating what would be an appropriate evidence of patient acceptability. This however requires careful considerations and therefore it cannot be implemented to the guideline at this stage. It is foreseen that future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline.
7	<u>General comments to the guideline</u> Validation expectations with regard to dosing accuracy and compatibility with the proposed vehicle are clear in existing regulatory guidance. However, expectations with regard to data used to validate the patient's or caregiver's ability to accurately prepare the drug product need to be clarified. Indeed, validation often is not possible with palatability studies performed as part of the clinical studies. It is more appropriate to use the term Evaluation and Justification,	Comment noted The term validation has been replaced by verification. The new section modification of oral dosage forms lists the types of studies that may be used for the verification and the term verification (of a modification) has been included in the glossary.

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	instead of validation. Proposal: Remove “validate/validated/validation” requirements (lines 286 and 287) for studies related to caregiver’s ability to accurately prepare drug products. Replace in terms of “evaluate/evaluated/evaluation” or “justify/justified/justification”. Clarify or publish a high-level guideline on • The number of patients this data should be collected from • Can visual confirmation of the patient’s ability to handle the product as described in the package literature be considered sufficient to justify the instructions and ease of use/acceptable handling attributes? • Can we use compliance record from clinical studies (e.g., % of volunteers of drop out) as indication of compliance?	
8	The Medicines Evaluation Board in the Netherlands (MEB) welcomes the next step in the finalisation of the Guideline on the pharmaceutical development of medicines for paediatric use. Such finalisation is greatly appreciated in view of the increasing number of new applications/variations for (generic and innovative) paediatric medicines in all four licensing procedures and the PIPs, which underline the need for a harmonized and consistent approach to their development and the assessment of the acquired data.	Response to the comment not applicable.

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	The MEB is especially pleased that the current guideline is open for public comments on three issues only. As a consequence, the MEB assumes that all other paragraphs/sections are to be regarded as finalised and will neither be modified as a result of comments submitted under this limited consultation nor any new scientific evidence (the latter would better fit into a first revision or Q&A). The MEB consider the current Guideline well structured and organized. All essential aspects are highlighted. Please find our comments on the three issues which are open to public consultation.	
6	The Global Alliance for Paediatric Therapeutics offers these comments to the *Draft Guideline on pharmaceutical development of medicines for paediatric use*, Reference # EMA/CHMP/QWP/805880/2012 Rev. 1. The Global Alliance for Paediatric Therapeutics (the Alliance) is a public-private consortium of industry, clinical and paediatric advocacy groups convened by the Institute for Paediatric Innovation (www.pediatricinnovation.org). The Institute is a 501(c)(3) non-profit corporation dedicated to improving paediatric care by improving processes for development of paediatric medical products. The Alliance has recently completed an update of the scientific literature review carried out by the European Medicines Agency in 2008 (Davies EH, Tuleu C., *J Pediatr.* 2008 Nov;153(5):599-604), with a specific focus on understanding the tools and methodologies used to assess palatability of oral dosage	Comment noted Comments support the Agency's position not to provide detailed guidance on acceptability testing in view of scares and fragmented information available on this topic. Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods currently employed, the Agency feels it is not appropriate to impose any method for acceptability testing at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The Agency is currently evaluating what would be an appropriate evidence of patient acceptability. This however requires careful considerations and therefore it cannot be

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	forms in paediatric populations. The key finding of this updated scientific literature search was that despite various pleas for a “call to action”, the scientific and pharmaceutical community has been slow to publish clinical research that describes the assessment of organoleptic properties in paediatric patients, and the impact of these factors on treatment compliance and adherence. The Alliance plans to publish the updated literature review. In addition, the Alliance conducted an extensive internet-based survey of leading pharmaceutical companies in February 2013, to better understand current industry best practices related to the assessment of palatability and swallowability in the overall clinical development program for paediatric dose forms. In general, while paediatric medicine is a strategic focus for the responding companies, there was no consistent approach amongst respondents to the assessment of organoleptic properties of liquid or solid dosage forms, including excipients. In the direct assessment of palatability in paediatric patients in clinical trials, the industry survey identified a variety of methods that are utilized across companies. However, no assessment method identified by any participant was acknowledged as validated or with any statistical correlates. Full analysis of survey results is in process and the results will lead to a publication. Based on both the scientific literature review and the preliminary results of the industry survey, the Alliance’s provisional conclusions are that: 1. Palatability is commonly being assessed in paediatric clinical trial subjects through the utilization of two	implemented to the guideline at this stage. It is foreseen that future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline.

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	scales that are widely accepted, but not validated. 2. Despite the wide use of these two clinical scales, there is no standard statistical methodology for analyzing the results of these scales nor cross-comparison of results across studies. The Alliance and its collaborators plan to publish a detailed report on the survey. The Alliance believes that there is a clinical rationale for establishing a standardized evaluation methodology for the assessment of palatability in clinical trials in paediatric populations, including but not limited to: 1. Adoption of one or more clinical scales as the operational standard for the clinical evaluation of palatability and swallowability in paediatric patients, and 2. Definition and validation of a standardized procedure for administration of the scales as well as standardized statistical benchmarks and methodology for analyzing the results. Further definition of these proposed standards requires additional information from other key stakeholders, including clinicians, paediatric advocacy organizations, regulatory science experts, and consumer product testing companies. The Alliance is continuing its ongoing initiatives to obtain such information and prepare a more detailed set of recommendations for development of a standard set of guidelines. The Alliance welcomes the participation of the European Medicines Agency in its project to develop and validate best practices for evaluation of palatability of	

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	paediatric formulations. For further information, please contact me at donald.lombardi@pediatricinnovation.org.	
10	**Handling of oral solid preparations to facilitate administration** The need to include information on handling of oral solid preparation is greatly recognised. The text encourages manufacturers to give detailed and validated information on how to handle drugs. We would like to point out, that this might unnecessarily result in different methods for each oral solid preparation, which in turn does not contribute to medication safety or feasibility in clinical and pharmaceutical practice. This problem especially arises with immediate release preparations and less with controlled release preparations. This is because procedures on how to handle oral solid preparations are often nationally and also locally standardised. So, scientific information should be provided in such a way that caregivers can apply this to their own setting. Examples are basic information such as stability data after handling and in different mediums (at least water), clinically relevant information on differences in pharmacokinetics between swallowing intact preparations and after handling. Problems with swallowing oral dosage forms are not limited to children, but include for example elderly people, patients not able to swallow due to illness and patients with feeding tubes. Guidelines on general information concerning handling of oral solid preparations to facilitate administration	Comment noted It is recognised that different instructions to identical types of medicines increase the potential for medication error. It is considered in the interest of children to obtain information on verified modifications which enable administration of the product. Although swallowing problems with elderly people are recognised, they are not necessarily associated with age and they may have a different origin. It was felt appropriate to discuss this problem in the paediatric guideline. With regards to administration through feeding tubes a dedicated section (section 6.2.3) is included in the guideline.

Stakeholder name	General comment (if any)	Outcome (if applicable)
	should be uniform for all patients with swallowing problems. One would expect that information on mixing with food and some relevant information on administration through feeding tubes is included in this section.	
11	The Special Interest Group (SIG) Pediatrics of the Dutch Hospital Pharmacists Association (NVZA) welcomes this intention to improve pediatric pharmacotherapy. The document addresses many relevant issues regarding drug formulations, which are experienced in daily pediatric clinical practice. However, the SIG fears that the demands for studies on each situation described in the guideline may lead to a delay or even abandoning of development of pediatric formulations. Also, the increased research costs will be extrapolated into the price of the final product, which may lead to decreased availability of licensed products in some countries, due to financial issues. Given the fact that all current SmPCs lack information on most of the raised issues, the feasibility of this guidance needs to be verified with relevant parties. In general, scientifically based and appropriate, preferably inexpensive and easy, methods are needed to investigate the raised issues. Academia may be encouraged to develop these methods. A prioritization may be needed in this stage.	Comment noted The guideline allows on great level of flexibility in development of paediatric medicines. The cost of development should not be the only criterion influencing the outcome. Other aspects should also be considered and often additional research is needed. The need for closer cooperation between academia, regulators and the industry is recognised and encouraged.
11	In clinical practice, pediatric patients' acceptability is foremost dependent on the taste of the formulation and a neutral taste is always preferred. The current section 10 may be hard to implement because of great variation of food	Comment noted It is indicated that there is no international harmonized agreement on the need for neutral tasting medicines over those with a specific, but very pleasant taste. It cannot be excluded that such preference may

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	and drinks, especially in different European countries. The information on the combination of the drug with water or dairy is considered most important, in combination with the aim for neutral taste of the formulation.	also differ depending on cultural aspects.
12	Comment: The documents looked good overall. The only minor point is that many state that paediatric medicines shouldn't taste "too good" (i.e., candy like) to avoid the risk for abuse potential. However no one ever cites data to support the validity of this point of view.	Comment noted It is indicated that there is no international harmonized agreement on the need for neutral tasting medicines over those with a specific, but very pleasant taste. It cannot be excluded that such preference may also differ depending on cultural aspects.
3	Whilst this comment relates to a section (Section 5, line 173) that is not formally re-opened for consultation, we ask that the following comment is considered, as the text as revised is perhaps inappropriate. The suggestion that mesylate salts should be avoided is considered overly precautionary. It is not clear that a mesylate salt (if suitably pure and controlled) cannot be a suitable salt form for a paediatric medicine. We are aware of particular safety concerns associated with impurities in sulfonate salts (i.e. the genotoxicity of alkyl sulfonate impurities) but these impurities can be avoided in the salt (through appropriate process design and controls associated with manufacturing) without having to avoid the salt form. Proposed change: Remove the reference to mesylate salts being an example of a salt form that should be avoided for paediatric medicines.	Accepted

Stakeholder name	General comment (if any)	Outcome (if applicable)
9	It is recommended that the terminology and definitions of dosage forms used in this guideline are aligned with those used in the European Pharmacopeia (Ph. Eur.) to avoid potential misunderstandings.	Comment noted Second consultation was limited to the sections 6.2.1 and 10. However, general changes which improved wording or the text in general have been accepted. The terminology of dosage forms and routes of administration has been harmonised with the Ph. Eur. and Standard Terms.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
223-302	10	The information on specific oral solid preparations includes information on handling, the text would be more clear to the reader if such information is moved to the section *Handling (…).*	Comment noted but not accepted Information on modifications included within the section 6.2.1, placed outside the paragraph "Modification (…)", refers specifically to a particular dosage form or to a specific type of preparation. It is considered more appropriate to keep this information as initially proposed rather than combining all messages into a single paragraph.
223-302	11	This section has much overlap with section 10. Also, this section is not very specific in its approach of "handling of drugs", especially with food and drinks. In our opinion, handling of a formulation is necessary if a formulation is not well suited for the target population. Important reasons to do this in daily practice are the need for dosage adaptations and problems with intake of solid dosage forms by young patients and children with feeding tubes. Generally, standard scoring of all tablets in half or quarters would be very welcomed and improve dosing accuracy, in comparison with the current method of using a tablet splitter (when liquids are not available). Information whether a tablet can be crushed is also welcomed, as well as information on the combination of the drug with water or (the most common) dairy products as main vehicles for	Comment noted but not accepted It should be considered that not all modifications are done to improve patient's acceptability. Modifications may also be needed to adjust the dose, etc. The paragraph refers specifically to oral solid dosage forms and it is considered more appropriate to maintain it within section 6.2.1.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		dissolving drugs.	
223-302	11	Some of the issues described are of importance for all of the oral solid preparations e.g. the risk of choking is mentioned for powders/granules in line 229 and for tablets in line 253; the risk of chewing or not chewing is mentioned for powders/granules in line 229, for tablets in line 253, and for orodispersible/chewable preparations in line 275. Proposed change (if any): These issues could be described in a general section.	Comment noted but not accepted Risks associated with the administration of a particular dosage form are discussed within the section which is dedicated to this dosage form. Having general discussion on these aspects could be an option, but it would detract focus from the risks associated with a particular dosage form. Therefore no changes to the current approach are proposed.
280	4	This section needs consolidating as it includes examples of duplication Proposed change (if any): Lines 294 to 300 duplicate largely what is said previously in the sub-section.	Commented noted but not accepted Considerations discussed in the paragraph (lines 294 – 300) refer to modification of tablets. This information is not a repetition of the discussion in the previous section on tablets. The section on tablets focusses on different aspects such as acceptability of various shapes and sizes etc.
280	5	“handling of solid oral preparations” Some people may find the term “Handling” confusing. At the very least it should be defined in the section on definitions. The origins of the term should be explained as some	Comment noted and partially accepted The term “handling” has been replaced by “modification” to avoid confusion. Furthermore an explanation of the term is included in the glossary.

