European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT GUIDELINE ON THE ROLE OF PHARMACOKINETICS IN THE DEVELOPMENT OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

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

	Name of Organisation or individual	Country
1	MSD	
2	Johnson and Johnson	
3	IPFA	
4	EFPIA	

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Table 2 MSD

GENERAL COMMENTS - OVERVIEW		
It is very important to stress that in this vulnerable population with limited blood volume that it is important that any new guidance follows other already completed guidances worldwide. It would be unacceptable for differences in requirements amongst agencies to result in additional clinical study burden in the paediatric population. *Response: We agree that this is important. The guideline is to be read with and will be in agreement with the ICH document Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). At present the FDA has published a draft guideline " General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products". We have not observed any major differences between the documents.*		
The document is totally silent on tissue levels. *Response: We agree that the distribution of drugs and metabolites may differ between paediatric and adult patients. A difference in tissue distribution may lead to a shift/change in the PK/PD relationship. This should be taken into account when choosing clinical development strategy and deciding how to use pharmacokinetic information and whether additional PK/PD documentation is needed.*		
SPECIFIC COMMENTS ON TEXT		
1 INTRODUCTION		
Page no. + para no.	**Comment and Rationale**	**Outcome**
Page 3, §3	The introduction would benefit from citing certain key ADME differences between children of various ages and adults.	*We have chosen not to include such information in the document as some is already presented in the guidelines CPMP/ICH/2711/99 and CPMP/EWP/462/95*
Page 3, §3	Rapid changes also occur in drug metabolism.	*We are of the opinion that this is reflected in the document.*
Page 4, §1	Suggest adding the sentence: "Sponsors considering new approaches should seek advice from competent authority".	*As the proposed Paediatric regulation includes agreement with the authorities (Paediatric Committee) on a paediatric plan, we do not find it necessary to include a statement on this in the guideline.*
2 USE OF PHARMACOKINETICS IN PAEDIATRIC DRUG DEVELOPMENT		
Page 4, §4	Bullet #1 states that "If a similar exposure in adult and paediatric patients can be assumed…" The document is too vague. More guidance on acceptable types of assumptions might be useful.	*This is an approach that is taken case-by-case or within a class of drugs. The strategy chosen should be justified by the applicant. We do not think that this bullet point could be more specific.*
Page 4, §4	Bullet #2 states that "If a similar exposure in adult and paediatric patients can be assumed…" The document is too vague. See above!	*This bullet point has been extended for clarity.*
Page 4, §5	Can paediatric PK data from one indication be used to provide a PK	*PK data from one indication can be extrapolated to another indication if*

	bridge in another indication?	*it can be assumed that the diseases are not affecting the pharmacokinetics of the drug. This has now been clarified in the guideline (p4). The use of the PK i.e. choice of main parameter, target criteria etc may differ between indications and should be justified by the applicant.*
Page 4, §8	Side effects of drug may not be dose dependent.	*We believe this is reflected in the document.*
Page 5, §1	Possible effect on growth and development: does the document refer to animal data or is it suggesting long term clinical trials.	*The document refers to indications on effects on growth and development from preclinical data and pharmacological-endocrinal knowledge which may need follow up in clinical studies possibly post-marketing. This will not be further discussed as it is out of the scope of the guideline. The sentence has now been deleted.*
Page 5, §2	"as discussed above, knowledge of pharmacokinetics…" This is wide open to interpretation. What does this mean?	*The parameters of interest depend on the drug and we prefer to keep this more general phrasing.*
3 STUDY DESIGN		
Page 5, §4	What should be the primary endpoint in paediatric study-exposure or clearance?	*Exposure, but the choice of endpoint should be based on what is known about PK/PD. For example, Cmin could be of more importance for a number of drugs.*
	When will single dose and/or multiple dose data be important?	*Multiple dose data is of importance to verify dose (and time) linearity or in situations where it is known that the pk shows dose/time-dependency.*
	When will metabolism be important to measure?	*A metabolite should be measured if it contributes or is likely to contribute to efficacy or adverse events and if the metabolite/parent drug exposure ratio may be significantly different from the ratio in the population used for reference. In certain circumstances, studies aiming at detecting differences in contribution of metabolic pathways could be performed e.g. in case there is a special need to predict drug interactions or formation/elimination of a toxic metabolite.*
Page 4	Study design focuses on PK yet on page 4/8, the document says one of the objectives is to recommend "Use of PK and PK/PD relationships in efficacy and safety assessments."	*We find it difficult to include more specific comments on this as the use of PK/PD is substance-dependent.*
Page 5, §6	First bullet: In the event that age groups are excluded, it is unclear if PK data can be extrapolated to such excluded age groups.	*The pk can be extrapolated if published or acquired knowledge on pharmacokinetics of other drugs with similar pharmacokinetic characteristics etc support a good prediction of the pk in a certain age*

		group. This applies especially to drugs which have a broad therapeutic margin.
Page 5, §7	Healthy children are rarely studied but may be in studies involving minimal risk in which subject gives assent (assent possible for typical 7 year old).	*We have chosen not to specify this issue more in the document. Preferably children involved in a clinical study should be in need of the drug.*
Page 6, §5 section 3.5	The choice of control group. As long as the stated conditions are met, can historical control be used for all types of PK studies or only specific studies?	*Historical controls can be used for all types of paediatric studies if the stated conditions are met.*
Page 6 §5, section 3.5	Is the document suggesting adult patients with the disease?	*Yes. Adult patients should be used if there are data available from a sufficient number of patients from studies.*
5. DEVELOPMENT OF DOSING RECOMMENDATIONS		
Page 8, §4	The last paragraph of Section 5 indicates that age ranges for dosing recommendations should be based on the data not on the ranges specified in the protocol. This implies that age should be analyzed as a continuous variable rather than a categorical variable. To do this well, it also means that we would need to enrol patients fairly uniformly across the age range to be studied, i.e. the 3-11 y.o. group should not be predominantly 10 and 11 y.o.	*This interpretation is correct.*
Page 8, section 5	How can a dosing be recommended based on PK data unless, at the minimum, a dose response study is performed?	*In absence of dose-response documentation pk can be used to support efficacy from adults to paediatric populations if there is convincing supportive data on PK/PD in adults and the paediatric population from other, very similar drugs.* *A clinical study usually does not have sufficient power to detect a difference in efficacy or safety in a specific subpopulation. Pharmacokinetic documentation may then be used to support efficacy and safety or support dose recommendations in a subgroup of the paediatric population unless there are reasons to believe that the PK/PD relationship differs in that specific subpopulation.*
Page 8, section 5	What methods are proposed to make dose choices for efficacy studies?	*This is out of the scope of this guideline.*
	Finally, one item that was omitted from document and we feel is important to consider is that there should be appropriate scaling of PK both for dosing and comparison across populations – either as mg/kg or mg/m^2.	*If possible, the body size normalisation should be performed using the covariate giving the best correlation with the pharmacokinetic parameter of interest. However, the difficulty of "calculating" body surface area, or other "indirect" determinations such as lean body mass, and the possibility of calculation errors should be kept in mind and, if there is no clinically relevant difference between the normalisations, bodyweight*

		may be used.

