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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS OF HUMAN PHARMACEUTICALS FOR PAEDIATRIC INDICATIONS

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

	Name of Organisation or individual	Country
1	PAREXEL Drug Development Consulting	UK
2	Drug Safety – Andrew Bartholomaeus	Australia
3	EFPIA	Belgium
4	Huntington Life Sciences	UK
5	JPMA	Japan
6	Pharmaceutical Research and Manufactures of America PhRMA	The United States
7	Schering-Plough	Begium
8		
9		

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW	
Comment and Rationale	**Outcome**
The initiative by SWP to better codify nonclinical approaches to the protection of juveniles participating is clinical trials (and to assessing potential safety concerns in juvenile patients in general) is welcomed. However, the draft guideline seems to approach this issue with an agenda that studies in juvenile animals are an almost essential part of any safety assessment paradigm. This is reflected in the title and in many other places in the draft guideline. Therefore, a major restructuring of the guideline is recommended with a new title that reflects safety assessment rather than juvenile animal testing; for example, "Approaches to the nonclinical safety assessment of human pharmaceuticals intended for paediatric indications". Secondly, it is not at all clear whether the recommendations on the use of juvenile animals in toxicity studies are evidence-based. In the 4th paragraph on page 4, it is implied/asserted that data from juvenile animal studies will be more predictive than other data in respect of potential toxicity in paediatric patients. As this is such a key consideration relating to the value of juvenile animal data, the supporting evidence should be provided so that others can make an independent review. In particular, it is necessary to present clearly the predictive ability of juvenile animal studies in the context of the concordance of animal results with human toxicity, and to indicate the extent of false negative and false positive predictions. This is critical importance because if a requirement for juvenile animal testing were to be established, regulatory agencies would presumably make decisions based on the results with an inbuilt assumption that the animal models are valid. This could lead to false confidence about the safety of a drug showing no adverse effects in animal models, and unnecessary caution in other cases, possibly depriving children of a valuable therapy. It would be helpful if the guideline could provide greater prominence/clarity on key issues. For example: • The principal purpose of any nonclinical safety assessment in this context is to ensure that children in clinical trials are adequately protected and not at risk of any unexpected toxicity. If this is accepted, then there are several important corollaries: o The results of any juvenile toxicity studies will in the normal course of events be superseded by clinical safety data in paediatric patients o If clinical trials in paediatric patients are in fact successfully undertaken without any prior evaluation in juvenile animals, then there	These comments are acknowledged. It is considered that these comments are taken care of in the guideline, as a case by case approach is emphasised, and that a number of considerations should be taken, including existing clinical safety data in both adults and paediatric population, as well as known class effects. No action considered needed.

should be no regulatory expectation of including data from such studies as part of the MAA, ie juvenile animal studies should not be a tickbox requirement in these circumstances, and it would be helpful to remind assessors of this fact by updating the D70 Critical Assessment Report template. • The circumstance in which juvenile animal studies are not needed should be more clearly and explicitly stated: o Not needed if there is an existing clinical safety database in children o Probably not needed if kinetics in juvenile/adult animals and/or patients are similar o Probably not needed in those therapeutic categories where for existing drugs the toxicity profile in children is similar to that in adult patients. • Guidance regarding the integration of animal/human data (at the clinical trial and/or MAA stage) as part of a risk assessment. A weight of evidence approach giving priority to clinical safety data is recommended.	
The general consensus on juvenile animal studies within DTES can be summarised as follows: As with any animal study there are limitations and traps in the extrapolation of observed effects to those expected in man. With juvenile animals these limitations are magnified by substantial differences in the early development of humans and laboratory animal species. Whilst laboratory animals are born, or quickly become, substantially more independent than human babies – particularly in terms of mobility – the fetal period in humans is greater than 60% of gestation as compared to about 20% in rats. Consequently some functions in humans are substantially more developed at birth in humans than in rodents, the blood brain barrier (esp p-glycoprotein) for example. In identifying potential hazards in the clinical setting the objective is to use the model(s) likely to be most closely analogous to the target population. In general the adult human is likely to be a better model for effects in young humans than is the juvenile laboratory animal, as there are no interspecies variants to confound interpretation of the observations. We can for example predict many problems of drug administration to neonates from a knowledge of the development of metabolic and excretory capacity in this population. Under these circumstances the ethical basis for routinely requiring studies in juvenile animals is likely to be weak. Where the pharmacology or toxicology of a compound in standard nonclinical (or for that matter clinical) studies raises the potential for specific hazards in young patients	No action needed, as this is supportive of the current guideline.