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		readers might be confused and surprised. In regulatory guidelines the term was mentioned previously in “Notice to Applicants, A guideline on summary of product characteristics” in Section 6.6 ‘Special precautions for disposal of a used medicinal product and other **handling** of the product’. In this guideline it is used to describe disposal or preparation of toxic medicines. My guess is that this is where the term “handling” has come from. Proposed change (if any): If the term “handling” has to be used in the guideline then it should at least be defined in the “Definitions” section preferably with some explanation of where the term has come from.	
280-302	11	Subsection ‘handling of oral solid preparations to facilitate administration’ is misplaced, since this is an important aspect of patient acceptability (line 650). Proposed change (if any): Move this paragraph to section 10.	Comment noted but not accepted Not all modifications are done to improve patient’s acceptability. Modification may also be needed to adjust the dose, etc. The paragraph refers specifically to oral solid dosage forms and it is more appropriate to maintain it within section 6.2.1
281-289 and 215 - 220	7	Lines 281 through 289 and Section 10 (inclusive) sufficiently address the need for developers to consider alternative dosing information for products not considered to be age appropriate. Lines 215-220 are redundant with lines 281-289 and Section 10 and appear to be adding	Not accepted Modification of a dosage form should be an option when alternative dosage forms are not available or are not appropriate to the age of the child or when a dose needs to adjusted.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		additional expectations for developers in those instances when a drug product *is designed and considered acceptable* for the specific paediatric population or subpopulation. Proposed change to text: Eliminate lines 215-220.	The text in lines 215 – 220 emphasises that the primary objective should always be the availability of an appropriate formulation that is well accepted by the child and/or its caregiver. Modifications should be seen as an exception beyond any age-appropriate formulation and should be justified.
282-302	8	This section of the guideline does not make a clear distinction to proposals that are adequately justified by the applicant and reflected in the SmPC/PIL and those that are not, but likely to be applied/unavoidable in daily practice. The MEB considers that the paragraph would benefit from a clear distinction between the two scenarios.	Comment noted It is the intention of the paragraph to stress that proposals that are adequately justified by the applicant should be reflected in the SmPC/PIL. An adadditional statement regarding modifications outside the approved label has been added.”
282	8	The GL emphasizes the need that children should both be able and willing to accept their medication. The MEB thinks it is very essential that this aspect is kept in the guideline i.e. not deleted because of comments from other stakeholders.	Accepted
283	4	Minor typographical error “In lack of (…)” is not clear. Proposed change (if any): Revise text “in lack of (…)” to read “In the absence of (…)”	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
284	4	Include capsule manipulation here Proposed change (if any): (e.g. dispersing or crushing of tablets, opening of capsules to release contents, mixing with food or drinks).	Accepted
284 - 285	8	The GL states that any alternative strategies are to be considered (285) (…) and proposed (285). For clarity reasons the MEB would recommend to add the following to both statements “by the applicant”.	Accepted
285-287	10	Alternative strategies will always be needed. Although validation from a qualitative point of view is preferred, feasibility by the manufacturers could be questioned. Caregivers are more helped with basic scientific information on compatibility with vehicles, impact on bioavailability etc. etc. than with a validated method. As stated earlier, methods are often standardised.	Comment noted and accepted The term “validated” has been replaced by “verified” to avoid confusion. Furthermore an explanation of the term has been included in the glossary. If the approach was verified it means that issues such as compatibility with vehicles, impact on bioavailability etc. have been considered during the development and are appropriately reflected in the SmPC and PIL.
285 - 289	3	Validation of the handling is a term which may cause confusion, since in a pharmaceutical environment the term validation is more associated with analytical and process validation, whereas here it is probably meant more in the sense of validation of usability as is used e.g. in a medical	Comments noted and accepted The term “validated” has been replaced by “verified” to avoid confusion. Furthermore an explanation of the term is included in the glossary.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		device development environment. Validation expectations with regard to dosing accuracy and compatibility with the proposed vehicle are clear in existing regulatory guidance. However, expectations with regard to data used to validate the patient's or caregiver's ability to accurately prepare the drug product need to be clarified. Evidence from a single clinical trial that the target patient demographic has prepared the drug product as described in the package literature and that organoleptic and administration attributes are acceptable can be provided to support the data set as outlined in FDA and Ph. Eur. guidance on tablet scoring. This combination of clinical and non-clinical data may support manipulation of the drug product for paediatric use. Comment: it is appreciated that the text wording "compatibility with the proposed vehicle" allows for the pre-determined selection of one (or a small number) of vehicles and does not require the underwriting of a number of different vehicles.	
286	8	In cases where the applicants do not propose such a strategy, it should nevertheless be clear to the user which type of handlings may result in which risk. This is	Comments noted Additional statement regarding modifications outside the label has been added. The discussion to verify the modification has been

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		especially important in cases where no alternative, age appropriate dosage forms have been developed and no other remedy exists. The MEB proposes to include a statement starting with “In lack of any alternative age appropriate dosage forms and an alternative strategy to administer the medicine to children who are not willing or able to accept the medicine as such, the following applies (…)”. The word validation is used in different contexts in the medical area. In regulatory dossiers it mainly refers to actual studies. It should be clear to the reader of this guideline that validation of the handling may be conducted by other means than actual studies i.e. sometimes a narrative discussion may be sufficient. We therefore propose the following wording: *Validation of the handling should include a discussion of aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risk for the person who will handle the dosage form. Where aspects can not be (fully) justified on basis of a narrative discussion, actual supportive studies should be conducted. Justification may involve reference to existing practices that have not been associated to relevant problems over substantial use.*	updated to better reflect the possibility to refer to literature data and well established practices which are not associated with problems over the period of use.

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286 - 287	4	Clarity is required in terms of what the agency means by *validation with respect to handling* - should this be verification? Some of the language sounds strange and should be re-phrased. Proposed change (if any): (…) the approach should be verified and clear instructions on how the product should be handled should be given in the SmPC and PIL. Verification of the handling (…)	Accepted The term “validated” has been replaced by “verified” to avoid confusion. Furthermore an explanation of the term is included in the glossary.
286	4	Don’t like “*handling(s) to be conducted”* Proposed change (if any): (…) clear instructions on acceptable dosage form manipulation(s) should be given...	Accepted The term “handling” has been replaced by “modification” to avoid confusion.
287	4	Remove “of the handling” Proposed change (if any): Validation should include (…)	See above
288	9	It is suggested to modify the sentence as follows: *“Validation of the handling should include (…) and any **safety** risks for the persons”.*	Accepted
288 (and	4	It is appreciated that the text wording “*compatibility with the proposed vehicle*” allows for the pre-determined	Comment noted

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300)		selection of one (or a small number) of vehicles and does not require the underwriting of a number of different vehicles. Proposed change (if any): No proposed change.	The EuPFI interpretation is correct.
288	5	Line 288 mentions the “potential impact on bioavailability”. This is too weak – it is a safety and efficacy issue – bioavailability studies will often have to be performed where dosage forms are manipulated. This is the status quo. Reputable Pharma companies conduct biostudies if they recommend “handling” or manipulation of the dosage form. A reluctance to mention pharmacokinetics is noted, as supposedly pharmacokinetics is out of scope of a quality guideline. This does not anticipate the needs of the guideline users. Help from PK experts is available. Perhaps they should be consulted. Proposed change (if any): A statement such as the one below is needed: “By “handling” or manipulation of the dosage form there may be some deviation from the formulation justified by clinical trials data. Evidence that “handling” has not	Comment noted It is not fully correct to say that bioavailability will always be needed for any modification of a dosage form as this is a case by case decision. Guidance on PKPD studies falls outside the scope of this guideline.

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		affected safety or efficacy will be needed. In some cases it may be possible to justify the change in others it will be necessary to perform a relative bioavailability study comparing the modified and unmodified dosage form".	
280-289	5	Lines 280 -289 when discussing handling there should be some discussion on when handling should be considered. Handling is linked to acceptability. If a product is well accepted by the age range in question there may be no need to "handle" or modify it. The guideline seems too pro-handling and does not seem to recognise that "handling" entails risk and undermines the formulation of the product. Proposed change (if any): Some text such as the following might be acceptable: "The aim of formulating a medicine for the paediatric population should be that all children in the indicated age range are able to take the medicines. It is understood that 100% acceptance will not always be achieved. In order to cater for those children who cannot take the medicine it may be necessary to have an alternative dosing strategy. This may be an alternative dosage form. If an alternative dosage form is not feasible then modification or "handling"	Comment noted but not accepted It is clearly stated in the section 6.2.1 (Modification of oral solid preparations to facilitate administration) that modifications should be investigated in absence of any alternative age appropriate dosage forms. Indeed the aim of the guideline is to stimulate development of age-appropriate medicines not requiring any modifications. It is considered that this notion is sufficiently stressed in the guideline and there is no need to repeat it again within another section of the guideline.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		of an existing dosage form might, where justified as an alternative dosing alternative strategy".	
290	8	We disagree with the following statement **"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".** If competent authorities consider that a tablet may not be broken to obtain fractions of the full tablet dose, then the MEB considers that this tablet should not have a score line as almost all health care professionals and patients will use the line for this purpose whenever a halved dose is necessary (either within or outside the label). The MEB also considers that adequate scoring should be demonstrated according to the requirements of the Ph. Eur. Thus additional requirements should not be asked, unless the exceptional case where a specific concern to a specific product exists. We feel that new scientific evidence on e.g. lack of content uniformity within a tablet should result in a change in the Ph. Eur. monograph and not in additional general requirements in a paediatric guideline as it may equally apply to tablets for other, adult age groups.	Partially accepted The paragraph has been revised to address the concern raised.
290 - 293	3	In case a score line is made in a tablet the tablet halves should comply to the general regulations. In general dose criticality should be considered in case of scoring lines.	Comment noted The paragraph has been revised to address the concern raised.