Table 3 Johnson and Johnson

GENERAL COMMENTS - OVERVIEW
The title indicates this guideline is about the role of "pharmacokinetics". However, "pharmacodynamics" is also discussed in the guidance. Therefore, we suggest the title be revised to include the "Role of Pharmacokinetics and/or Pharmacodynamics" ((PK/PD). *Response: We prefer to leave the title as it is. The scope of the document is mainly pharmacokinetics.*
Open communication between the sponsors and the Agencies is very important and should be emphasised in this guideline: If a company would like to apply the modelling and simulation technique to get an exemption from conducting an actual paediatric clinical trial, the responsibility should be shared among companies, regulatory authorities, health professionals, and society as a whole. *Response: As the proposed Paediatric regulation includes agreement with the authorities (Paediatric Board) on a paediatric plan, we no not consider it necessary to include a statement on this in the guideline.*
There is no mention of the criteria for adequate documentation for use in paediatrics if the mechanism of action is considered different in the paediatric patient, or the disease state is considered significantly different in paediatrics as compared to adults. Further recommendations are needed. *Response: We are of the opinion that this is sufficiently covered in the guideline. In the scenario you describe, mainly extrapolation of efficacy and safety within the paediatric population can be performed.*
The guideline does not discuss how to interpret the case of having similar exposure in adult and paediatric population in some age groups of the paediatric population but not in other age groups. What if a certain age group within the paediatric population is different from other age groups and adults? Clarification is requested. *Response: This scenario is already covered in the guideline (page 4, section 2 as well as page 8, section 5)*
This guideline should include development of controlled/sustained release formulations and biologics in paediatrics. The selection of formulation type, strength, etc., may have a potential impact on the pharmacokinetics in paediatrics of interest. This guideline should include a paediatric formulation selection and its general rule. *Response. Development of sustained release formulations is of interest from a patient perspective but may also be problematic due to possible difficulties in dose adjustment (several strengths may be required). Depending on the kind of formulation developed, the formulation may also be more difficult to administer to smaller children due to formulation size etc. We think that this topic should not be discussed in this document. More information on this is found in the reflection paper "Formulations of choice for paediatric medicines".*

SPECIFIC COMMENTS ON TEXT

2 USE OF PHARMACOKINETICS IN PAEDIATRIC DRUG DEVELOPMENT		
page no. + para no.	**Comment and Rationale**	**Outcome**
Page 4, §4	Under number 2, first bullet, it states: "If similar exposure in adult and paediatric patients can be assumed to result in similar efficacy,	*These topics are already included in section 4.1 and 5. More specific information on these matters will not be included. We do not interpret"*

	pharmacokinetic data alone can be used to extrapolate efficacy." • The demonstration of adequacy of an exposure-efficacy (PK/PK) relationship should be requested. A more clear statement could be as follows: "If similar exposure in adult and paediatric patients can be used to extrapolate efficacy for paediatric patients using paediatric PK data alone with an adequate evidence of goodness of the PK/PD model in its predictability in adults." • The FDA guidance has a similar statement. However, some FDA reviewing divisions have interpreted "similar" to mean "identical". Paediatric PK parameters of a given drug will almost never be identical to those obtained in adults. Typically, children (except for neonates and very young infants) clear drugs faster than adults. Therefore, to obtain a similar AUC, one needs to dose them more frequently. More frequent dosing may be associated with several C_{max} values over a given period of time. However, even when those C_{max} values are not higher than those observed in adults, some FDA Division fell uncomfortable and point to the difference as a reason not to extrapolate the paediatric PK data to adults. Thereby, requiring sponsors to conduct full safety and efficacy studies in children. It may be worth to try a better definition of 'similar'. Perhaps similar in this case can be defined based on AUCs and C_{max} vales not exceeding certain percent of the adult values in a given period of time (within 24 hours of dosing).	*similar" as "identical". The expression "similar" includes an evaluation of which deviation may be acceptable based on the efficacy and safety of the drug.*
Page 4, §4	Second bullet: "If similar relationship between concentration and pharmacodynamic response has not been substantiated, paediatric PK/PD data can be used to extrapolate efficacy." • Once paediatric PK/PD data is obtained, there may be no need to extrapolate. Provide cases when extrapolation is possible.	*The clinical efficacy and safety may be extrapolated based on biomarkers. This has now been clarified in the document.*
Page 4, §5	Below the second bullet, it states, "The same approaches may be used when extrapolating efficacy between paediatric age groups." • This recommendation is applicable to the first bullet, not to the 2nd bullet point because if there is no support for similarity	*We are of the opinion that both scenarios apply also to extrapolations within the paediatric population.*

	between age group 1 and 2, sponsors cannot extrapolate efficacy due to lack of PK/PD model in paediatrics. A suggestion is to add this sentence within the 1st bullet point.	
Page 4, §7	Page 4, 5th line from the bottom, "Pharmacokinetic data will then be important for identification of sub-groups in which the exposure differs from the overall study population to a clinically relevant extent." • It is not clear what kind of criteria are envisaged to support clinical relevance using sub-group analysis with paediatric PK data. Modelling provides more power to detect difference among sub-groups. A suggestion is that clinically relevant differences among sub-groups can be supported if population PK modelling approach from paediatric data identifies a variable (such as age, renal function, body weight, etc.) that forms sub-groups as a statistically significant covariate and simulation using the model shows clinical significance.	*In general we agree with the suggested approach. Regardless of the method used to identify differences between sub-groups, the degree of change that is considered clinically relevant should be based on prior knowledge.*
Page 5, §1	First paragraph on page 5, second to last sentence reads: "The possibility of a markedly higher incidence of side effects should be discussed, taking into account the preclinical and clinical pharmacology of the drug…" • The perception of vulnerability (i.e. possibility of a markedly higher incidence of side effects) in children is based on therapeutic misadventures of the past. This has been due precisely to the paucity of adequate information of the drug disposition in paediatric patients. However, when drugs are appropriately studied in children, there should not be an inherently higher incidence of adverse events just because the population is paediatric. Regarding preclinical information: In the presence of adult safety data, one has to evaluate any preclinical signals in juvenile animals with a critical mind. In the words of David R. Jones, senior toxicologist with MHRA, when discussing the value of juvenile toxicology studies: "When paediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant safety data and should generally be available before paediatric clinical trials are started."	*We agree that adult safety data represents the basis of the safety assessment in paediatrics. However, there may be mechanisms which lead to a different (higher or lower) risk of adverse events specifically in children. This has to be taken into account in the safety assessment. The word "higher" has now been replaced with "different".*