there may be a need for studies of specific endpoints in juvenile laboratory animals. In such cases the model chosen would need to have comparable developmental stages for the relevant physiological process(es) to that in humans in order to be informative. Thus, selection of the appropriate model (species, strain, age) for a specific endpoint is critical to the utility and interpretation of a study in juvenile animals. The Draft EMEA guidance is generally consistent with the points above and allows ample scope for designing a test strategy targeting specific endpoints of concern, but greater emphasis could usefully be placed on a couple of these aspects as discussed below.	
EFPIA welcome the initiative by the EMEA to provide guidance on the need for non-clinical testing in juvenile animals of medicinal products to support paediatric use. In general the guidance is considered to be appropriately formulated in that it allows flexibility in the approach on a case-by-case basis to determine the need for specific juvenile animal studies. Furthermore it enables such studies to be designed in the most appropriate manner to address risks to the paediatric population. In general it is felt that the document is clearly laid out, however, the latter part of the guideline would benefit from some re-structuring – see specific comments on section 4. ***Pre-and Postnatal Reproduction Studies*** As mentioned previously, Section 4.1 indicates that a full reproductive toxicity programme should be available prior to the commencement of trials in the paediatric population." The wording of this later section suggests that "Before performing a juvenile toxicity study…" developmental toxicity issues might be addressed in a modified pre-and postnatal development study. This again raises the question of the most appropriate approach to take in scheduling pre-clinical studies, taking into account resources and economical use of use of animals.	
Supplementary comment on number of animals The draft guideline makes no recommendation or suggestion on the number of animals that are considered to be appropriate for these investigations. Reproductive studies usually follow international guideline principles that the litter should be considered as the basic unit for assessment and group size of mated animals is commonly targeted at achieving 20 pregnant females per group; this is likely to yield around 200 fetuses or newborn offspring per group in developmental toxicity and pre-and postnatal studies in	A comment has been included, addressing that the number of animals should be sufficient to draw scientifically sound conclusions, but not use

rodents. However, general toxicity studies performed on the same test material will commonly be conducted with smaller group sizes. While there is a case for using group sizes in the region of 20, in a study which bridges the gap between a pre-and postnatal and toxicity studies in adults, a study of this dimension can result in group sizes of 80 males and 80 females, even with culling of litter size to 4 males and 4 females, a number higher than used in oncogenicity studies. As larger group sizes also favour greater statistical power this could have a bearing on determination of relative 'effect' levels between the adult and juvenile model. It is possible to design these studies using within-litter allocation to different groups/sub-sets to maximise genetic balance/maternal litter interactions within each group or to design the study with replicate sub-sets of investigations within each litter. This policy has been adopted by the US EPA for assessment of Developmental Neurotoxicity (DNT) where the basic number of animals committed to each battery of tests is 10, but 12 litters are commonly used to maintain adequate numbers through the study. Because of the number of options that are possible in relation to allocation of animals, it is suggested that some guidance is given on this aspect to avoid excessive use/wastage of animals.	
The sentence "*Even if adverse effects on developing organs can be predicted from adult human or animal data, studies in juvenile animals might be warranted in order to address a specific concern or to study reversibility or possible aggravation pf the expected findings, as well as to establish safety factors" (which is also found under 4.1)* can be easily misinterpreted as a suggestion to carry out juvenile studies anyway if the product will be administered to children. This is in contrast with other statements in the remaining parts of the document, especially the last sentence under 4.1 General considerations: *Studies in juvenile animals should be performed on a case-by-case basis and only after a careful consideration of the available data.* So, a better balance should be expressed: (proposal: Although studies in juvenile animals appear to be redundant is adverse effects on developing organs can be predicted from adult human or animal data, studies in juvenile animals might be helpful to address a specific concern or to study reversibility or possible aggravation of the expected findings etc.).	Agreed
PhRMA appreciates the Agency's efforts to provide guidance on non-clinical studies to support the development of pharmaceuticals for pediatric indications and is pleased to have this opportunity to provide these comments.	