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		Hereby there is no difference between the paediatric and adult populations. Please refer to existing guidance.	
290-293	1	Comment 1: To differentiate between score lines that are not intended to be functional (e.g. those used to designate a design or unique company identifier), it is suggested that the reference to score lines used to facilitate breaking and/or to obtain a fraction of a full tablet dose be described as a 'functional score line'. Comment 2: In case a score line is applied, the product must meet the requirements of the Ph. Eur. on divisibility even if both subparts of the tablet are supposed to be taken (dosage uniformity to be confirmed by an analytical person). We would therefore propose to add a sentence in this sense. Proposed change (if any): Functional score lines are used to enable the administration of a full tablet dose or to facilitate breaking for ease of swallowing. The use of functional 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	Comment 1 noted and partially accepted In line with the guideline on the SmPC it now states that the function of the break mark should be stated in the SmPC and PIL. Comment 2 noted and partially accepted Specific reference to Ph. Eur. is not included in the guideline, instead a general reference on the suitability of subdivision is added. See comment above.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		with (a) functional score line(s) should be demonstrated. The use of score lines in tablets is only acceptable in case the divisibility according to Ph. Eur. requirements can be demonstrated.	
290-296	5	Lines 290 – 296 discuss score lines on tablets and halving tablets. Clear guidance on tablet splitting is provided by the FDA. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf "*Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*" An opportunity is being missed here to clarify what is required in terms of: 1. stability of half tablets 2. meeting FPS requirements 3. setting content uniformity requirements 4. dissolution requirements* *There seems no reason why a tablet that is halved should not comply with exiting EU guidance "*Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** section 4.2.2. In vitro dissolution tests in support of biowaiver of strengths*". A 5mg and 10mg tablet would need dissolution in accordance with the f_2 statistical	Not accepted If the FDA guideline on tablet splitting is to be adopted it should be equally applicable to products for adults use. In this case it must be remembered that breaking for cost reduction is not (yet) so popular in the EU as the USA.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		test to achieve a biowaiver for one of the strengths. Surely a 10mg tablet that can be divided into two 5 mg tablets would require the same treatment. Proposed change (if any): Adopt the FDA guidance (with some minor adjustments) and take into account the existing EU guidelines i.e. "*Guideline on the investigation of bioequivalence".* Many companies are already working to these requirements.	
290 - 298	4	There is some repetition regarding ease of swallowing in these paragraphs. Proposed change (if any): (…) remove "or to facilitate breaking for ease of swallowing" from line 290 (as this is addressed in the following paragraph).	The comment is noted, but the proposal for revision was not accepted. Some repetitions in the guideline may be needed to flag the importance of certain aspects.
291	4	Recommend comment about SmPC & PIL info. Proposed change (if any): (…) ease of swallowing; their intended function should be stated in the SmPC and PIL.	Accepted
291-293	9	*"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 comment has been partially accepted The paragraph has been revised, and the term 'break mark' was introduced in accordance with the Ph.Eur. terminology.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Ph. Eur. is using the term “break marks” instead of “score lines”. Proposed change: *“In case the use of break marks is recommended in the SmPC and PIL to obtain fractions of the dose, accuracy of the **subdivision** needs to be demonstrated according to Ph. Eur. Breaking devices might be useful to increase dosing accuracy.”*	Specific reference to Ph. Eur. has not been included in the guideline, instead a general reference on the suitability of subdivision is added.
293	8	**“The ease of breaking tablet with score line(s) should be demonstrated”.** The MEB appreciates this statement and considers that it holds a very import user aspect. However a harmonised method has not yet been developed. Therefore the MEB proposes to include the following to this phrase “for the majority of the indicated patient population”. The MEB considers that studies on ease of breaking by other people (e.g. analytical staff) may not be representative of real life situations.	Comment noted Further amendments to the text have been introduced. It is accepted that providing detailed guidance and acceptance criteria for the ease of breaking is premature and not appropriate at this early stage.
294-300	8	**“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”.**	Comment noted and partially accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		For clarity reasons we would recommend to state subdivision of un-scored tablets, as otherwise the former paragraph applies. This phrase holds an option / general information, but no real guidance. The MEB consider guidance should either be added (e.g. risk information on such handlings) or the paragraph deleted from the guideline.	
294 – 302	3	This paragraph is not novel. Opening of capsules, breaking of tablets is already mentioned one paragraph earlier. Please re-word this whole section to prevent overlap. **Suggestion:** (…) to swallow ~~the take~~ a tablet intact. It may also be an option to disperse or dissolve a tablet in a liquid prior to administration ~~intake~~.	Accepted
295-296	1	Comment: Typo. Proposed change (if any): "(…) for administering a tablet to children who have difficulties to swallow the tablet intact."	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
298 - 302	3	Proposed change: The guidance should state that compatibility may be demonstrated by appropriate in-use stability studies and the time during which the drug product in the vehicle remains acceptable, based on such studies, should be indicated in the SmPC and PIL.	Accepted This issue is being addressed in detail in section 10 to which a reference is made in this section.
300	4	*handling(s)* sounds very strange. Proposed change (if any): handling procedure(s)	Accepted The term “handling” has been replaced by “modification”. Furthermore an explanation of the term is included in the definitions section.
301	4	Comment: The earlier text in this section is clear that handling to deliver a product may not be required or proposed. This is considered appropriate. However this final sentence seems to suggest that the PIL/SmPC will contain a statement if such handling is not appropriate. It would not be reasonable for the applicant to consider and warn against all potential handling approaches that a caregiver could adopt. We propose that the applicant limit statements to cover any handling which is known to be inappropriate e.g. certain modified release products should not be crushed. Proposed change (if any): Please consider how to clarify the text on this point, perhaps to read “Where the product	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		may be handled to facilitate administration but some handling approaches are prevented (e.g. the crushing of a Modified Release product) it should be made clear (in the SmPC and PIL) which handling approaches are appropriate and which are not appropriate."	
302	4	Suggest add an example. Proposed change (if any): e.g. MR monolithic dosage forms.	Accepted Specific examples are added.
section 10	3	This guideline does not provide information about how to measure palatability. Do such measures exist and if so, can they be included in the guidance?	Comment noted Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods currently employed, the Agency feels it is not appropriate to impose any method for palatability testing at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The Agency is currently evaluating what would be an appropriate evidence of patient acceptability. This however requires careful considerations and therefore it cannot be implemented to the guideline at this stage. It is foreseen that

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
			future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline.
Section 10 (general comment)	4	What about generic products where the innovator is not mixed with food?	Comment noted Every product should be used as indicated in the SmPC. This is also applicable to mixing with food and drinks. However there may be situations when different types of food and drinks will be proposed for generic and reference products. These differences may be due to e.g. different composition of these products. For every new application, including generic, the information on mixing with food and drinks should be considered and discussed in the dossier. Where relevant this information should be reflected in the SmPC and PIL.
642	4	It is unclear what aspects of Patient Acceptability should be addressed in then Paediatric Investigational Plan and will be reviewed and agreed with the PDCO. Proposed change (if any): Please clarify what aspects of Patient Acceptability should be included in the PIP.	Comment noted The aspects to be addressed in the PIP should be consistent with the principles of the Guideline however deviations are acceptable because of the early phase of development at which the PIP is submitted.
642-737	8	The MEB generally agrees with the paragraph patient acceptability and mixing medicines with food in view of the wide range of opinions to both aspects and the need for harmonisation. Consequently, the MEB thinks that no	Comment noted and partially endorsed Please refer to the revised text of the Guideline.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		essential changes should be made to paragraph 10. If the QWP/PDCO would consider a change, the MEB would like the group to take their original opinion into consideration e.g. 1) Dedicated patient acceptance studies would need ethical approval, which may not be granted. This aspect should be acknowledged. 2) Mixing medicines with food is a common practice for many years that has not resulted in essential clinical problems except for some types of food children are very unlikely to take (e.g. grape fruit). Hence direct food contact should normally be considered acceptable if 1) the type of food is not contra-indicated; 2) the medicine should not be taken in the fasted condition; 3) the amount of food is small; 4) the temperature of the food not too high or low; 5) direct contact is unlikely to cause physical or chemical changes or changes to the release mechanism and the medicine within short time use. 6) the medicine is taken within minutes after mixing. In all such cases information in the SmPC can be left to the general statement that mixing is not recommended and the responsibility of the user, however if mixed the medicine should be mixed with small portions of food only, the food should be at room temperature and the mixed medicine should be taken immediately. In all other cases a warning should be included that the medicine may not be	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		mixed with food and for what reason.	
642-737	11	Semi-solid food is not discussed in section 10, although it is referred to in section 6.2.1. as a specific vehicle for co-administration. Proposed change (if any): -	Comment noted Terms food or drinks are normally used in the Guideline and semi-solid food is considered as a subtype of food. This term is used only when necessary to differentiate from other types of food.
643	4	Do not interchange acceptance and acceptability	Accepted The term “acceptance” has been replaced by “acceptability”
643 – 647	3	Change Patient acceptance to Patient acceptability Proposed change: Please clarify what aspects of Patient Acceptability should be included in the PIP.	Accepted The term “acceptance” has been replaced by “acceptability” The aspects to be addressed in the PIP with regards to the acceptability testing should be consistent with the principles of the Guideline however deviations are acceptable, if adequately justified, e.g. because of the early phase of development at which the PIP is submitted.
649	4	Texture also relevant and swallowability (not only palatability) Proposed change (if any): (…) (size, shape and texture);	Accepted
649	8	Appearance may be another important aspect to patient adherence (e.g. colour, shape, embossing).	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
649-655	4	Suggest cross refer to sections of document where each of these aspects are discussed. Proposed change (if any):	Not accepted Not all aspects listed are discussed in the guideline.
652	4	DURATION is missing Proposed change (if any): add (…) frequency; duration of treatment.	Accepted
656-662	4	The text states that "*evaluation of the patient acceptability of a paediatric medicine should be an integral part of the pharmaceutical development studies*" and this is appropriate. However, the next sentence states "*patient acceptability of the product should be studied in children themselves as part of any clinical study using the proposed product*." It needs to be clear that this does not mean that clinical studies MUST be conducted with the proposed product (as it may be relevant and appropriate to conduct the clinical evaluation using a preliminary product, prior to the introduction of the proposed commercial product). It should be made clear that there are other appropriate ways to evaluate the patient acceptability of the product	Comment noted The exact wording has not been implemented however further revisions to the text have been introduced to pronounce the fact that acceptability testing does not always involve clinical studies.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		rather than in a clinical study, just as palatability can be evaluated outside the setting of a clinical study. Proposed change (if any): Revise text to read “Unless there is a suitable alternative approach to establishing acceptability, patient acceptability of the medicinal product should be studied in children themselves as part of any clinical study involving the proposed product or in a suitably designed study if the clinical evaluations have been completed using a preliminary product.” In justified cases where no paediatric clinical studies will be conducted or where patient acceptability will not be studied as part of the paediatric clinical studies, adequate patient acceptability of the medicinal product(s) as proposed for marketing should be demonstrated by other means.	
656 - 663	3	The second and third sentences are kind of contradicting each other. The text states that “evaluation of the patient acceptability of a paediatric medicine should be an integral part of the pharmaceutical development studies” and this is appropriate. However, the next sentence states “patient acceptability of the product should be studied in children themselves as part of any clinical study using the proposed product.” It needs to be clear that this does not	See above

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		mean that clinical studies MUST be conducted with the proposed product (as it may be relevant and appropriate to conduct the clinical evaluation using a preliminary product, prior to the introduction of the proposed commercial product). It should be made clear that there are other appropriate ways to evaluate the patient acceptability of the product rather than in a clinical study, just as palatability can be evaluated outside the setting of a clinical study. Additionally, when clinical evaluation is necessary, we believe that a proper acceptability test performed in one clinical study should be sufficient. The current text "(…) as part of any clinical study (…)" seems to set a requirement for acceptability testing in all paediatric clinical trials involving the product. Proposed change: Revise text to read "Unless there is a suitable alternative approach to establishing acceptability, patient acceptability of the medicinal product should be studied in children themselves as part of **a** clinical study involving the proposed product or in a suitably designed study if the clinical evaluations have been completed using a preliminary product."	
656-663	1	The second and third sentences are kind of contradicting each other.	See above

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Evaluation of the patient acceptability of a paediatric medicine should be an integral part of the pharmaceutical development studies and paediatric clinical development programme. The overall strategy to evaluate patient acceptability should be discussed and appropriately justified. Preferably, patient acceptability of the medicinal product should be studied in children themselves as part of paediatric clinical studies involving the proposed product. In justified cases (…)	
659	4	Clarification that applies to CTs in children Proposed change (if any): (…) studies will be conducted in children or in justified cases...	Accepted
662-663	4	Why are oral liquids mentioned here? Proposed change (if any): Suggest remove sentence or add comments about the acceptability of other dosage forms.	Accepted
664-667	4	Paragraph difficult to understand, sentence unclear – re-word Proposed change (if any): For authorised paediatric	Comment noted The text has been revised to reflect the proposed clarification.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		medicinal products for which patient acceptability was tested during development, adequate patient acceptability will have been assured. In cases of subsequent variation(s) to the authorised product, e.g. composition of formulation, the impact of the change should be evaluated and patient acceptability should be re-evaluated and reassured.	
664 - 667	3	Suggestion line 664: (This is a cryptic phrase, not fully understood (…) Comment: It needs to be clearer which Variations may result in the need to re-evaluate patient acceptability as not every Variation will have a significant impact on the patient acceptability of the product. This may need to be built into the Variations guidelines currently under review to provide appropriately focussed guidance. Proposed change: Revise text to read “In the cases of some Variations to the composition of the authorised formulation, its packaging or its usage, the impact of the change should be evaluated by the company to assess that the product remains suitably acceptable to the patients.”	Comment noted The text has been revised to reflect the proposed clarification.
664-665	1	It is not clear if the sentence means that the acceptability	Comment noted