Page 5, §1	The last statement in the 1st paragraph, Page 5: "In addition, possible effects on growth and development should be considered." • Assessment of growth and development should not be a part of a PK/PD study because PK/PD studies are not long enough to explore the influence of PK exposure on growth and development.	*We do not mean that this should be evaluated in the pharmacokinetic studies. Effects on development should be considered in addition to the part of the safety assessment which is based on extrapolation of adult safety data. We have now deleted the sentence the document, as this is unrelated to pharmacokinetics.*
3 STUDY DESIGN		
Page 5, section 3	The document does not guide on how to select an initial dose. Please provide clarification.	*This is beyond the scope of this guideline.*
Page 5, section 3	Since patients receiving chronic concomitant therapy are enrolled into these studies, the pharmacokinetics of the drug in question may be influenced by these other medications. Covariate analysis in the population PK analysis will reveal the pharmacokinetics of the drug, if there are sufficient numbers of patients with the same concomitant therapies. Further recommendations regarding study design are needed to account for potential drug-drug interactions.	*In younger children, especially in newborns, infants and toddlers, marked differences in drug interactions may be present as compared to adults. In these patients, it is difficult to obtain interaction information from conventional studies and population PK analysis of commonly used drugs may be a way to obtain information. However, it must be kept in mind that this kind of analysis has limitations in this respect. The guideline now contains a subsection on drug interactions where more information is available.*
Page 5, section 3	Influence of organ function maturation and age on the study design: The guideline provides approaches for studying the effects of age on pharmacokinetics. It is critical to enrol subjects at the younger ranges of the specified spectrum. This proves to be a challenge to recruit these subjects. What is the recommendation to overcome this hurdle?	*We acknowledge that it is more difficult to include the younger patients of an age range. However, the information obtained is important and effort should be made to include such patients.*
Page 5, §6	Clarification is needed regarding when to choose between the 2 proposed approaches of studying the age range in question, i.e. studying the age interval expected to be the most different versus balancing the study population across the entire age range. In addition, recommendations for the second alternative approach should further state: In order to balance the study population according to age, it should be divided into ranges based on knowledge of organ function maturation, disease state, and the known pharmacokinetic characteristics of the drug. Every attempt should be made to recruit patients evenly within the age ranges.	*The choice of strategy has to be made case-by-case dependent on therapeutic index and prior knowledge on the pk of the drug.* *A proposal to divide in age ranges based on organ function has now been included in the text (p6).*
Page 5, section 3	The guideline should mention the necessity of developing analytical methods to allow for small sample volumes, and potentially also, lower concentrations, that may not have been previously detectable.	*We agree that this is important. This is already included in the document*

Page 6, §3 ***Section 3.3 - Specific considerations in children***	The age range for children is defined as 2 to 11 years of age. As children approach adolescence earlier these days, consideration should be given to reducing the lower limit of the age range to 10 years, and/or adding some criteria around a measure of developmental secondary sex characteristics to allow for children who are truly in adolescence to be properly categorized.	*This was included in the guideline but has now been included also in section 4.2.3.*
Page 6, §4 ***Section 3.4 - Specific considerations for adolescents***	In a previous submission for paediatric exclusivity to the FDA, data from 17 year-olds were included. Should the adolescent age category include 17 year-olds also?	*Seventeen-year-olds have now been included as according to the CPMP paediatrics guideline* (CPMP/EWP/462/95)*, adulthood starts at 18 years of age. The limit for adulthood in the ICH guideline is 16-18 years (and is stated to depend on region).*
Page 7, §1 ***Section 3.6 – Population Pharmacokinetics***	Due to the difficulty in sampling blood, sparse sampling is recommended as implied in the Guideline. However, it is not clear if the population-PK approach replaces the data-rich PK study, or if this approach is complementary.	*Population analysis and sparse sampling can replace conventionally designed pk studies.*
Page 7, §1 ***Section 3.6 – Population Pharmacokinetics***	This section includes use of simulation in addition to modelling. A more appropriate title may be "Population PK and/or PK-PD modelling and simulation. PD part should be also included because efficacy may be extrapolated by using PK-PD modelling and simulation.	*It is difficult to be more specific regarding the PD part of the document as the approach has to be taken case-by-case.*
Page 7, §1 ***Section 3.6 – Population Pharmacokinetics***	The draft guideline suggests use of population PK analysis but does not provide the reasoning. For ethical reasons, population PK approach with sparse sampling should generally be encouraged for characterizing PK in paediatric patients. Sometimes, the data quality from the paediatric studies may not be optimal; it could be because of insufficient number of subjects and/or samples, or because of sub-optimal sparse sampling scheme. In either case, the model development solely based on the paediatric data may not be adequate. It would be helpful that the guideline could give some recommendation in dealing with those situations, such as "the rich and robust PK data from adults can be merged with the sparsely sampled paediatric PK data to get better estimates of PK in paediatrics".	*Adult data may be used as a priori information and may be included in the analysis as long as there is sufficient data of satisfactory distribution in paediatric patients and the prediction in children is satisfactory.*
Page 7, §1 ***Section 3.6 –***	This section includes use of simulation. The importance of model qualification before applying the model to simulation and the use of	*We agree. This is very important. This has now been included more specifically in the guideline (p8).*

Population Pharmacokinetics	uncertainty in simulation should be mentioned.	
4. DATA ANALYSIS		
Page 7, §3 ***Section 4.1 – Parameter Estimation***	Method of analysis to estimate PK parameters (model-dependent versus non-compartmental analysis, use of mixed effects modelling approach) needs to be specified.	*This will not be specified in the guideline, as this has to be decided case-by-case. A non-specific sentence has been added (p7).*
5. DEVELOPMENT OF DOSING RECOMMENDATIONS		
Page 8, §2	In case the exposure-response has not been established, how will the PK data in infants help to determine a dosing regimen?	*If, based on prior knowledge, it may be assumed that the concentration-response relationship is the same as in other paediatric age-groups, the dosing recommendation may be supported by pharmacokinetic documentation. This also holds true when considering dose-adjustments for specific subgroups within the studied infant population assuming that the concentration-response relationship is similar within the whole studied infant population.*
Page 8 §2	Regarding the recommendation to minimize overall variability in exposure within the study population, further clarification is necessary. There will be many sources of variability in these types of investigations, i.e. limited number qualifying study subjects, multiple study centres, limited number of blood samples, etc. What are the recommendations to minimize the variability, keeping in mind that large sample sizes may not be practical?	*We are referring to resulting variability in predicted exposure in the target patient population. This sentence has now been removed from the guideline to avoid misunderstandings..*