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Outcome
4.1	More emphasis should be placed on the fact that existing studies yield considerable information about juvenile animals. Although the issues are touched on to some extent throughout the document a better balance would be created by adding a paragraph to this section along the following lines; In general, current preclinical study programs generate considerable information relevant to a consideration of safety in paediatric patients. Rats used in repeat dose and reproduction studies for example normally commence treatment at 5 to 6 weeks of age. As sexual maturity in the rat is achieved at approximately 13 weeks, these animals are sexually and developmentally immature at the start of treatment. Commencement of treatment at 4 weeks of age in some of these studies would significantly enhance the information obtainable from them without a need for increased animal usage or additional studies. Further, the F1 pups in a 2 generation reproduction study, when performed, are treated from weaning through to sexual maturation and mating, with the females continuing on treatment through pregnancy, delivery of pups and through to weaning of their litters. Although uncommon for pharmaceuticals, where a drug is administered in the feed, considerable exposure of the pups occurs through consumption of the maternal feed from approximately 10 days after birth. Where the drug is excreted in the milk exposure of the pups occurs from birth. Thus, the 2 generation reproduction study provides limited toxicity information on juvenile animals from at least the time of weaning through to sexual maturation and, with minor modifications such as the addition of a Functional Observation Battery (FOB) and extended necropsy, has the potential to provide	Not included, available information considered sufficient

	considerable information without the need to design and conduct separate additional dedicated juvenile animal studies.	
4.3.4	The relationship between pharmaco-/toxico- kinetics in juvenile animals compared to adults of the same species is frequently very different to the relationship between infants and adult humans (eg linezolid). Although the limited kinetic parameters recommended in this section ***may***be sufficient to identify these differences, in many cases they will not be. This is particularly so where the marked CYP450 differences between infant and adult animals results in a metabolite profile very different to that seen in human infants, despite similarity between adult animals and humans. Consequently there is also a need to examine metabolism parameters in cases where a ***difference*** in toxicokinetic parameters might be expected. Indeed this should be established before an animal model is selected for use.	Covered by first sentence in this paragraph.
Last Sentence	Clarity is needed to indicate that the intent of this guideline is to make recommendations on the timing and utility of juvenile toxicity studies. This guideline also makes recommendations on the timing and utility of juvenile animal **toxicity** studies in relation to phases of clinical development.	Focus is not on support for clinical trials; reference is made to ICH M3
EXECUTIVE SUMMARY	The main aim of non-clinical studies to support the development of medicinal products to be used in paediatric patients is to obtain information on the potential different safety profiles from those seen in adults. Juvenile animal studies can be used to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. Serious adverse reactions that may be irreversible are of particular concern. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted in order to address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety	Agreed and amended in the Executive Summary. In other instances the term Guidance is used when making reference to a document that is referred to as Guidance.

	factors. The guidance[1] also makes recommendations on the timing and utility of juvenile animal studies in relation to phases of clinical development. 1) Does "The guidance" stand for EMEA guideline EMEA/CHMP/SWP/169215/2005, or is it used in a meaning different from guideline? If they are used in a same meaning, we recommend to unify the description to avoid a new definition of word.	
	The executive summary should indicate that juvenile animal studies are not always routinely needed. This aspect could be added at the beginning of the paragraph (*see proposal in next column*) The following could be added as the second sentence of the executive summary section: "In general, a medicinal product can be studied in the paediatric population when adequate efficacy and safety data are available in adults. However,…"	These additions are not considered needed in the executive summary. Thus, not adopted.
	The scope of the guidance could also be clarified in the executive summary by adding that this guidance applies to "initial medicinal products applications and also to authorised medicinal products being further developed to include paediatric indications."	These additions are not considered needed in the executive summary. Thus, not adopted.