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		should be maintained during life cycle. Does it mean that for established products for which the acceptability of the formulation was not formally tested during development no re-evaluation of acceptability needs to be done in case of formulation changes? Proposed change (if any): For authorised medicinal products for which acceptability of the current formulation was tested during the development the adequate patient acceptability should be assured during life cycle. Or (depending on the intention) For authorised medicinal products for which acceptability of the current formulation was tested during the development or established by market experience the adequate patient acceptability should be assured during life cycle.	The text has been revised to include the requested clarification.
664-665	11	Typo (not necessary to be included in web-publicated document with comments) Proposed change (if any): "(…) during the development, adequate patient acceptability (…)"	Accepted
665	4	Comment: it needs to be clearer which Variations may result in the need to re-evaluate patient acceptability as	Comment noted/accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		not every Variation will have any significant impact on the patient acceptability of the product. This may need to be built into the Variations guidance currently under review to provide appropriately focussed guidance. Proposed change (if any): Revise text to read “In the cases of some Variations to the composition of the authorised formulation, its packaging, or its usage, the impact of the change should be evaluated by the company to assess that the product remains suitably acceptable to the patients.”	The text has been revised to include the requested clarification.
665 -667	5	Lines 655 -667 state “In cases of variations to the composition of authorised formulations the impact of the change should be evaluated by the company and the acceptability should remain to be assured”. This is a really vague statement offering very little guidance on Variations. An opportunity to provide guidance has been missed. Other regulatory documents give vague guidance. This guideline was a chance to give some firm guidance. A chance that has been missed. Communication from the Commission - Guideline on the details of the various categories of variations (…) (2010/C 17/01) states the following in Variation B.II.a .3 “Changes to the	See above

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		composition (excipients) of the finished product" in condition 7.which states "Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations". There have been questions from companies on what data is required to demonstrate no negative impact on taste acceptability. Proposed change (if any): Examples of variations to a solid oral dosage form or an oral liquid with the kind of studies necessary would provide more guidance (see suggested text above).	
656-675	5	Line 656 – 675 Patient Acceptability. An opportunity to give clear guidance on what is required to demonstrate patient acceptability has been missed. It is understood that this is an evolving area and presents some difficulties. Greater clarity, and a more useful guideline, would be achieved if clear examples were given. The following examples could be used as they comprise a large proportion of paediatric medicines where acceptability is an issue: A. Solid oral dosage forms B. Oral liquid medicines	Not accepted It is explained in the guideline that clinical studies are preferred but not necessarily the only means for demonstration of acceptability. Inclusion of the proposed amendments in the guideline would impose strict requirements on the industry and would expose children to additional clinical testing. Various approaches can be employed to demonstrate patient acceptability. It is up to the applicant to choose and justify the approach. Such level of flexibility is envisaged in the Guideline. Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		It would also be useful to state what is acceptable in the case of - New or innovator medicines - Generics - Variations Proposed change (if any): The following text is suggested, although I would imagine it will be ignored: A. Solid Oral Dosage form For a new product placebo tablets or capsules could be made and tested to see if the intended age groups can take them. Alternatively data may already be available on the acceptability of the solid dosage form of the size, shape and design being considered. Patient acceptability of the finished product could be confirmed by clinical trails where patient acceptability will be one outcome of the trial. Generic medicines should be interchangeable with the reference product. If the generic tablet/capsule has the same or smaller dimensions than the innovator and does not differ in other properties such as coating; then with suitable justification, it may be assumed to have similar acceptability to the reference product.	yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods currently employed, the Agency feels it is not appropriate to impose any method at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The Agency is currently evaluating what would be an appropriate evidence of patient acceptability. This however requires careful considerations and therefore it cannot be implemented to the guideline at this stage. It is foreseen that future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Similarly for variations to the oral solid dosage forms, there would be no need to test for patient acceptability provided adequate justification was provided (e.g. the size, shape, taste, mouth feel was unaltered by the variation) B. Oral liquid medicines There may be different aspects to acceptability that will need to be considered separately. For example, there may be measuring device acceptability and taste acceptability with liquid oral medicines that should be considered separately. Taste acceptability or palatability should be investigated at early stages of formulation development. Palatability of the active may be a factor in selecting the dosage form. During development of an oral liquid medicine different taste masking systems may be tested. This is an evolving area and specific methods cannot be recommended. Although in-vitro testing by methods such as the electronic tongue may be used in the early stages of development the correlation to taste in humans is not fully understood. At some stage testing in humans will be necessary. This might be by adult panel or expert tasters. If the medicine is toxic then this may not be possible. An example of a	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		method used to circumvent this problem, for bitter medicines, is the use of placebo medication containing quinine. An electronic tongue is used to determine how much quinine is equivalent in terms of bitterness to the active. The various formulations are tested with the electronic tongue to determine which masks the bitterness the best. This is just one example and the limitations of this method are acknowledged, however, it may be used in the early stages of development and results confirmed later during trials in humans. Other methods may also be used. For a new or innovator medicine taste acceptability should be confirmed during clinical trials. There are several methods but taste acceptability or palatability studies are often based on the use of a visual analogue scales (e.g. five face rating scale). If children will be doing the tasting the methods used will to be need to be appropriate for their age. Whatever method is selected it should be suitably justified. Generic oral liquids should be interchangeable with the reference product. There appears to be a link between therapeutic compliance and taste acceptability (*Cohen et al 2009 Study of antibiotic syrups, suspensions and oral solutions prescribed to paediatric outpatients Eur J Pediatr*	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		(2009) 168:851–857). If the taste of a generic oral liquid is less acceptable than the innovator there could be public health concerns. Some oral liquids will require a relative bioavailability study comparing the generic to the reference product (e.g. most suspensions). Evaluation of taste could be conducted during the biostudy. Comparative bioequivalence studies are usually conducted on adult volunteers, even in the case of paediatric medicines. The purpose of the study is to detect differences in the formulation so it is not necessary to do the study with children. Although evaluation of taste in adults is not ideal this could be done during the comparative bioequivalence test without the need to needlessly expose children to the medicines. Although taste testing in children is preferable adult data may be accepted in the case of generic medicines with suitable justifications. A method such as the five face rating scale could be used although other suitably justified methods might also be acceptable. Limits of "equivalence" or "non-inferiority" of acceptability should be discussed and justified where appropriate. Some generic oral liquids (e.g. some oral solutions) may not require biostudies. Evaluation of taste acceptability by other justified means should be undertaken. As generic medicines are already used by patients it might be possible to use a panel of patients. Although, ideally they	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		should be in the age range indicated this may not always be practical and the use of adult panels or expert tasters may be accepted where justified. Variations to the taste masking systems of oral liquid formulations may sometimes be necessary. Although techniques such as the electronic tongue might be used to optimise the change, demonstration of comparability in terms of taste acceptance in the old and new formulation may only be adequately achieved by tasting in human subjects. Ideally children in the appropriate age range would be used but other techniques such as the use of expert tasters or adult panels (volunteers or patients) might be acceptable. If the change to the taste masking system is very small it may be possible to justify the change without the use of human volunteers.	
668 - 675	3	Some guidance of what EMA considers appropriate evidence of patient acceptability would be useful. Why doesn't EMA/CHMP provide a proposal in this guidance document? Is there (an operational) definition for patient acceptability?	Comments noted Acceptability testing, including palatability, should be embedded in the development program. Currently several methods have been described in literature, however knowledge is still scarce and fragmented and it has not yet been possible to arrive at an internationally harmonized method. In order to allow for new and innovative approaches and to provide better evidence for methods

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Patient acceptability of taste should be accompanied with a validated measure. There is acceptable palatability which may differ from liking the medication. Where/how should a sponsor 'discuss' the suitability of methods? In the PIP? Comment line 671: The text states that "appropriate limits are applied" to acceptability but it is not clear what these are (and given the somewhat subjective and inconsistent nature of the matter, this suggestion of concrete and consistent acceptance criteria may be inappropriate). Proposed change (If any): Remove the words "and the appropriateness of the limits to be applied." Comment line 672: The example stated (the emergence of microbiological resistance) is a very important one but it is unclear how the issue in this example can be extrapolated to other products, as seems to be suggested. Comment line 674: The text uses the phrase "incidental use" and it is unclear what this means. Proposed change: Please clarify this term (acute usage?)	currently employed, the Agency feels it is not appropriate to impose any method for acceptability testing at this early stage. Therefore the choice of the method and the criteria applied are left to the industry however the selected approach should be described and justified for the intended aim. The work is in progress and the Agency is currently evaluating what would be an appropriate evidence of patient acceptability. This however requires careful considerations and therefore it cannot be implemented to the guideline at this stage. It is foreseen that future updates, e.g. in the form of Question and Answer documents, will be published to complement the guideline. Deletion of the line "appropriate limits are applied" is not accepted. Applicants are expected to propose and justify the acceptance criteria. The emergence of microbiological resistance is used only as an example, to demonstrate the magnitude of the problem (underdosing caused by non-acceptance of the formulation). Underdosing may also be dangerous in case of products containing potent active substances but it is not the intention of the guideline to provide an exhaustive list of all potential risks. "Incidental" has been replaced by "single".

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		and its usage here or omit the use of this term.	
671	4	The text states that “appropriate limits are applied” to acceptability but it is not clear what these are (and given the somewhat subjective and inconsistent nature of the matter, this suggestion of concrete acceptance limits may be inappropriate). Proposed change (if any): Remove the words “and the appropriateness of the limits to be applied”.	Not accepted Deletion of the line “appropriate limits are applied” is not accepted. Applicants are expected to propose and justify the acceptance criteria.
672	4	Comment: The example stated (the emergence of microbiological resistance) is a very important one but is very particular and it is unclear how the issue in this example can be extrapolated to other products.	Comment noted The emergence of microbiological resistance is used only as an example, to demonstrate the magnitude of the problem (underdosing caused by non-acceptance of the formulation). Underdosing may also be dangerous in case of products containing potent active substances but it is not the intention of the guideline to provide an exhaustive list of all potential risks.
674	4	The text uses the phrase “incidental use” and it is unclear what this means. Proposed change (if any): Please clarify this term (acute usage? accidental?) and its usage here or omit the use of this term.	Accepted “Incidental” has been replaced by “single”