Table 4 IPFA

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
1 INTRODUCTION		
Page no. + para no.	**Comment and Rationale**	**Outcome**
Page 3, 1§&2§	It mentioned that it is more difficult to perform full demonstration of efficacy and safety in the paediatric population. However, the number of samples to be taken during PK studies might be much more important than those for clinical endpoints.	*We agree in the case pharmacokinetics may be used to extrapolate efficacy and safety.*
Page 4, 1§	What does it mean? Does it imply the various ages and the various stages of maturation of different systems? Could it be described?	*We do not understand the question.*
2. USE OF PHARMACOKINETICS IN PAEDIATRIC DRUG DEVELOPMENT		
Page 4, §4	There is inconsistency between both conditions in the use of the words "assumed" and "substantiated".	*The second bullet point has now been extended for clarity.*
Page 4, §7	It would be useful to already mention here the possibility of choosing the one most relevant sub-population, depending of the drug. Indeed, in order to maintain an ethical relevant number of paediatric patients, if several sub-population need to be investigated, the total number of children might be quite high. This is further described in *3. Study design,* "first approach", and in *3.1 Age classification,* involving the variables to be considered.	*Although we agree that this is important we do not wish to repeat the information in this subsection.*
Page 5, §1	"The possibility of markedly higher incidence of side effects should be discussed…." could be further explained already.	*As this is not related to pharmacokinetics, we do not want to extend this statement further. The word "higher" has been replaced by "different" reflecting that differences in both directions are possible (p4).*
3 STUDY DESIGN		
Page 5, §7	"For ethical reasons, pharmacokinetic studies are *often* preformed in patients, who may potentially benefit from the treatment." Either the PK study should be *always* performed in patients, who may potentially benefit from the treatment, or the question of compensation of minor	*We have chosen not to specify this issue more in the document. Preferably children involved in a clinical study should be in need of the drug.*

	patients should be addressed if no or only moderate benefit is expected from the research.	
Page 6, §4 ***3.4 Specific considerations for adolescents.***	It could be foreseen that 'no specific study' could be accepted in certain cases.	*This is possible based on the therapeutic index of the drug and prior knowledge on the maturation of the organs/enzymes involved in the pharmacokinetics of the drug.*
Page 7, §1 ***3.6 Population pharmacokinetics***	"The methodology could allow the sampling procedure to be carried out during routine visits". This seems rather dreamlike, because the sampling is directly linked to the half-life of the product.	*We agree but still think that in several cases, sampling at routine visits could be possible.*
Appreciated items		
	The possibility to obtain knowledge from other drugs. Once acquired for a therapeutic drug class, is it really necessary to perform systematically for all applying drugs? Choice of focusing on the age of particular importance. The classification of the population based on variable as gestational age, renal function, metabolic function, and the maturation of all organ or system particularly involved.	

Table 5 EFPIA

GENERAL COMMENTS - OVERVIEW
EFPIA praises the initiative on a guideline highlighting the role and relevance of pharmacokinetics in understanding safety and efficacy in the paediatric population. The level of interest is demonstrated by the many comments that have been received from the membership on this draft guideline. The following commentary consolidates the comments. Some general comments are reiterated in comments on the specific section of the guideline.
GENERAL COMMENTS The title of the document indicates this Guideline is about the role of PK. However, PD in addition to PK is also included in the Guideline. Therefore, we suggest the title should include role of PK and/or PD. *Response We prefer to leave the title unchanged. The document mainly focuses on PK.*
The intention of the guidance is appreciated considering the complexities of designing and implementing clinical pharmacology studies in paediatrics. However, this guidance is still very much at a conceptual stage and while ably describing the challenges of these studies in the paediatric population, it is not yet complete in the provision of guidance on this subject and the stated objectives are not necessarily fulfilled. For example the Table of Contents does not necessarily match the topic title as the guidance has extensive discussions of both study design (section 3) and data analysis (section 4) considerations. This guidance provides key principles and common practices for conducting a paediatric clinical pharmacokinetic trial and the utility of the PK information for dosage recommendation. However, this guidance would be more helpful if it could offer more detailed guidance on some key issues and challenges for conducting a paediatric clinical pharmacokinetic trial. *Response: We prefer not to go into such details. Some information is available in the ICH guideline and there is no need to repeat this here as we cross-refer to the ICH guideline. Both "study design" and "data analysis" are included both in the table of contents as well as in the description of the aims of the document.*
It is also very important to stress that in this vulnerable population with limited blood volume, any new guidance should take into account other already finalised guidance worldwide to ensure harmonisation of requirements. It would be unacceptable for differences in requirements amongst agencies to result in additional clinical study burden in the paediatric population. It should be advisable to harmonise paediatric ages of reference in agreement with ICH guideline E11 and the EU Draft Regulation on paediatrics. *Response We agree that this is important. The guideline is to be read with and will be in agreement with the ICH document Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). At present the FDA has published a draft guideline " General Considerations for Paediatric Pharmacokinetic Studies for Drugs and Biological Products". We have not observed any major differences between the documents.* *See question below on the age limit for adulthood.*
The current proposal is limited to the use of age as a descriptor of size and developmental changes, providing unclear guidance on how appropriate scaling factors can be identified for dose selection and dosing regimen in the paediatric indication. *Response: We agree. More information has now been inserted in section 5 to further clarify this.*

The guidance lacks details on how understanding of pharmacokinetics and concentration-effect relationships can guide the choice for different development strategies to predict exposure, efficacy and safety. There appears to be an underlying, but unstated assumption that children will be slow metabolisers compared to adults. While this may be most conservative with respect to safety concerns, there are examples where children metabolise drugs faster than adults and this will have implications for efficacy.

Response We agree that children may have a faster metabolism of a drug, in particular if normalising CL for bodyweight. Children may also be less susceptible to some adverse events. A slight rewording has been made in section 2 in order to better reflect this.

Whilst traditionally pharmacokinetic studies in healthy adults may have been considered independently in Phase I trials, an attempt should be made to incorporate pharmacokinetics to PK/PD modelling as a primary component of the paediatric development programme. If this set of concepts is to become standard tools in such trials, it is essential that different aspects of the use of nonlinear mixed-effects modelling are presented clearly and brought into context.

The proposed approaches on how time-dependent factors contribute to changes in pharmacokinetics overlook underlying developmental processes, which do not necessarily correlate with age and consequently pharmacodynamics, safety and/or efficacy. In that sense, the text seems to disregard the role of weight and size as drivers for changes in physiological processes. The document is also insufficient in describing the requirements for bridging, extrapolation between and interpolation within populations.