1 INTRODUCTION

Line no. + para no.	**Comment and Rationale**	**Outcome**
Paragraph 4	In addition to the immature systems already listed, the skeletal system should also be included as it continues to mature well into adulthood. Organs or tissue in involved in absorption metabolism, distribution and elimination should also be mentioned. Modify last sentence of section 1, paragraph 4 to: "…especially **effects** on immature systems such as developing brain, the pulmonary system, **the reproductive system, the immune system, the skeletal system and the organs or tissues which play a role in the ADME of drugs.**	Sentence amended

	Most medicinal products currently used in paediatric patients have not been properly developed for the use in this age group. In most cases, an extrapolation from the clinical experience in adults was used to support the paediatric use. Approval of medicinal products intended for paediatric patients requires a special risk/benefit assessment, where the possible effects of the product on the developmental processes ongoing in the age group(s) to be treated are also taken into consideration. This risk/benefit assessment should be based on safety and pharmacokinetic data from non-clinical and clinical studies. In some instances, additional studies in juvenile animals will be required to allow such an assessment. There have been several examples of medicinal products that have different safety profiles in adults compared with paediatric patients. Such differences might be qualitative and/or quantitative, immediate and/or delayed. 1) They might be caused by pharmacokinetic/dynamic differences as well as 2) developmental differences in growth and function of target organs and 3) expression of receptor systems, immune system maturation, body weight etc. Standard non-clinical studies using adult animals, or safety information from adult humans, cannot always adequately predict these differences in safety profiles for all paediatric age groups, especially reaction on immature systems such as the developing brain, the pulmonary system, the kidneys, the reproductive and the immune systems. 4)…… 1) Inserting examples of different safety profiles observed between adult and children facilitates for the applicant to get better understanding of the importance of juvenile animal study implementation. 2) “as well as” would be replaced with “, (comma) ”. 3) “and” would be replaced with “or”. 4) “Skeletal system” should be added in this sentence considering its importance in evaluation of growth of juvenile animals. And in adition “kidney, and the skeletal, reproductive and immune	Addition of examples not supported, to keep the guideline concise Comments 2-4 agreed.

	systems" may be grammatically correct.	
	Nothing has been mentioned about an approach in case of pharmaceutical products to be developed specifically for premature born babies. Obviously there is a need for a specific approach, e.g. in the selection of a relevant species with respect to state of maturity. "	This is covered in several parts of the guideline, and therefore no need for further emphasis
4 paragraph	Suggest addition of skeletal system as another relevant system Organs or tissue in involved in the absorption metabolism, distribution and elimination should also be mentioned. "… especially **effects** on immature systems such as the developing brain, the pulmonary system, the kidneys, **the skeleton**, the reproductive and the immune systems or tissues playing a role in absorption and elimination of drugs."	Sentence amended
6 paragraph	We appreciate and endorse the recommendation that actual need for studies in juvenile animals would be determined on a case-by-case basis only after careful and thorough assessment of existing clinical and preclinical data.	Comment noted
1 paragraph	"*Most medicinal products currently used in paediatric patients have not been properly developed for the use in this age group. In most cases, an extrapolation from the clinical experience in adults was used to support the paediatric use."* Change "properly" in the first sentence to "formally" for better clarity. If there were no previous requirements then how was it improper? As presently written, this could imply that previous practices were unethical. The second sentence could also be clarified by adding / elaborating that this was previously an accepted practice by clinicians and regulatory agencies. "Most medicinal products currently used in paediatric patients have not been ~~properly~~ formally developed for the use in this age group…."	We see no need for this addition.
3 paragraph	It would be useful to provide some references or more information for the following statement: "*There have been several examples of*	Not included, too extensive for this guideline text