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
681	4	Excipients also influence palatability – needs to be mentioned somewhere. Proposed change (if any): (…) medicinal dosage form. (The influence on palatability of included excipients is also an important consideration.) Information on the palatability (…)	Accepted
681 - 686	3	Comment: It is noted that the text states that the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or drinks. This stipulation could have the effect of driving up the level of excipients in the product beyond the levels that could be used if there was an allowance for achieving palatability using foods or drinks as part of administration. Proposed change: Please consider if this absolute stipulation for unsupported palatability is truly the expectation. Revise text to read “It is preferable that the palatability of a paediatric medicine is evaluated and, if possible, developed to be satisfactory without the need for mixing with food or drinks, but this approach can be employed to achieve satisfactory palatability.”	Comment noted but not accepted The statement starts with “Unless otherwise justified, “which implies that the requirement discussed is not the only possibility. Need for mixing with food may be employed where justified. The statement does not exclude the possibility for mixing with food or drinks. When such approach is proposed it is expected however that applicant will provide a sound rationale for it. It should not be a first choice approach but rather an approach when for various reasons palatable formulation cannot be developed. The aim of pharmaceutical development should be to obtain a palatable dosage form. The qualitative and quantitative composition of excipients should be justified, including safety aspects. If this is not possible mixing with food or drinks may be an alternative to assure an adequate palatability.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
681, 684, 697	11	What is meant by the term 'finished (medicinal) dosage form'? Proposed change (if any): The term 'finished' could be deleted.	Not accepted The term "finished medicinal product" means the product which is marketed, which will be given to the patient. This is a standard phrase used for pharmaceutical products.
Line 683 Line 733	12	Comment: 1. "The palatability of the active substance should contribute to the choice of the selected finished dosage form(s) and route(s) of administration." Should this be "could be considered" so it does not lead to replacing an oral dosage form with an injectable. Early on, we can recommend optimizing the oral formulation and/or dosage form, the palatability can be improved significantly. 2. "This may affect product characteristics, bioavailability, acceptability by the patient and the pharmacokinetic behaviour." Proposed change (if any): 1. Early on, we can recommend optimizing the oral formulation and/or dosage form, the palatability can be improved significantly. 2. Suggest replacing "product performance" with product characteristics, bioavailability, acceptability by the patient"	Partially accepted Comment 1: not accepted as the statement "should contribute" means that these properties of the active substance should be taken into consideration when developing the dosage form. Palatability issues with the active substance will influence the final composition and the need for using certain types of excipients, e.g. sweetener(s), flavours(s), etc. Comment 2: Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		as highlighted in yellow.	
685	4	Comment: It is noted that the text states that the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or drinks. This stipulation could have the effect of driving up the level of excipients in the product beyond the levels that could be used if there was an allowance for achieving palatability using foods or drinks as part of administration. Proposed change (if any): Please consider if this absolute stipulation for unsupported palatability is truly the expectation. Revise text to read: "It is preferable that the palatability of a paediatric medicine is evaluated and, if possible, developed to be satisfactory without the need for mixing with food or drinks, but this approach can be employed to achieve satisfactory palatability."	Comment noted but not accepted The statement starts with "Unless otherwise justified, "which implies that the requirement discussed is not the only possibility. Need for mixing with food may be employed where justified. The statement does not exclude the possibility for mixing with food or drinks. When such approach is proposed it is expected however that applicant will provide a sound rationale for it. It should not be a first choice approach but rather an approach when for various reasons palatable formulation cannot be developed. The aim of pharmaceutical development should be to obtain a palatable dosage form. The qualitative and quantitative composition of excipients should be justified, including safety aspects. If this is not possible mixing with food or drinks may be an alternative to assure an adequate palatability.
685-686	1	Even though the approach that the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or drinks) is generally acceptable, there are cases where this concept is not applicable. Would it make sense to at least mention the most important one(s) for sake of clearness in this point?	Comment noted but not accepted The statement starts with "Unless otherwise justified, "which implies that the requirement discussed is not the only possibility. Need for mixing with food may be employed where justified. The statement does not exclude the possibility for mixing with food or drinks. When such approach is proposed it is expected however

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Furthermore, it should be pointed out how to handle the application of multiple oral liquid solutions, if multiple preparations have to be administered at the same time according to treatment regimes.	that applicant will provide a sound rationale for it. It should not be a first choice approach but rather an approach when for various reasons palatable formulation cannot be developed. In case of application of multiple oral liquid solutions, it is anticipated that they are given after each other. Any prior mixing of oral liquid solutions would require additional justification.
687-693	7	This guideline appears to favour taste neutral and implies for any chronic indications taste-neutral formulation is a "default" choice. The guideline supports taste-neutral so much that it encourages relatively complex development approaches such as less soluble salts, coating of the active substances or the formulations, and complexation that could potentially significantly alter bioperformance. **We are concerned about this one-sided push and believe use of flavour agents and sweeteners should be acceptable as long as the excipients used are safe and the medicine is not loaded with excessive sugar or flavour agents**. Furthermore, medicine with adequate taste can potentially eliminate the need of mixing with food/drink and thus minimizing corresponding administration errors. In addition, there is no definition of "taste-neutral"? Does it mean no flavour, no sweetener, and no texture like water? Finally if additional excipients (e.g., coating and complexation) are needed to reach	Comment noted Importance of flavouring agents and sweeteners has been acknowledged in previous parts of the guideline, please see section 9.3 and 9.5 where appropriate discussion on these substances is included. For the purpose of the Guideline "Taste–neutral" should be understood as not having a specific taste (e.g. strawberry, banana, etc.) or not overly sweet.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		taste-neutral, safety concern of these “enabling” excipients could become another issue. Proposed change to text: A paediatric medicinal product with a neutral taste or a paediatric medicinal product with a specific and generally acceptable taste may be developed. The choice for either of these profiles should be justified. **For chronic conditions, the choice and level of excipients used to enable acceptable taste (taste-neutral or specific taste) should be discussed and justified.** 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. Additional proposal Define what is taste-neutral?	
687-693	4	Comment: This paragraph is confusing and should be re-written. Ideally, a paediatric medicinal product with a neutral taste should be developed. However, for some APIs it is necessary to add a flavour to help mask their unpleasant taste. In addition, the strategy for taste-masking should be defined as part of the development	Comment noted No amendments have been proposed as it is both options flavourless and flavoured formulations are discussed in the guideline. No strict requirement was imposed that flavouring agents should not be used.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		process, based upon the taste characteristics of the API and type of dosage form. The key aim is to develop a product that has acceptable taste. Proposed change (if any):	
687 - 693	3	The desire for taste NEUTRAL medications is understandable as strongly flavoured medications may be less acceptable over time. However, what is taste neutral—no flavour, no sweetness, no texture-like water? Important is to realize, that the inclusion of sweeteners and flavours is the simplest means for taste masking. Other means carry more expense and PK risk if complexation, coating and other approaches are required. The desire for taste neutral medication contrasts with meeting the paediatric needs in as simplified a composition as required. Moreover if the desire for taste neutral formulations is to encourage alteration of the formulation for custom approaches, again industry would ask the EMA to consider the development work on paediatric formulation development and testing is to reach a new norm where paediatric medicine is taken as has been studied clinically with-out the need for adulteration. The same issue applies here that the formulation that is	Comment noted and partially accepted Taste is a parameter that contributes to palatability of the formulation. It is accepted that in situations where palatability has been confirmed it can be also assumed that the flavouring system used is justified. For the purpose of the Guideline “Taste–neutral” should be understood as not having a specific taste (e.g. strawberry, banana, etc.) or not overly sweet.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		moved to clinical trials in paediatric patients, will have first only been assessed in adults, and may have been considered as 'neutral' and/or 'palatable'/'acceptable', but then once assessed in paediatric patients it is determined not to be 'palatable'. In this case, it may be best to have the medicine mixed with food (if appropriate) rather than to start pharmaceutical development again. The current information in this section is not clear as to what is considered "justified" in order to move a non-neutral, non palatable/acceptable formulation into paediatric clinical studies or to ultimately decide to instead mix with food. Comment: Further guidance is needed on how to justify the choice for either a neutral or a specific acceptable taste for a product. It would be useful to provide examples of methods that can be used to determine the best profile. Proposed change: “The choice for either of these profiles should be justified using appropriate methods, e.g. using a swirl and spit/spill test, or a palatability questionnaire used in a clinical study”. Comment line 691 – 693:	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Please remove all wording after clearly described. The Applicant will provide one optimal formulation and will not evaluate alternative compositions or dosage forms since this would include clinical evaluation of all these alternative compositions and dosage forms and that would increase the burden of clinical evaluation on the patients.	
Lines 687-693	12	Agree that one way to address reductions in palatability due to chronic administration is a neutral taste. Another approach would be to offer a multiple flavour offering (ex. Chewable or liquid formats that come in several child-preferred flavours.) This approach will also reduce palatability changes over time. Proposed change (if any):	Comment noted It is known that such an approach is currently employed in the US market however it is still a new concept in the EU market.
Notes/Sec 6.2.1. & 10, Page 2/24	12	I have read sections 6.2.1 and 10, dealing with the Handling of oral solid presentations (…) and Mixing with food and pediatric acceptability, respectively, and believe that the guidance is comprehensive. It has and I believe continues to be a challenge for developers to provide the smallest dosage presentation coupled with an acceptable taste profile for a child with a chronic disease as well as a patient with an acute condition. I believe the position that we test the dosage presentation when mixed with food is correct rather than assuming the bioavailability is unaffected. It would also be prudent to validate the	Comment noted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		integrity of the drug over time when mixed with food prior to checking the bioavailability of the presentation. It may appear as overkill but identifying the brand of food used may be equally important. Proposed change (if any):	
691-693	11	Typo (not necessary to be included in web-published document with comments) Sentence probably incorrect: 'The development of the intended palatability (…)'. Proposed change (if any): 'The development **of a dosage form with** the intended target palatability (…)',	Accepted
692	4	It is unclear why one would need to provide information on relevant alternative compositions" to the proposed palatable product, especially if a neutral product is proposed. Proposed change (if any): Revise text to read: "The development of the intended target palatability (neutral or a specific taste) should be described and, if the proposed product is strongly flavoured, information on other alternative compositions evaluated (e.g. to try and achieve	Comment noted The need to include information on relevant alternative compositions or dosage forms has been removed from the sentence.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		neutral product flavour) should be provided.	
694-701	7	Caution should be given when modification to drug substance (e.g., coating of API or change of particle size) or formulations (coating with functional polymers, complexation with cyclodextrin) are performed to achieve “taste-neutral”. Especially, significant changes to bioavailability can occur for certain type of molecules (e.g., BCS 2 or molecules absorbed only in the early portion of small intestines). Thus risk of bioperformance must be taken into consideration again the benefits of acceptable taste. Proposed change to text: 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 complexation agent (e.g. cyclodextrin) 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	Comment noted The choice of a particular taste masking technology/formulation approach always includes considerations on potential effects on PK and bioavailability.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		to children (candy like) as this is known to increase the rate of accidental poisoning. **Furthermore, impact on bioperformance should be considered when modifications to drug substance or formulation are utilized to achieve acceptable taste.**	
698-699	9	It seems unclear what is meant by *"(…) for liquid preparations: lowering the amount of free active ingredient in solution by choice of a different strength and subsequent change in volume".* Does this refer to increasing the drug concentration in the liquid formulation? – please clarify.	Comment noted It is meant as lowering the concentration and giving a higher volume.
698-699	11	Important is also the appropriateness of the concentration of the liquid formulation in relation to the recommended dose. Proposed change (if any): Information could be added.	See above
702 onwards Section 10 mixing with food	4	Although mixing with food is recognized to be important for paediatric medicines there is still very little guidance as to **how such studies will be undertaken** – typically these are conducted in adults with subsequent extrapolation into paediatric populations. Does this logic still stand? Again there should be more emphasis on predictive methods or the reliability of extrapolation from adult	Comment noted Extrapolation of findings from food interactions in adults is often possible in order to justify the approach for (not)mixing the medicine with food or drinks prior administration in children. Further guidance on conducting food interaction studies can be found in relevant clinical guidelines.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		studies. This is a complex, time consuming and expensive aspect of medicines development therefore clear guidance would be extremely useful.	
702-707	3	General Comment on Mixing: The section on mixing encourages misuse and incorrect administration of medicines by the general public. Medicines should be administered by simple means and recommendations should be as standardized as possible (i.e. drink with a glass of water). It is not possible or feasible to conduct sufficient studies to safety support mixing with food recommendations. Such type of approach should be limited to very few cases where administration of the product absolutely requires mixing with food and not contemplated as a way to make medicine administration easier. Comments in this paragraph seem to be based on preferences. Not on practical applications or testing. How can guidance be based on this? Comment: A certain percentage of children might refuse to take the medication even if the dosage from is age appropriate and thoroughly developed. If mixing with food or drink helps to overcome this general aversion and	Comment noted and partially reflected in the revised text.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		increase compliance this should be considered acceptable provided that the interactions of the dosage form with the food/drink have been adequately tested. The demonstration that no further improvement in palatability is possible is considered extremely difficult and the iterative development of optimally palatable product should not be expected – only the development of a suitably palatable product. Proposed change: Delete last sentence of the paragraph	
702-737	1	Products that are mixed with soft foods should not be chewed and should be labelled as such. Not only can any taste masking effects be negatively affected by chewing, but for certain product types (i.e., extended-release products) the release mechanism may also be impacted by chewing. Proposed change (if any): If chewing of the product is expected to negatively affect the patient acceptability and/or product performance, the SmPC and PIL should clearly state that chewing after mixing with food must be avoided. For compounds with a narrow therapeutic range, mixing	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		with food is generally discouraged.	
703 & 705	4	State that this is relevant for oral products. Use of either?? (there is no "or"). Proposed change (if any):	Accepted
703 and 718	11	Typo (not necessary to be included in web-published document with comments). Food and drinks. Proposed change (if any): Food or drinks	Accepted
704	4	Spelling Proposed change (if any): the rationale should (…)	Accepted
705-707	4	Palatability rather than taste, and word changes Proposed change (if any): (…) mask the unsatisfactory palatability of a medicinal product in cases where demonstrated that it cannot be further improved and where alternative dosage forms cannot be developed.	Accepted
708 – 716 and in particular lines 711 –	9	There is a contradiction of the statement in lines 711-713 *"Therefore, the effect of mixing of the medicinal product with certain type(s) of common foods or drinks for children* ***should be discussed for every*** *paediatric medicine"*	Comment noted and partially accepted. Reference is made to the revised text. Proposal to delete the statement "*Moreover, the lack of*