Response We interpret time-dependent changes as dependent on all factors changing during development such as renal function, hepatic function, possibly bioavailability ie intestinal maturation, weight, body surface area etc. We propose that, when needed, these cofactors are used in the population PK analysis in order to find a suitable factor for dosing adapted to the patients individual maturational stage. We think that the document reflects this.

The technical part regarding population pharmacokinetics and data analysis is too general and lacks accuracy in describing nonlinear mixed-effects modelling and alternative Bayesian methodologies as tools in handling sparse, unbalanced data sets, as usually occurs in paediatric trials. In addition, the approach to covariate identification may not be appropriate, particularly in some of the 'preferred' ICH age ranges. By proposing balanced cohorts in the evaluation of covariates, it neglects the developmental features of disease in the paediatric population, which have varying incidence and prevalence rates. These can constitute a limitation to recruitment and access to patients.

Response: The text was written for being applicable to both non-compartmental and population PK analyses. We have rewritten the text in order to separate the modes of analysis and giving more suitable advice.

There are topics that EFPIA would like to have seen addressed in the guideline, e.g. the following:

- The document does not mention tissue levels.

Response: We agree that the distribution of drugs and metabolites may differ between paediatric and adult patients. A difference in tissue distribution may lead to a shift/change in the PK/PD relationship. This should be taken into account when choosing clinical development strategy and deciding how to use pharmacokinetic information and whether additional PK/PD documentation is needed.

- There should be appropriate scaling of PK both for dosing and comparison across populations – either as mg/kg or mg/m2.

Response: The dose recommendations should be based on the covariate analysis and simulations. This is now further explained in section 5.

Additionally, EFPIA considers that open communication between the sponsors and the agencies is very important and that can be emphasised in this guideline. If a company would like to apply the modelling and simulation technique to get an exemption from conducting an actual paediatric clinical trial, the responsibility should be shared among companies, regulatory authorities, health professionals, and society as a whole.

Response: As the proposed Paediatric regulation includes agreement with the authorities (Paediatric Committee) on a paediatric plan, we do not find it necessary to include a statement on this in the guideline.

SPECIFIC COMMENTS ON TEXT

1 INTRODUCTION		
Page no. + para no.	**Comment and Rationale**	**Outcome**
Page 3, §1	The document states that "*an application for paediatric use of a medicinal product should include sufficient documentation to establish efficacy and safety"* and that *'….it is more difficult to document a medicinal product in paediatric patients, particularly in very young patients."* The use of the word "*documentation"* does not necessarily imply (scientific) evidence. This is an essential aspect of a realistic paediatric development plan, which should take into account ethical and practical limitations of controlled clinical research in the paediatric population. We suggest replacing it by the word "*information*".	*The word has been changed.*
Page 4, §1	It is important that guidance on this matter is based on the learning-confirm paradigm presented by Lewis Sheiner [ref], ensuring that sufficient direct or indirect evidence is available and that the rationale for pharmacokinetic studies is aimed at establishing the relationship between dose, concentration, exposure and pharmacodynamic or clinical effects. Direct evidence can be defined by studies in which PK/PD relationships (including efficacy and/or safety) are assessed in the target population. Indirect evidence can be defined by bridging studies or predictive modelling, by which extrapolation of PK/PD relationships (including efficacy and/or safety) can be inferred from data arising from other population groups.	*We agree. The guideline is written in this spirit. We do not see where more information should be given to further emphasis this.*
Page 4, section 1	Characterisation of variability, a key question underpinning the development programme is not discussed. The document should address the concept of statistical distributions in the assessment of	*More detailed advice on population PK analysis is considered to be out of the scope of this guideline. The text describing data analysis and presentation has been revised.*

	pharmacokinetics, pharmacodynamics and efficacy. Distributions form the basis for understanding parameterisation of pharmacokinetics and pharmacodynamics in fixed and random effects, the latter element being used to identify sources of variability and quantify within and between subject variation a given population This is in contrast with traditional adult pharmacokinetic studies which are often, and unfortunately, described and summarised non-parametrically, using non-compartmental techniques.	
Page 4, section 1	In recommendations for study design, age is presented as the only descriptor of developmental changes in pharmacokinetics. That is not accurate and is scientifically incorrect as an approach for covariate selection, as any a priori stratification by age should first exclude the relevance of any other scaling factor for size	*We would like for several other factors to be tested. And think that this is mentioned at several places in the document. A clarification is now included also in section 5.*
Page 4, section 1	The definition of a control group seems inappropriate, particularly if the indication exists only in the paediatric population. The word reference should be used for comparative purposes. Moreover, in cases where an adult indication exists, the document does not promote the use of an integrated approach, which can be achieved by the pharmacokinetic and/or pharmacokinetic-pharmacodynamic modelling, whereby one evaluates whether a target group within the patient population is part of the parameter distribution of overall population (e.g., is CL in infants part of the same distribution of CL in adolescents?).	*In pharmacokinetic studies we often talk about the reference group as a control/historical control group. Therefore we do not wish to change the word. However "reference" has been added for clarification.*
Page 4, section 1	The introduction would benefit from citing certain key ADME differences between children of various ages and adults.	*This is already included in the general CPMP and ICH guidelines (CPMP/ICH/2711/99 and CPMP/EWP/462/95) and we think that giving more detailed information is inappropriate in a guideline.*
Page 4 ,§1	EFPIA suggest adding the sentence: ***"Sponsors considering new approaches should seek advice from competent authority".***	*As the proposed Paediatric regulation includes agreement with the authorities (Paediatric Committee) on a paediatric plan, we do not find it necessary to include a statement on this in the guideline.*

2 USE OF PHARMACOKINETICS IN PAEDIATRIC DRUG DEVELOPMENT		
Page no. + para no.	**Comment and Rationale**	**Outcome**
Page4	The section quite nicely presents the potential use of pharmacokinetic (exposure) information to extrapolate clinical efficacy and safety. It	*We agree that the pharmacokinetic and PK/PD knowledge should be integrated in the efficacy and safety assessment including dose/dose*