	medicinal products that have different safety profiles in adults compared with paediatric patients."	
GUIDELINE SECTION TITLE – 2. SCOPE		
	A clear definition of the paediatric populations should be given. Suggest addition of basic table defining categories of paediatric populations, e.g. neonates, infants etc Recommend EMEA propose an appropriate table	It is not considered needed here, but reference to all relevant ICH guidelines has been added under Legal Basis, as there are definitions in relevant ICH guidelines,.
	It could be helpful to specify the upper age of paediatric use for the purposes of this guidance.	Not included, not considered necessary, definition available in other guidelines/legislation
GUIDELINE SECTION TITLE – 3. LEGAL BASIS		
	"…….all relevant CHMP/HMPC guidelines."	Not amended
	This document should be read in conjunction with Directive 2001/83/EC (as amended) and all relevant CHMP Guidelines.	this statement has been amended
GUIDELINE SECTION TITLE – 4. MAIN GUIDELINE TEXT **Section 4.1 General Considerations**		
1st para 3rd sentence	*"At a minimum available results from appropriate repeat dose toxicity studies, the standard battery of genotoxicity tests and a full reproductive test programme should be available prior to the commencement of trials in a paediatric population."* 1. Safety pharmacology testing is part of the standard non-clinical package, and should be specified here. This section suggests that results from a full reproductive toxicology package including embryo/foetal development, male female fertility and pre-and postnatal development studies are required at a minimum before paediatric trials can commence The minimum should be that any data from the reproductive toxicology programme needed to progress the paediatric programme in the age group under study be completed prior to the start of trial. This would also be more consistent with Section 4.3.6. of the document. For example, study in female paediatric subjects that have not reached child bearing age would not require embryo-foetal development or pre- and postnatal development studies	Comment included into the guideline text. Not endorsed

	since these study designs are intended to evaluate the risk of in utero and/or milk exposure. "At a minimum, available results from appropriate repeat dose toxicity studies, the standard battery of genotoxicity tests, **the core safety pharmacology package**, **data from reproductive toxicity studies relevant to the age of the patient populations under study, in a relevant juvenile animal model** should be available prior to the commencement of trials in a paediatric population." *pharmacological effect of the test compound will affect developing organ(s).* should be itemized	
Between 3rd & 4th para	The potential differences in hepatic metabolism and protein binding (etc) as a determining factor of whether bespoke juvenile toxicity studies are required should be sufficiently emphasised. Suggested new paragraph: **Medicinal products with extensive hepatic metabolism will in many cases have different profiles in neonates, juveniles and adults due to the maturation of certain enzyme metabolising systems. Hepatic metabolism will be an important determinant of exposure. Renal clearance and protein binding may also be different between juveniles and adults. Given that age related ADME differences are to a certain extent expected, whether these alone trigger the requirement for juvenile toxicity studies will be dependant on the overall dataset regarding target organs, safety margins and magnitude of exposure difference between adults and the juveniles at administered doses of clinical relevance.**	This comment has been taken into account
4th paragraph, 1st sentence	*"Studies in juvenile animals will usually not be needed for compounds with a well-known use, …etc"* Suggest clarification of what "well known use" refers to: is that in adults or paediatrics? If it is the latter, then whole sentence could be simplified as proposed. Studies in juvenile animals will usually not be needed for compounds	Text removed

	that have been safely used in the paediatric population.	
5th para. 1st sentence	*"This predictability could be high, e.g. in children 2 to 11 years, or low, e.g. in preterm newborns and infants up to 2 years old."* What is the basis for this statement? We are not aware of data suggesting that responses in children between 2-11 years are highly predictable when compared to adult data; data available does suggest, however, that responses are generally predictable for older children (over 12 years of age). Replace sentence by: "**Predictability within the paediatric population can be age dependent, e.g. preterm newborns to 11 years show variability while older children show similarities to adults**." If the sentence is not changed, please provide examples	Wording amended in accordance with comment
Between 5th & 6th paragraphs	It is possible that the paediatric formulation requires the use of a novel excipient. In this case, it is necessary to consider whether additional safety data need to be generated as part of juvenile toxicity studies. Insert: **Consideration should be given to any novel aspects of the intended paediatric formulation and whether additional safety data are required to support the specific formulation.**	Agreed comment included
	The situation of bibliographic applications/authorisation is not addressed in the first paragraph. Does the forth paragraph mean that WEU products are not addressed by the guideline? The term "compounds with well-known use" is not defined in legislation. Does it mean WEU substances?	This comment has been taken into account
	The draft guideline states that "At minimum, available results from repeat dose toxicity studies, the standard battery of genotoxicity tests and a full reproductive toxicity programme should be available prior to the commencement of trials in the paediatric population." In relation to non-clinical reproductive toxicity studies, our experience suggests that the pre-and postnatal study (ICH 4.1.2) is usually the last of the three ICH studies (comprising 'Most Probable Option') to be performed. The conventional pre-and postnatal study does not involve direct treatment of the juvenile population, therefore, it could be argued that, for drugs	