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
713		with the statement in lines 714-716: *"If mixing with foods or drinks is not recommended the SmPC and PIL should clearly state that the mixing of the medicinal products (…)* ***has not been studied*** *and is in the responsibility of the user"* **Comment (1):** Not recommending mixing of the medicinal product with food can be based on two reasons: (1) it has not been studied (according to lines 714-716) or (2) studies have shown, that mixing with (certain) common foods or drinks cannot be recommended due to stability, compatibility and/or bioavailability issues (as mentioned in lines 717-718). **Proposed changes:** - Delete statements (lines 709-711) "*Moreover, the lack of recommendations on mixing (…)"* and delete statement (lines 711 – 713) "*Therefore, the effect of mixing of the medicinal product (…) should be discussed for every paediatric medicine"* Rewording of the whole paragraph (lines 708-716) is suggested as follows: *"Mixing recommendations can also*	*recommendations on mixing…"* is not accepted. The absence 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 medicine with certain type(s) of common food or drinks for children should be discussed in the MAA or PIP. The proposal to include in the guideline examples of *"common food or drinks"* is not accepted. It is up to the applicant to propose and justify the type of food or drinks which can be used for mixing with the medicine. The choice of the type of food or drinks will be driven by properties of the active substance and the dosage form.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		be applied as a further means to improve the patient acceptability and the ease of swallowing of an otherwise already palatable medicinal product. The SmPC and PIL should always contain clear information if the product can or cannot be mixed with foods or drinks. ***(Add) In case mixing with foods or drinks is recommended, the effect of mixing the medicinal product with certain type(s) of common foods or drinks for children should be discussed and/or studied.*** *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 the user* ***or studied incompatibilities should be listed.*** **Comment (2):** Some guidance or definition by the agency on what is considered as *"certain types of common foods or drinks"* would be very useful. Examples for drinks: full or low fat milk, tap or still (mineral) water, fruit juices (apple, orange w/o pulp). For foods this might be more difficult unless specific food	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		items incl. their composition is provided, as food-drug interactions depend on the qualitative and quantitative composition (e.g. high vs. low fat) or pH etc.	
708-716	7	This section seems contradictory. On one hand it states that mixing recommendations can also be applied as a **further means** to improve patient acceptability. It also states that "the lack of recommendations for mixing (…) will not assure that caregivers will not employ this method (…). Therefore effects of mixing (…) should be **discussed and or studied for every paediatric medicine.**" On the other hand, it requires (lines 714-716) if mixing is not recommended, the developer should state "that mixing of the medicinal product with foods or drinks has not been studied and is the responsibility of the user." We believe the studies on food/drink are required only for dosage forms where labelling indicates mixing with food/drink. Proposed change to text: (lines 711) "Therefore, **for age appropriate dosage forms**, **if mixing with food or liquid is part of the label**, the effect of mixing the medicinal product with certain types(s) of food or drinks for children should be discussed and /or studied. **(remove "for every paediatric medicine")** (…) (line 714) "If mixing with foods or drinks is not recommended, the	Comment noted The proposal to delete "and studied" was accepted. It is acknowledged that it should not be a standard requirement to study food interactions for all products as discussion may be sufficient as well.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		SmPC and PIL should clearly state the mixing of the medicinal product with food **is either not recommended or** has not been studied and is the responsibility of the user."	
708 - 716	3	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. Proposed change: "If mixing with foods or drinks is not recommended **or the impact of mixing is not known** the SmPC and PIL should clearly state that **mixing with foods or drink is not recommended or the impact of mixing** of the medicinal product with food or drinks has not been studied and is the responsibility of the user. It is unclear what is the reason or value of stating that mixing with foods or drink when this has not been studied "is the responsibility of the user". Is this to create awareness to the user around risk or due to legal reasons? If it's the first, suggest rewording to "and such mixing	Comments noted The text has been revised to reflect the comments.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		might have an impact on the safety and efficacy of the product" ***Alternatively screening for certain classes of food characteristics (e.g. pH, lactose containing) suffices. The duration of compatibility testing can be justified based on an appropriate period of mixing with food and administration of the mixture to the patient.*** Comment Line 710: This section of the guidance is confusing. Line 714 is clear in stating that "if mixing with foods or drinks is not recommended the SmPC and PIL should clearly state that the mixing of the medicinal product with foods or drinks has not been studied and is the responsibility of the user." Why then does the earlier text at line 710/711 state that "the effect of mixing the medicinal product with certain types (not clarified!) of common foods and drinks be discussed and/or studied for every paediatric medicine"? Also in the earlier text (lines 288 and 300) it had been noted that "compatibility with the proposed vehicle" only need be evaluated and presented, which clearly allows for the pre-determined selection of one (or a small number) of vehicles and does not require the underwriting of a	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		number of different vehicles. Proposed change (if any): The paragraph beginning at line 708 should be revised to give consistent guidance across the whole document. We recommend the following text: "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. If a common food/drink vehicle (or vehicles) has been evaluated as a mixing agent, such information should be provided in the SmPC/PIL. If mixing with food and drinks has not been studied this should be stated on the SmPC/PIL and any such mixing should be the responsibility of the user. If mixing with food and drinks has been evaluated and found to be unsuitable, such warning information must be provided in the SmPC/PIL, along with a statement of the basis for the warning." This text would also serve to cover the current text at line 717 and thus sentence 717 beginning "In addition, appropriate warnings should be added (…)" could be omitted.	
710	4	This section of the guidance is confusing. Line 714 is clear in stating that "*if mixing with foods or*	See above

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		drinks is not recommended the SmPC and PIL should clearly state that the mixing of the medicinal product with foods or drinks has not been studied and is the responsibility of the user." Why then does the earlier text at line 710/711 state that "*the effect of mixing the medicinal product with certain types (not clarified!) of common foods and drinks be discussed and/or studied for every paediatric medicine*"? Also in the earlier text (lines 288 and 300) it had been noted that "*compatibility with the proposed vehicle*" only need be evaluated and presented, which clearly allows for the pre-determined selection of one (or a small number) of vehicles and does not require the underwriting of a number of different vehicles. Proposed change (if any): The paragraph beginning at line 708 should be revised to give consistent guidance across the whole document. We recommend the following text: "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. If a common food/drink vehicle (or vehicles) has been evaluated as a mixing agent, such information should be provided in the SmPC/PIL. If mixing with food and	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		drinks has not been studied this should be stated on the SmPC/PIL and any such mixing should be the responsibility of the user. If mixing with food and drinks has been evaluated and found to be unsuitable, such warning information must be provided in the SmPC/PIL, along with a statement of the basis for the warning. " This text would also serve to cover the current text at line 717 and thus sentence 717 beginning "In addition, appropriate warnings should be added (…)" could be omitted.	
711-713	7	Lines 711 through 713 talks about effect of mixing of product with certain types of common foods or drinks (…) This is tough to follow since "common" foods and drinks could vary between regions (even within EU itself) and hence it is difficult to narrow down a list. Conducting all the testing recommended throughout this guideline will be a huge cost and timeline burden on pharma. The developer should justify and list foods or drinks that have been studied. When multiple sources are available for a certain type of common foods (e.g. apple sauce) or drinks (e.g. apple juice), samples from a name brand can be considered representative of that particular type of food/drink.	Not accepted The proposal to include in the guideline examples of *"common food or drinks"* is not accepted. It is up to the applicant to propose and justify the type of food or drink which can be used for mixing with the medicine. The choice of the type of food or drinks will be driven by properties of the active substance and the dosage form.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change to text: The effect of mixing medicinal product with certain type(s) of common foods or drinks for children should be discussed and/or studied. **Selection of foods and/or drinks should be clearly stated and supported with appropriate evaluation and justification. Sources of foods and drinks should be documented. When multiple sources are available for a certain type of common foods (e.g., apple sauce) or drinks (e.g., apple juice), samples from a name brand can be considered representative of that particular type of food/drink.**	
711-716	10	On the types of food. Please note that the type of common food will probably vary from country to country. Also caregivers will need more information than whether the drug can or cannot be mixed with food. It will be helpful to give information on which factors affect the stability and pharmacokinetics of the drug. At least stability in water should be known and also the extent of impact of food on bioavailability. It will also be helpful to give information on the mechanism of food interaction, if possible. This kind of information will help the caregiver to assess the risk of mixing drugs with food.	Not accepted Mixing with food or drinks is not a standard approach unless otherwise justified. Companies should aim at developing acceptable formulations, not requiring mixing with food or drinks. Providing detailed information, as proposed in the comment, could be seen as an encouragement and this should be avoided. Furthermore it is not possible to impose studies on mixing with food and drinks on all types of paediatric medicines.
711-716	1	There is a contradiction between the sentence “Therefore, the effect of mixing the medicinal product with certain	Comments noted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		type(s) of common foods or drinks for children should be discussed and/or studied for every paediatric medicine." and "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 the user." Proposed change (if any): 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 is not recommended as it may affect the performance of the product.	The text has been revised to reflect the comments.
712-713	4	The testing of the effect of mixing with food on every paediatric medicine is not feasible. For example, what would be the rationale for testing the mixing of a tablet intended for adolescents with food? This is most relevant for e.g. granules, beads, powders and/or young patients. Proposed change (if any): Re-word - should be discussed where relevant.	Comments noted The text has been revised to reflect the comments. It is noted that swallowing difficulties may also relate to the type of a disease or condition rather to the age of the child.
714-715	8	**If mixing with foods or drinks is not recommended the SmPC 7and PIL should clearly state that the mixing of the medicinal product with food or drinks has not been studied and is the responsibility of the**	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		user. For reasons of consistent interpretation, it is recommended to change this sentence as follows*: If mixing with foods or drinks is not recommended* ***in*** *the SmPC and PIL,* ***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 the user.*	
715-716	4	Comment: "not been studied" is probably not the case – needs changing. Proposed change (if any): (…) with food or drinks is not recommended and that any such mixing is therefore the responsibility of the user.	Comment noted The text has been revised to reflect the comment.
717	4	See previous comment on the potential omission of this sentence. However, if this sentence is commented upon we note that the text states "appropriate warnings should be added (…) where incompatibilities (…) are foreseen." We consider this is unclear and impractical and should be revised. Proposed change (if any): Revise text to read "In addition, appropriate warnings should be added in cases where incompatibilities with certain type(s) of foods and drinks	Comments noted The text has been revised to reflect the comments.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		are demonstrated."	
717 - 724	3	Line 717-737 Comment: This paragraph is very vague and duplicating some of the text above. Added value of this section not clear. Comment Line 717: See previous comment on the potential omission of this sentence. However, if this sentence is commented upon we note that the text states "appropriate warnings should be added (…) where incompatibilities (…) are foreseen." We consider this is unclear and impractical and should be revised. Proposed change (if any): Revise text to read "In addition, appropriate warnings should be added in cases where incompatibilities with certain type(s) of foods and drinks are demonstrated."	Comments noted The text has been revised to reflect the comments.
719	10	Comment on 'temperature conditions': If this is meant for compounds that are not stable in high temperature conditions, caregivers will need scientific information on degradation, for example degradation and temperature relationships. The patient will need language	Comment noted The guideline clearly explains that any restrictions on the temperature of food or drinks should be indicated in the SmPC and PIL. Restrictions on the temperature refer to elevated as well as to low temperatures.