	should, however, emphasise the need for an integrated approach to achieve that objective. *Ad hoc* planning of pharmacokinetic studies, without explicit objective to further use the information in the analysis of the underlying concentration-effect (i.e., pharmacodynamics, safety or efficacy) relationships, may lead to inappropriate study design and dose selection.	*regime selection. However we believe that the present text sufficiently reflects this. Evaluation of the PK-PD relationship in dose-ranging studies or multiple dose level studies is encouraged as such information may be very valuable for dose-selection. This has now been included in subsection 2 of the guideline.*
Page4	The rationale for a scaling factor that describes and predicts the impact of developmental changes, as well as time-dependent processes requiring maturation is absent. The document refers to age as the only descriptor of changes and does not consider the possibility that in some specific cases no dose adjustment may be required at all. In addition it ignores that in some circumstances a dose increase might be recommended.	*Time-dependent changes includes all factors changing during development such as renal function, hepatic function, possibly bioavailability i.e. intestinal maturation, weight, body surface area etc. We propose that, when needed, these cofactors are used in the population PK analysis in order to find a suitable factor for dosing adapted to the patients individual maturational stage. This is reflected in the document and has now been clarified also in section 5.*
Page 4, §4	The demonstration of adequacy of an exposure-efficacy (PK/PD) relationship is important a more clear statement is suggested: *"If similar exposure in adult and paediatric patients can be assumed to result in similar efficacy,* ***the adult PK/PD relationship can be used to extrapolate efficacy for paediatric patients using paediatric PK data alone with an adequate evidence of goodness of the PK/PD model in its predictability in adults."***	*The use of pharmacokinetic data according to the first bullet point is possible also in situations where knowledge about the therapeutic effect, etiology of the disease, available information from drugs of the same class etc is sufficient to support extrapolation based on PK. Therefore we prefer to have a more general statement.*
Page 4, §4	The FDA guidance has a similar statement. However, some FDA reviewing divisions have interpreted "similar" to mean "identical." Paediatric PK parameters of a given drug will almost never be identical to those obtained in adults. Typically, children (except for neonates and very young infants) clear drugs faster than adults. Therefore, to obtain a similar AUC, one needs to dose them more frequently. More frequent dosing may be associated with several C_{max} values over a given period of time. However, even when those C_{max} values are not higher than those observed in adults, some FDA Division feel uncomfortable and point to the difference as a reason not to extrapolate the paediatric PK data to adults. Thereby requiring sponsors to conduct full safety and efficacy studies in children. **It may be worth to try a better definition of 'similar.'** Perhaps similar in this case can be defined based on AUCs and C_{max} values not exceeding certain percent of the adult values in a given period of time (within 24 hours of dosing).	*It is not possible to have a predefined range for which the word similar would apply. This is dependent on the concentration-effect relationship for safety and efficacy of the specific drug.*
Page 4, §4	Under the second bullet the guidance states that when a PK/PD relationship has not been substantiated," *paediatric PK/PD can be used*	*The clinical efficacy and safety may be extrapolated based on biomarkers. This has now been clarified in the document (p4).*

	to extrapolate efficacy." Clarification is needed as to what data is to be used for the extrapolation. The sentence implies that if a similar relationship between concentration and pharmacodynamic response in adult and paediatric patients is not found, paediatric PK/PD data can be used to extrapolate efficacy. It is not clear if paediatric PK/PD data need to be collected to establish a paediatric PK/PD relationship to extrapolate PK/PD to unstudied paediatric age group. Once paediatric PK/PD data is obtained, there is no need to extrapolate. Clarification is required.	
Page 4, §7	It is not clear what kinds of criteria are used to support clinical relevance using sub-group analysis with paediatric PK data. Modelling provides more power to detect difference among sub-groups. A suggestion is that clinically relevant differences among sub-groups can be supported if population PK modeling approach from paediatric data identifies a variable (such as age, renal function, etc.) that forms sub-groups as a statistically significant covariate and simulation using the model shows clinical significance.	*We agree that this is a satisfactory approach. However, even if no population pharmacokinetic analysis has been performed the data from studies including non-compartmental analysis may be sufficient for an outlying group of patients to be observed. This approach would also be sufficient.*
Page 4, §8	**The paediatric development programme is often restricted in terms of number of patients included.. Therefore, the safety assessment for systemically as well as locally acting drugs often has to be based in adults."** We suggest replacing the term *"based in adults"* by "***extrapolated from data obtained in adults or bridged from a different target group within the paediatric population".***	*We agree and have inserted a very similar text (p4).*
Page 5, §1	We assume that the sentence reading "Possible effect on growth and development should be considered" refers to animal data and is not suggesting the conduct of long term clinical trials. It would be helpful to clarify what the position is on this matter	*This sentence has now been removed as it is out of the scope of this guideline.*
Page 5, §1	The perception of vulnerability (i.e., possibility of a markedly higher incidence of side effects) in children is based on therapeutic misadventures of the past. This has been due precisely to the paucity of adequate information of the drug disposition in paediatric patients. However, when drugs are appropriately studied in children, there should not be an inherently higher incidence of adverse events just because the population is paediatrics. We suggest modifying this sentence.	*We agree and have slightly modified the text. The word "higher" has been replaced by "different"(p4).*

Page 5, §4	"The exposure of active substances in paediatric patients should be discussed in comparison with exposures in pre-clinical studies in adult and juvenile animals." Relevant information arises from adult subjects who are usually exposed to a new chemical entity and other data obtained from different routes of administration and formulations. There are more similarities between adults and children than between animal and children. Evidence of the magnitude of differences derived from metabolic or physiological process, including ontology of metabolic pathways in various age and weight groups has been shown for many compounds [see Ginsberg et al.]. Currently, the status of juvenile toxicology sciences does not enable accurate clinical judgment of positive findings, particularly if dose selection and achieved exposure ranges are beyond clinical relevance, as usually occurs in toxicology studies. The use of juvenile toxicology studies ought to provide information of delayed drug effect upon chronic (long term) exposure. Such experiments ought to be performed only when the clinical exposure range has been identified for the target paediatric population and findings evaluated in conjunction with adult safety data. Therefore we recommend that the reference to juvenile animal studies be revised to avoid the implication that exposure data from such studies is always required in the development of drugs for paediatric use.	*Juvenile toxicity studies are not always performed but when they are, the exposure in the animals should be taken into account. The paragraph has been slightly changed for clarity (p5).*
3 STUDY DESIGN		
Page no. + paragraph no.	**Comment and Rationale**	**Outcome**
Page 5, section 3	**<u>General comments on Section 3</u>** The document does not guide on how to select an initial dose. The following considerations are submitted to the Efficacy Working Party: **Dose selection:**	*Information on initial dose selection is out of the scope of this guideline* *The choice to perform single- or multiple-dose studied depend on a number of factors such as choice of analysis, ability to perform sampling, predicted dose-or time-dependencies, sensitivity of the analytical method*