	intended for (or likely to be used in) treatment of juveniles, a juvenile toxicity study is more relevant in the assessment of potential toxicity to the target patient population. In some situations, the absence of a full pre-and postnatal study should not preclude commencement of trials in a paediatric group if precedence has been given to conducting a focused juvenile toxicity study in a relevant species. However, we would support the need for a robust preliminary pre-and postnatal study to provide some information on severe adverse reaction on offspring before commencing pre-clinical studies in juveniles; such a study would be in harmony with the recently finalised US FDA CDER Guidance for Industry: Nonclinical safety evaluation of paediatric drug products (February 2006) which mentions modification of Segment III (equivalent to ICH 4.1.2) as being useful in identifying concerns for post natal toxicity (Section IV.A.). Section V.A of the same guidance document mentions ' Modifications of standard ICH studies designed to address developmental stages C-F would include ensuring adequate exposure in juvenile animals during the postnatal period and assessment of developmental endpoints appropriate for the pediatric population. We would like to see some clarification of the EMEA's view of the value and timing of the pre-and postnatal study.	The guideline has been revised, with a more open wording related to need for reproductive toxicity data, thus the comment has been taken into account
	The conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group. Situations which would justify toxicity studies in juvenile animals include, but are not limited to, findings in non-clinical studies that indicate target organ or systemic toxicity relevant for developing systems, possible effects on growth and/or development in the intended age group or if a pharmacological effect of the test compound will affect developing organ(s).[1)] Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted in order to address a specific	

	concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors. In addition, potential differences between the mature and immature systems for the potential target organs identified should be taken into account, including the consideration whether the end-points investigated are similar and/or relevant for the intended paediatric population. Studies in juvenile animals will usually not be needed for compounds with a well-known use, especially one that has been used for other indications in the paediatric population. The predictability for the paediatric population, based on clinical and nonclinical study results in adults, will be the key issue for the decision on whether studies in juvenile animals are needed prior to the inclusion of paediatric participants onto clinical trials. This predictability could be high, e.g. in children 2 to 11 years, or low, e.g. in preterm newborns and infants up to 2 years old. In conclusion, studies in juvenile animals should be performed on a case-by-case basis and only after a careful consideration of the available data and the age and duration of treatment of the intended paediatric population. 1) Itemization of the description is recommended to avoid confusion and/or mislead resulted from long sentences. 2) In some cases, expression "case-by-case" seems to be meaningless, and supplementation of relevant examples in this paragraph is recommended to lead the applicant to exact goal.	This change was not considered needed, and not in line with usual structure of guidelines.
	A differentiation should be made scientifically between the approach that the paediatric population might show a higher (or lower) sensitivity (direct pharmaco-toxicological effect), and that the development of the juvenile animals will be changed (developmental toxic effects) even after termination of the administration of the compound. This is shortly mentioned in the introduction, but did not return in the guidance elsewhere in the document. The paragraph on compounds with a well-known use might be deleted.	This comment has been taken into account, thus adopted.

	The paragraph on predictability" should mention that the applicant should justify whether studies are not needed.	
1 paragraph	*"At a minimum, available results from appropriate repeat dose toxicity studies, the standard battery of genotoxicity tests and a full reproductive toxicity test programme should be available prior to the commencement of trials in a paediatric population."* Safety pharmacology testing is also part of the standard non-clinical package. *"a full reproductive toxicity test programme"* is understood to comprise the following per ICH guidelines: • Embryo-fetal development study in rats and rabbits • Female fertility and early embryonic development study in rats • Male fertility study in rats • Pre-and post natal development study in rats In some cases, the pediatric development program may precede adult clinical trials, and the reproduction studies may or may not be relevant to the age of the intended pediatric population. For example, for clinical studies in children 2-9 years of age, it would not seem relevant to conduct tests in pregnant or lactating animals. Instead, one may consider fertility assessments as part of the juvenile animal toxicology study, in response to peri-pubertal drug exposure, rather than to perform fertility assessments following treatment of adult animals per standard ICH studies. Thus, the minimum should not be the *"full reproductive toxicity test programme"*, but only those data from the reproductive toxicology programme specifically relevant to the clinical population. This approach would also be more consistent with Section 4.3.6 of the draft guideline. "At minimum, available results from appropriate repeat dose toxicity studies, **core safety pharmacology package**, the standard battery of genotoxicity **data, and reproductive toxicity studies relevant to the age of he patient populations under study** should be available prior to the commencement of trials in a pediatric population."`	Wording revised in accordance with comment
4 paragraph	Presumably *"well known use"* refers to pediatric use specifically. "Studies in juvenile animals will usually not be needed for compounds	Text removed