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		that is appropriate, for example ‘hot’ or ‘cold’.	Regarding the language that should be used in the PIL, this is governed by appropriate guidelines on the product information and confirmed by user testing of the PIL.
720	4	Useful to explain why to user Proposed change (if any): (…) should be instructed that, to facilitate administration of the whole dose, the medicinal product (…)	Accepted
721	10	Comment on ‘clearly specified time’: This should be a feasible time for patients or caregivers in all kinds of settings. It is very realistic that the specified time is exceeded in practice. Caregivers will also need scientific information (degradation kinetics), in order to assess the risk when the specified time is exceeded.	Comment noted The feasibility of the patient to meet the specified time in all settings is to be considered in the original proposal from the company by the regulatory authorities.
723	4	One glass full - volume depends on size of glass e.g. half a tumbler is approx. 100 ml. Proposed change (if any):	Comment noted
724	4	Explain implication Proposed change (if any): (…) take the full quantity and therefore will not receive the full intended dose of	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		medicine.	
725 - 734	3	Comment (line 730): It is accepted that stability data on mixing should be provided. It should be clarified that this stability data need only underwrite the “clearly specified time after mixing” that need be provided to support administration. Proposed change (if any): Revise text to read “Unless otherwise justified, information on the stability of the product in the mixing vehicle(s) appropriate to show stability across the administration period identified should be provided.”	Comments noted The text has been revised to reflect the comments. The guideline clearly explains that the time during which the mixed medicine remains acceptable should be indicated in the SmPC and PIL.
729	3	See also comment on line 710. This text should be revised to ensure overall consistency of the guidance. Proposed change (if any): Revise the text to read “Nevertheless, the SmPC and PIL should give clear instructions on what food and drinks, if any, have been demonstrated to be appropriate for the medicinal product to be mixed with.”	Comments noted The text has been revised to reflect the comments.
729	4	Might be categorised rather than actual food & drink? Proposed change (if any): (…) on what types of food	Comments noted The text has been revised to reflect the comments.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		and/or drink have been (…)	
730	4	It is accepted that stability data on mixing should be provided. It should be clarified that this stability data need only underwrite the "clearly specified time after mixing" that need be provided to support administration. Proposed change (if any): Revise text to read "Unless otherwise justified, information on the stability of the product in the mixing vehicle(s) appropriate to show stability across the administration period identified should be provided."	Comments noted The text has been revised to reflect the comments. The guideline clearly explains that the time during which the mixed medicine remains acceptable should be indicated in the SmPC and PIL.
733-736	5	Lines 733 – 736 state "This may affect product performance and the pharmacokinetic behaviour. When mixing with food and drinks is proposed the possible effect on biopharmaceutical characteristics of the product should be discussed". Specific biopharmaceutical testing such as dissolution testing is not discussed in the guideline. Dissolution may be a means to justify the use of other food stuffs without the need for further biostudies. Dissolution of medicines mixed with food is possible (see Figure 1 dissolution of tegaserod tablets crushed in applesausce *Carrier et al Stability and compatability of tegaserod from crushed*	Not accepted In addition, dissolution testing for products mixed with food is not a standard practice and no validated methods are available at present. A single experiment should not be used to impose new requirements if relevance of the results is not known.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		tablets mixed in bevages and foods Am J health-Syst Pharm – Vol 61 Jun 1 2004 pp 1135 - 42) Proposed change (if any):	
733 -737	4	All this text should be consolidated in one paragraph as all is related to potential impact on PK of the product. It would be helpful to include a concluding remark noting that if the product has been used in the clinic as a mix in food then no further PK evaluation would be required. Proposed change (if any): Consolidate all this PK related text in one paragraph. Add a final sentence to the effect "If the product has been evaluated in the clinic as a mix for administration no further evaluation may be needed."	Comments noted The text has been revised to reflect the comments
735-737	4	The text notes that "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." It is considered impractical and unnecessary to consider biopharmaceutical impacts in every possible food or drink, and considering the volume to be used may be very small. If a 5ml spoonful of food is being used it should be possible to rationalise that this has	Comment noted and partially accepted The text has been further revised. It is not an intention of the guideline to consider biopharmaceutical impacts in every possible food or drink. It is obvious that such considerations should be given only when mixing with food and drinks is proposed. Only the type of food and drinks proposed should be addressed in addition to the rational for foods that should not be used

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		no impact on PK without experimental evaluation. Proposed change (if any): Revise the text to make clear that only the proposed vehicle(s) to be used should be considered or evaluated. If evaluation in one vehicle can be rationalised to cover the effect in other proposed vehicles such justification should be provided along with the data from one evaluation.	
735 - 737	3	Comment: From how this paragraph is written it is unclear in which cases additional BA data is indeed required when paediatric medicines are mixed with food and/or drinks. Food effect studies usually are carried out in adults in the fasted and fed states. Is it feasible to use those data for missing data from food effect studies in children even though dosage form and type of food applied in the adult trials may be different? Line 736: product should be discussed Comment: Where should this discussion take place? In the SmPC,	Comment noted and partially reflected in the revised text Although the type of food applied in the adult trials may not be directly applicable to the paediatric population, it may be possible to conclude on acceptable or not acceptable approaches for mixing with food or drinks. If for example it has been demonstrated that the product should not be mixed with acidic foods or drinks by analogy it will be easy to explain why the product should not be mixed with orange juice, etc. Whenever the need for discussion or justification is indicated in the guideline it refers either to relevant sections of the CTD dossier (in case of MAA) or PIP dossier.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		CTD Module 2.5? Please clarify. Comment – The text notes that "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." It is considered impractical and unnecessary to consider biopharmaceutical impacts in every possible food or drink, and considering the volume to be used may be very small. If a 5ml spoonful of food is being used it should be possible to rationalise that this has no impact on PK without experimental evaluation. Proposed change (if any): Revise the text to make clear that only the proposed vehicle(s) to be used should be considered or evaluated. If evaluation in one vehicle can be rationalised to cover the effect in other proposed vehicles such justification should be provided along with the data from one evaluation. Comment (Line 733 – 737) – All this text should be consolidated in one paragraph as all is related to potential	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		impact on PK of the product. It would be helpful to include a concluding remark noting that if the product has been used in the clinic as a mix in food then no further PK evaluation would be required. Proposed change: Consolidate all this PK related text in one paragraph. Add a final sentence to the effect “If the product has been evaluated in the clinic as a mix for administration no further evaluation may be needed.”	
735-737	1	From the way this paragraph is written, it is unclear in which cases additional bioavailability data are indeed required when paediatric medicines are mixed with food and/or drinks. Food effect studies are usually carried out in adults in the fasted and fed states. Is it feasible to use those data for missing data from food effect studies in children even though dosage form and type of food applied in the adult trials may be different?	See above
736	4	Need to qualify bioavailability Proposed change (if any): Relative bioavailability (…) Replace bioavailability testing with assessment of impact on bioavailability	Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
736	5	Line 736 “Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine”. This is the only mention of bioequivalence in the section on mixing with food. It is difficult to understand e.g. what is meant by previous studies. It does not give adequate guidance. For example the phrase, “Bioavailability testing may be needed” is vague. It would be useful to specify when it will be needed. Firmer guidance on “mixing with food” is needed. Hardly any products on the market currently have mixing with food instructions. In the future many more medicines seem likely to be mixed with food. There may be safety issues if this change is not handled correctly. Especially with regard to generic medicines which may confuse the market if they are recommending practices not recommended by the reference product. Proposed change (if any): Text along the lines of the following is suggested: “For a new medicine or innovator product that may be mixed with food justification will be either by clinical trial or by performing a relative bioavailability study comparing	Comment noted The text has been revised to reflect the comments, where appropriate. Every product should be used as indicated in the SmPC. This is also applicable to mixing with food and drinks. However there may situations when different types of food and drinks will be proposed for generic and reference products. These differences may be due to e.g. different composition of these products. For every new application, including generic, the information on mixing with food and drinks should be considered and discussed in the dossier. Where relevant this information should be reflected in the SmPC and PIL.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		formulation used in the trial to the formulation mixed with food. Instructions on mixing with food should be based on what food was used in the bioavailability study. Extrapolation to other foods should be based on compatibility studies, biopharmaceutical and pharmacokinetic characteristics. Discussion of pharmacokinetic characteristics should include discussion of any “food effect”. In the case of generic medicines where the innovator is not mixed with food there should be no requirement to mix with food. The SmPC and instructions with regard to mixing with food of innovator and generic should be similar. Having generics give instructions for mixing with food without biostudies would cause a risk of pharmacokinetic in equivalence. If the innovator can be mixed with food then the generic should also be able to be mixed with food. If generic and innovator are bioequivalent then there may be no need to perform an additional food-mix-biostudy if good justifications can be given”. A generic medicine may elect to be mixed with food. Bioavailability to the reference product should be demonstrated for the generic product mixed with food. It may be necessary to differentiate the generic from the	

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		innovator or other generics so as not to cause confusion as to which formulation may be mixed with food.	
103-131	2	Consistency with the so called “Paediatric Regulation” (Regulation EC No 1901/2006) regarding bibliographic applications should be taken into account. Therefore the Guideline should be read in conjunction with the Paediatric Regulation. Article 9 of the Paediatric Regulation states that the General authorization requirements in Article 7 and 8 (i.e. requirement of a Paediatric Investigation Plan within the application) shall not apply to products authorized according to 10a, 13 to 16 or 16a-i of Directive 2001/83/EC. Products under these Articles are in particular well-established use medicinal products, homeopathic medicinal products and traditional use herbal medicinal products. For well-established use, homeopathic and traditional use herbal medicinal products efficacy is generally - for all age groups - demonstrated by reference to bibliographic data and/or traditional use. There is, therefore, no need to facilitate clinical research for these products in children. In order to ensure consistency of the Guideline with the binding Paediatric Regulation it should be clarified that the	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted As already explained after the first consultation, 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. 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.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		concerned products are excluded within the scope of the Guideline. Proposed change (if any): **As a result we propose to <u>insert the following wording in paragraph 2</u> ("Scope") of the Guideline as follows:** ***<u>"According to Article 9 of the Paediatric Regulation well-established use, homeopathic and traditional herbal medicinal products shall not require clinical data in line with an agreed paediatric investigation plan. Therefore the present Guideline should not apply to those products".</u>***	
116-119	4	*The guidance mentions relevant bridging studies for formulation switching in paediatric populations.* Proposed change (if any): It would be useful to have additional details regarding how bridging is managed and whether biowaiver like in vitro bridge would be acceptable as with adults, followed by subsequent extrapolation. This is a complex area where additional guidance is required to ensure safety of a product.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted, it is not within the remits of this guideline to provide detailed information on managing the bridging studies.
127-129	2	Re-evaluation of already authorized products needs to take into account characteristics of specific products.	See above Second consultation is limited to the sections 6.2.1 and 10.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		According to the Guideline already authorized paediatric medicines should be re-evaluated by pharmaceutical companies to maintain a positive benefit-risk balance. However, in the context of such a re-evaluation the specific characteristics of different categories of products need to be taken into account. According to Article 1 (5) of Directive 2001/83/EC homeopathic medicinal products are defined as “any medicinal product produced in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the Member States.” The herein described manufacturing methods and substances (excipients) reflect the homeopathic tradition. Applicable official pharmacopoeias like the German Homeopathic Pharmacopoeia restrict the use of innovative dosage forms (e.g. oral liquid forms are restricted to drops, orodispersable tablets, flavouring compounds and colourants are not foreseen). Accordingly the development of innovative, appropriate dosage forms of homeopathic products for children is limited. Moreover, a positive benefit-risk balance can already be justified by the safe long-term use of the traditional homeopathic dosage forms.	However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Point not accepted 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.* It is accepted that the specific characteristics of different categories of products need to be taken into account. Not performing the re-evaluation is an option and it is up to the applicant to justify it.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): **We therefore propose to change the wording in paragraph 2 ("Scope") of the Guideline as follows:** ***"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 should not apply in situations where restrictions in product development due to binding manufacturing procedures in pharmacopoeias are given (e.g. traditional homeopathic dosage forms). As a consequence competent authorities and regulatory bodies are encouraged to reconsider the revision of traditional pharmacopoeial monographs in line with innovative developments of appropriate products for children".***	
208	4	The guideline text as revised states that "*Taking part of a liquid prepared from such a dosage form should normally not be used as a means to achieve age-appropriate paediatric medicines"* and this is questioned. It would seem possible to divide a solution so prepared in	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Point not accepted the sentence has been taken out of context, as it is clear that the paragraph in question discusses solid oral unit