	Dose selection is critical to assure the safety of paediatric patients as well to show efficacy. Different doses may be given to different age groups or different development stages for a paediatric PK trial. In this regard, guidance should give an either an example what was done, or general procedures or processes to select the dose(s). PK or PK-PD modelling and simulation should be considered, as this would offer a lot of value for dose selection. **Single dose PK vs. Steady-State PK:** Both single dose and steady-state PK studies have utility in the characterization of drug exposures and the utility of each in the paediatric populations needs to be clarified. It would be helpful to describe which one is preferred under particular conditions.	*e.g. to detect well concentrations in the terminal phase, the indication etc. However, as this involves so many factors and the decision has to be taken on a case-by-case basis, we do not want to include more specific advice on this. The text included in the introduction of section 3 reflects our general view on this.*
Page 5, section 3	**Multiple dose levels vs. one dose level:** When exploring the PK-PD relationship, a dose ranging study or multiple dose level approach should be warranted as it is difficult to get the dose right first time in a paediatric clinical PK trial	*We agree and have included a clarifying statement on this in section 4.1, bullet point 2 (p4).*
Page 5, section 3	**Gender consideration:** In particular adequate number of boys and girls or stratification by gender may be considered in adolescent groups.	*This has now been clarified in the document (p6).*
Page 5, section 3	**Concomitant therapy** Since patients receiving chronic concomitant therapy are enrolled into these studies, the pharmacokinetics of the drug in question may be influenced by these other medications. Covariate analysis in the population PK analysis will reveal the pharmacokinetics of the drug, if there are sufficient numbers of patients with the same concomitant therapies. Further recommendations regarding study design are needed to account for potential drug-drug interactions.	*A specific section on drug-drug interactions has been included (p7).*
Page 5, section 3	**Influence of organ function maturation and age on the study design:** The guideline provides approaches for studying the effects of age on pharmacokinetics. It is critical to enrol subjects at the younger ranges of the specified spectrum. This proves to be a challenge to recruit these subjects. What is the recommendation to overcome this hurdle?	*We understand that inclusion of the youngest children may be the more difficult. However, this is often the patient group where the most marked differences may be expected. Therefore gaining the information is important for the future drug treatment to be effective and safe in this age group.*
Page 5, section 3	Clarification is needed regarding when to choose between the 2 proposed approaches of studying the age range in question, i.e. studying the age interval expected to be the most different versus balancing the study population across the entire age range. In addition,	*The division of the patient population into subgroups is mentioned in section 4.2.1 (last sentence).and more information has been included in the second bullet point in section 4.2 (p5).*

	recommendations for the second alternative approach should further state: In order to balance the study population according to age, it should be divided into ranges based on knowledge of organ function maturation, disease state, and the known pharmacokinetic characteristics of the drug. Every attempt should be made to recruit patients evenly within the age ranges.	
Page 5, section 3	It would be helpful to clarify what should be the primary endpoint of choice in paediatric study –exposure or clearance?	*Exposure, but the choice of endpoint should be based on what is known about PK/PD. For example, Cmin could be of more importance for efficacy of a number of drugs.*
Page 5, section 3	It would be helpful to give some advice on when it is important to measure metabolites	*If there is a pharmacologically active metabolite, this metabolite should be measured unless it may be assumed that the exposure ratio metabolite/parent drug is be similar in the paediatric age group and the reference age group. Not measuring an active metabolite should be justified. In populations where the protein binding of drugs may be different (e.g. in newborns) measuring the free fraction of the metabolite should be considered. This has now been included in section 4.2 (p5)..*
Page 5, §7	**Specific comments on Section 3** Healthy children are rarely studied but may be in studies involving minimal risk in which subject gives assent (assent possible for typical 7 years old).	*We have chosen not to specify this issue more in the document. Preferably children involved in a clinical study should be in need of the drug.*
Page 5, §6	We believe this recommendation is applicable to the first bullet, not to the 2nd bullet point, because if there is no support for similarity between age group 1 and 2, sponsors cannot extrapolate efficacy due to lack of PK/PD model in paediatrics. A suggestion is to add this sentence within the 1st bullet point.	*The paragraph is relevant also for bullet point 2. Also in this situation, the pharmacokinetic documentation can be supported by information from other sources.*
Page 6 §1	**3.1 Age Classification** It would be important to make sure that the recommendations regarding these aspects are consistent in all CHMP guidelines.	*In the ICH guideline, the age limits are the same as proposed here with the exception of the higher age limit of adolescents, which is 16-18 years due to national variations. In most European countries, patients who are 18 years old are considered adults. The figure 16 years was put by mistake. This has now been corrected. Unfortunately the age limit may not be the same worldwide.*
Page 6, §5	**3.5 The choice of control group** The guidance regarding the choice of a control group in paediatric PK and PK/PD trials needs further clarification. First, the purpose of a	*It is true that a control group may not be needed depending on the additional clinical and PK/PD documentation available. However, the document is not stating that a control group is mandatory – only what to*

	control group in these clinical trials should be more clearly defined. With a specified purpose, the needed control group may be more easily identified. Given the guidance in Section 2, one purpose of a control group would be to support dosing recommendations for the medical product in paediatric patients. In this case, the control group (specifically, a historical control) would consist of adult patients with the same disease as that observed in the paediatric patient population. This control group would provide PK/PD, efficacy, and safety measurements taken during the course of controlled clinical trials. Second, the guidance should acknowledge that scientifically defensible recommendations can be based upon paediatric PK and PK/PD trials that were conducted without a control group. Companies have experience of completing acceptable paediatric studies without control groups in these circumstances .	*consider if such a group is used.*
	Further definition of "Pooled PK data of adequate quality" is required.	*We find it to voluminous to expand this further. Adequate quality should be justified by the applicant.*
Page 7, §1	**3.6 Population pharmacokinetics** Due to the difficulty in sampling blood, sparse sampling is recommended as implied in the Guideline. However, it is not clear if the population-PK approach replace the data-rich PK study, or this approach is complementary.	*Population analysis and sparse sampling can replace conventionally designed pk studies.*
Page 7, §1	This section includes use of simulation in addition to modelling. A more appropriate title is "Population PK and/or PK-PD modelling and simulation". PD should be also included because efficacy may be extrapolated by using PK-PD modelling and simulation.	*It is difficult to be more specific regarding the PD part of the document as the approach has to be taken case-by-case.*
Page 7, §1	The draft guideline suggests use of population PK analysis but does not provide the reason. For ethical reasons, population PK approach with sparse sampling should be always encouraged for characterizing PK in paediatric patients. Sometimes, the data quality from the paediatric studies may not be optimal; it could be because of insufficient number of subjects and/or samples, or because of sub-optimal sparse sampling scheme. In either case, the model development solely based on the paediatric data may not be adequate. It would be helpful that the guideline could give some recommendation in dealing with those situations, such as "the rich and robust PK data from adults can be merged with the sparsely sampled paediatric PK data to get better	*Adult data may be used as a priori information and may be included in the analysis as long as there is sufficient data of satisfactory distribution in paediatric patients and the prediction in children is satisfactory. Markedly more detailed information on how to perform the analysis will not be provided. Section 4.3 has been revised and some more information has been added (p7).*

	estimates of PK in paediatrics".	
Page 7, §1	This section includes use of simulation. The importance of model qualification before applying the model to simulation and the use of uncertainty in simulation should be mentioned.	*We agree. This is very important. This has now been included more specifically in the guideline (p8).*