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		an accurate manner. **It should also be made clear that this text in no way means that multi-dose oral liquid products are unacceptable products for paediatric medicine.** Proposed change (if any): Revise text to read "*Taking part of a liquid prepared from such a dosage form should not be seen as a preferred means to achieve age-appropriate paediatric medicines. Note this does not refer to taking part of a formulated multi-dose oral liquid product*."	dose preparations and not multi-dose oral liquids. Furthermore, it is clear in the guideline that multi-dose oral liquid products are acceptable products for paediatric medicine (please refer to the paragraph starting in line 311 of the published revised guideline).
208	3	The guideline text as revised states that "Taking part of a liquid prepared from such a dosage form should normally not be used as a means to achieve age-appropriate paediatric medicines" but this is questioned. It would be possible to divide a solution so prepared in an accurate manner. It should also be made clear that this text in no way means that multi-dose oral liquid products are unacceptable products for paediatric medicine. Proposed change: Revise text to read "Taking part of a liquid prepared from such a dosage form should not be seen as a preferred means to achieve age-appropriate	See above

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		paediatric medicines. Note that this does not refer to taking part of a formulated multi-dose oral liquid product."	
225-228	7	A more specific guidance from EMA of the type of "liquids" or "semi-solid" delivery vehicles is needed. The recommendation will streamline trials, testing, and post-filing communications with the agency. Add a text to allow sourcing drink/food locally. Proposed change to text: "Powders and granules may be given to children from birth provided they can be administered as a liquid. In their solid form, they are usually co-administered with semi-solid food. If mixed with semi-solid food, they can be considered acceptable from the moment the infant is able to accept the semi-solid food, which is usually around six months of age. **The delivery aids can be sourced at the country of interest**. Additional proposal: The guideline should include examples of drinks and foods suitable for children of different ages in Europe.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Comment noted, the text under "mixing with food or drinks" (section 10) has been further revised.
226	9	on *"…can be administered as a liquid"*	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change: "(…) can be administered as a **liquid preparation**" (official term of Ph. Eur.)	text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
226-228	11	The guideline states that powder and granules can be considered acceptable if mixed with semi-solid food**.** Proposed change (if any): Here should be referred to section 10, where aspects of mixing with food are further discussed.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
229-231	3	Powders and granules are usually administered as a liquid/ co-administered with food. More factual guidance in terms of acceptable powder/granule particle size and shape relative to patient age (if indeed these factors have an impact on the risk of aspiration or choking when such methods of administration are employed) would be welcomed. Drug substance characteristics have absolutely nothing to do with choking or risk of aspiration. Risk of aspiration, choking and chewing are different physiological issues. Chewing is mostly voluntary whereas aspiration and choking are not. **Please revise wording completely to avoid**	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		misconception.	
229-231 and 251-253	11	For more information on the suitability of tablets, powders and granules in children in relation to the associated risks (underdosing, choking, aspiration and chewing), the guideline refers to section 8. However, this section does not clearly describe which characteristics of these dosage forms enhance those risks. Proposed change (if any):	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted (reference to section 8 removed)
235-237	11	The guideline is referring to section 10 for more information about the acceptability of size and shape of tablets by the target age group(s). However, this aspect of patient acceptability is not discussed in that section. Proposed change (if any): Add information	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted (reference to section 10 removed)
235-250	4	There is disappointment that the guidance on acceptable tablet sizes with respect to age has been removed; although literature data are limited, it would be most helpful if some information could have been included.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Comment noted
235	4	Sentence wording could be improved	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The size and shape of a tablet are fundamental to the ability of a child to swallow it.	text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
235-244	7	Since swallowability and palatability evaluations are not typical end points on pediatric studies, not much guidance is in the literature. Thus, a high level recommendation from EMA on acceptable tablet shapes and swallowability issues is recommended. Regarding palatability, EMA should consider the use of adult panels for palatability evaluations. Proposed change to text: "The tablet size and shape are fundamental to the ability of a child to swallow a tablet. The acceptability of the size and shape of the tablets by the target age group(s) should be justified, and supported by appropriate studies or clinical evidence, where relevant (see section 10). It should be noted that limited data are available in the literature regarding the influence of size, shape and number of tablets on acceptability in different age groups. **In the case of tablet shape, it is expected that forms with higher surface area to mass ratio may be more prone to swallowability issues than forms with a**	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted. In view of the current limited knowledge it is up to the applicant to propose and justify the testing method. The use of an adult panel is one of the possible options that can be selected.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		lower ratio. (…) however, palatability issues may significantly affect the acceptability of these tablet types". **In the absence of paediatric data, alternatively the use of adult panels to establish palatability acceptance can be used. Other methods can be utilized if justified.**	
235- 240	3	Proposed change: The tablet size ~~is fundamental to~~ *plays a role in* the ability of a child to swallow a tablet. Young children may 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.* It would help to provide what little guidance there is as a general rule, as described, e.g. on tablet size (from EMA paed. workshop Nov2011): *3-5mm >2yo* *5-10mm >6yo* *10-15mm >12yo* *15mm + >18yo*	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted. Currently there is no evidence supporting precise acceptance criteria for tablets. More research needs to be done and experience gained. As earlier communicated after the first consultation in view of the limited data available the reference to the tablet (capsule) size has been removed from the Guideline in order not to stop development in this field, as such limits could be used as a "tick box".

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
240 - 244	3	Proposed change: 'Solid oral dispersible tablets will also enable dosing flexibility, if parts of the dispersed solution are taken. 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 to be taken. *The applicant should streamline the procedure and show the ability to prepare reproducibly.*	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Comment noted. The text has been revised to reflect the comments in the section of the guideline that was opened for the second consultation.
243	4	Comma needed to improve reading of sentence Proposed change (if any): (…) tablets, considerations (…)	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
245 -250	3	Proposed change: Please reword: If several tablets need to be taken to provide a dose (etc.) Comment: Any guidance as to what would be the maximum number of tablets for acceptability in different age groups would be helpful.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted due to limited knowledge on this subject.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
251 - 253	3	Comment 1: It is not clear what is meant with different health condition. In most cases a pharmaceutical product will be developed for a limited number of indications/conditions. Is the guideline referring here to different disease stages, or to different conditions? It is proposed to delete the above words, because of their lack of usefulness. Comment 2: Underdosing is not relevant here, because it is immediately obvious that when a patient does not take the complete dose he or she will be underdosed. Please remove.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted Re comment 1: there are situations where the same product is used for more than one indication Re comment 2: under-dosing has been corrected to under- or overdosing
252	9	**Proposed change: "**(…) risks associated with **over–** and underdosing"	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
254	9	**Proposed change:** remove "(…) *i.e. where they may not be chewed"* as this is mentioned in the first part of the	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		sentence.	sections other than open for consultation are not taken on board. Accepted
254	4	Wording can be changed to avoid duplication and stress "must" Proposed change (if any): SmPC and PILs where tablets must be swallowed intact, i.e. where they must not be chewed.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
255-258	9	"*Immediate release tablets are normally intended to be swallowed intact, but unless otherwise indicated in the SmPC and PIL, they may also in many cases be chewed. Where chewing of immediate release tablets is an option, the potential effect of chewing on the product performance such as palatability should be discussed"* **Comments:** (1) Immediate release tablets should not be chewed, unless they are clearly designed and developed as chewing tablets. (2) Chewable tablets usually have a different (bigger) size, composition and release profile due to the use of different excipients (no disintegrants). Chewing might	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted, text updated as per the second proposed change.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		lead to a number of complications with respect to taste masking, local irritation, different drug absorption, bioavailability. (3) Palatibility is not part of the product performance (such as dissolution, stability). It is a consequence of the product design. **Proposed change: Delete sentence:** "*Where chewing of immediate release tablets is an option, the potential effect of chewing on the product performance such as palatability should be discussed"* - In case the sentence is kept it should read "(…) *effect of chewing on the product performance **and** palatability should be discussed".*	
260	4	Clarification as not all Hard Capsules contain powder or granule Proposed change (if any): Where appropriately justified, hard capsules containing powder or granule may also (…)	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
260-266	7	Does the agency consider the opening of sachets and capsules and emptying of contents into food or liquids an operation that can be performed by any caregiver, including parents/custodians? A current trend in some countries (e.g., Spain and UK) is to consider the above	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		operation a manufacturing step that can only be performed by licensed pharmacists. This needs further clarification. Proposed change to text: Add another sentence "**We view opening capsules as equivalent to opening sachets."** to the end of line 266.	Comment noted. The guideline already foresees the possibility for opening the capsules by the patient. It is certainly not considered a manufacturing step that can only be performed by a licensed pharmacist. 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.
262	4	Feasibility means "has" singular rather than "have" plural Proposed change (if any): (…) capsules has been (…)	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
267-269	3	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. All capsule are oval shape, therefore there is no impact to shape. Proposed change: 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. Guidance on capsule size would be welcomed.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
269	4	Remove comma to improve reading of sentence	Second consultation is limited to the sections 6.2.1 and 10.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): (…) and shape and any (…)	However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
270-274	9	Orodispersible tablets and chewable tablets have different compositions. Both are not designed to be swallowed intact. The statement *"may be swallowed without a liquid"* is not an exception. They are intended to be placed into the mouth without using a liquid (see Ph. Eur.).	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Accepted
270-279	11	Subsection 'Orodispersible and chewable preparations' could be moved to the subsection 'Tablets', as these formulations are already mentioned at the 'Tablets' subsection in line 242.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted, the term "preparations" includes tablets among other dosage forms but is not limited to tablets only.
270-279	11	Subsection 'Orodispersible and chewable preparations' does not mention the importance of palatability for patient acceptance. The aspect of palatability is, especially for this kind of dosage form, very important for enhancing patient acceptability. This is now mentioned in line 244 in the subsection 'Tablets'.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted, the section on patient acceptability applies to all dosage forms, including orodispersible and chewable preparations.

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
313-314 and line 355	4	The proposed guidance states that reconstitution with solvents other than water must be provided for liquid preparations that are prepared from a solid oral dosage form –this is a sensible approach in this situation. However, there is no such statement for effervescent, soluble and dispersible preparations. Proposed change (if any): There needs to be some consistency and thought behind the vehicles used for reconstitution	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted, this is not a paediatric-specific issue. It is a standard practice that effervescent and dispersible tablets are to be dissolved/dispersed in a standard medium which is water.
Section 6.3 (line 388) And section 6.4 (line 398)	4	It is felt that the sections on nasal preparations and preparations for inhalation are limited. The selection of appropriate inhalation delivery device with respect to patient age is especially important.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. Not accepted, for further guidance please refer to existing guidelines.
612	3	What is meant with "justify a particular flavour?" We agree by justification of a flavour but is it useful to justify a particular flavour? Depending on the country, choice and preference are not the same.	Second consultation is limited to the sections 6.2.1 and 10. However, general changes to the text that improve wording or the text in general are adopted, changes on scientific content of sections other than open for consultation are not taken on board. The comment not clear. If the intention is to confirm that

Line number(s) of the relevant text	Stakeholder name	Comment and rationale; proposed changes	Outcome
			medicines may be developed with different flavours this is correct. However the use of each flavour should be justified.

Please add more rows if needed.