4 DATA ANALYSIS		
Page no. + para no.	**Comment and Rationale**	**Outcome**
Page 7, §4	*"The choice of pivotal pharmacokinetic parameters to be used in dosage adjustment strategies should be justified…"*. It would be helpful to define *'pivotal'* **4.2 Presentation of the data**	*This will not be specified in the guideline as this has to be decided case-by-case. A non-specific sentence has been added (p7).*
Page 7, section 4.2	Presentation of data is ambiguous and not accurate, as it describes the display of data in the way it is conventionally done for rich sampling, and non-compartmental data analysis only.	*Section 4.3.2 has been revised and some more information has been added.*
Page 7, section 4.2	Non-linear mixed-effects modelling is mandatory if the population approach is used. There is no 'observed' pharmacokinetic parameter. Parameters are always estimated. Estimates can be derived for the overall population (mean parameter and its distribution) as well as for the individual subjects. Exposure profiles (AUC) can also be derived per subject.	*Section 4.3.2 has been revised and some more information has been added.*
Page 7, section 4.2	Model diagnostics are an essential part of the evaluation of the data analysis. Bias and reproducibility of the data by model parameter estimates is essential to understanding whether the sampled population is truly reflected in the parameterisation.	*We agree that this is important. This is now included in the section. More information on this will be included in a guideline under development.*
Page 7, section 4.2	Graphical description must include model diagnostics first. Subsequently, exploratory stepwise covariate search should be performed presenting the relationship of post-hoc Bayesian estimates (individually predicted parameters) and all relevant descriptors of size and maturation investigated.	*More information on this will be included in a guideline under development.*
Page 7, section 4.2	Descriptive statistics as indicated in the text raise concerns for the following reasons: Population modelling data analysis should be summarised by presentation of typical population parameters 95% Confidence Intervals and precision of the estimates, including residual variability. Point	*More information on this will be included in a guideline under development.*

	estimate is given by geometric means, not arithmetic means.	
Page 7, section 4.2	***"…It should be noted that the relationship between covariates and exposure observed is valid only for the range studied and should not be extrapolated to other groups unless there is other information supporting such an extrapolation."*** The aforementioned paragraph is inconsistent with the use of an integrated approach based on nonlinear mixed-effects modelling, which enables identification of relevant sources of variability and hence have predictive value for extrapolation. In addition, the paragraph omits the value of modelling to "interpolate" data.	*We do not agree to extrapolate outside the covariate range studied unless there is other information supporting the extrapolation. In fact, there may be situations where the number of subjects in parts of range (such as in the outer ends) may be too low to allow for a satisfactory prediction and assessment of variability. The sentence has been slightly changed for clarity (p8)*
Page 7, section 4.2	- PK parameters of interest should include V; it is the primary determinant of PK of a drug	*The choice of parameters could be decided case by case.*
Page 7, section 4.2	- Time over an established effective drug concentration is a PD parameter, not PK. The last paragraph appears to contradict the premise of the guidance and the use of PK/PD to extrapolate to efficacy.	*We do not understand the comment about time and think that this classification is irrelevant. The last paragraph seems to have been misinterpreted.*

5 DEVELOPMENT OF DOSING RECOMMENDATIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Page 8, section 5	**<u>General comment on Section 5</u>** Acknowledging the reality that guidance documents tend to speak to generalities, a better connection could still be made between the guidance provided for data analysis and that provided for paediatric dosing. The Data Analysis section describes methods for relating PK/PD endpoints measured in children to their covariates. However, the Dosing Recommendations section provides little guidance on relating measured PK/PD endpoints to dosing recommendations given specified values of these covariates. Also, the guidance should acknowledge that simulations of steady state exposures in support of dosing recommendations are unnecessary for medical products that are not given repeatedly to children, for example ant-emetics given post-operatively or in cancer chemotherapy. In case the exposure-response has not been established, how will the PK data in infants help to determine a dosing regimen?	*How the available PK/PD knowledge should be reflected in the dose-recommendations is dependent on several different factors related to the pharmacology, intended use and efficacy and safety of the drug. This has to be a case-by-case decision and it is not possible to go into these details in this document.* *We agree that there is no need to simulate steady state foe a drug given as one single-dose. The sentence has been slightly reworded (p8).* *In case an exposure-response relationship has not been established, the exposure in subpopulations of the paediatric population should be as close to the mean exposure of the overall paediatric populations as possible bearing in mind variability and clinical efficacy and safety of the drug, i.e. whether over- or under-exposure would have the worst clinical consequences.*

Page 8, §2	*"…Effort should be put into decreasing the overall variability in exposure in the population and not only evaluating mean data"* This statement ought to be modified because variability in exposure itself is not an issue. It is the therapeutic window of a compound that determines whether variability has any impact on efficacy and safety. Therefore, efforts should be made to identify relevant sources of variability and control them if necessary.	*We agree, this is a general wish not relating to situations where the therapeutic margin is so wide that controlling variability is not an issue.* *However, we feel that there is little reason to get into more detail on this point.*
Page 8, section 5	As previously mentioned, the use of nonlinear mixed-effects modelling requires understanding of distributions (i.e., point estimate, kurtosis and skewness). Model estimated parameter distributions ought to be used as descriptors of variability within and between subjects and we must remember that the summary of parameter distributions by point estimates and 95% confidence intervals is standard in modelling practice.	*We are aware of this but feel that this does not have to be mentioned in the guideline.*
Page 8, §2	Regarding the recommendation to minimise overall variability in exposure within the study population, further clarification is necessary. There will be many sources of variability in these types of investigations, i.e. limited number of qualifying study subjects, multiple study centres, limited numbers of blood samples, etc. It would be helpful to make recommendations on how to minimise the variability, keeping in mind that large sample sizes may not be practical.	*We are not referring to variability due to study design and conditions. The sentence has been removed as it has been misinterpreted but its essence has been kept in remaining text.*
Page 8, §4	"*The study population that forms the basis for the dosage recommendation …"*. This point and the further qualification are really design considerations and should preferably be covered under section 3 rather than here. Also these two sentences do not sit well with the point made in the first sentence in this paragraph. It would be helpful to clarify what methods are proposed to make dose choices for efficacy studies.	*We prefer to keep the text in this section, as it is important to evaluate this in the stage of deciding dose recommendations. We do not see any contradiction between the sentences.* *This is out of the scope of this guideline.*
	MINOR COMMENTS	
Page 6, §3.3	**Section 3** **" Specific considerations in children"** "Relation" should probably be "relationship"	*This has been corrected.*
Page 7, §3.6	**" Population Pharmacokinetics", Last line** "Tool" should be "tools".	*This has been corrected.*