	that have been safely used for other indications in the paediatric population."	
	It is possible that the paediatric formulation requires the use of a novel exicpient which should be considered. "**Consideration should be given to any novel aspects of the intended paediatric formulation and whether additional data is required to support the specific formulation.**"	Comment taken into account
Bullets	Suggest addition of 2 bullet points • Skeletal system: Development up to adulthood • Organs and / or systems involved in absorption and metabolism of drugs	Comment taken into account
3 paragraph	While we agree, "*If any of the major functional systems are shown* bullet 6 *to be potential targets, either from human or nonclinical studies, juvenile animal studies should be considered."* ; the decision to conduct such studies, however, must be made on a case by case basis taking into account other pertinent information. It is important to avoid recommending juvenile toxicity studies in all cases where major functional organ systems are potentially affected. Organ pathologies are not all equal and changes of little consequence should not trigger the need for a separate juvenile toxicity study. Suggest removing this paragraph because the message is understood from points listed under "Clinical Aspects" (Adult human data, Adverse reactions data) and under "Nonclinical Aspects" (Target organs/tissues identified).	Comment taken into account.
	Section 4.1 refers to pharmacological effects of the test compound in developing organs as a trigger point justifying the need for a juvenile toxicity study. Therefore, section 4.2 could make a general point regarding the varied role of pharmacological endpoints in the decision process to conduct juvenile toxicity studies(e.g., when exaggerated pharmacology in a developing organ is the main concern vs. when there is no reason to associate toxicity with pharmacodymanics).	Comment taken into account.

4.1 4 paragraph	The following statement seems out of place and needs further clarification: *"Studies in juvenile animals will usually not be needed for compounds with a well-known use, especially one that has been used for other indications in the paediatric population."* It is suggested to move this particular statement to the end of the second paragraph. Also further clarify that this applies to compounds approved for use in adults with adequate clinical experience in the paediatric population.	Text removed
4.1 5 paragraph 2 sentence	*"This predictability could be high, e.g. in children 2 to 11 years, or low, e.g. in preterm newborns and infants up to 2 years old."* Perhaps rephrase as "the accuracy of the predication would be higher … or lower …". It would also be useful to include some examples and references.	Text has been rephrased
Section 4.2 Key Elements for the Need for Juvenile Animal Studies		
Structure	Recommend revision of structure for clarity: **4.2 Key elements for the need for Juvenile Animal Studies** **4.2.1 Clinical Aspects** **4.2.2 Non-clinical aspects** **4.2.3 Influence of Pre & post natal reproduction studies**	Slightly modified and taken into account
4.2 Nonclinical Aspects, bullet 5	*"Pharmacokinetic data show exposure of organs with significant postnatal development"* is too non-specific, but it could be helpful to note consideration of age-dependent pharmacokinetics and metabolism. **"Pharmacokinetics and metabolism in light of potential age-dependent differences."**	Taken into account.
4.2 Nonclinical Aspects, bullet 5	*"Pharmacokinetic data show exposure of organs with significant postnatal development"* is too non-specific, but it could be helpful to note consideration of age-dependent pharmacokinetics and metabolism. **"Pharmacokinetics and metabolism in light of potential age-dependent differences."**	Taken into account.
Bullets	Insert additional bullet point: **Skeletal system: Development up to adulthood**	Comment taken into account
1st sentence,	It is important that consideration is given to the development of systems	Comment taken into account

1st paragraph	involved in ADME of drugs. Insert new sentence after 1st sentence: **It should also be remembered that in humans, the maturation of certain ADME functions may take up to 2 years.**	
3rd paragraph	*"If any of the major functional systems are shown to be potential targets, either from human or from non-clinical studies, studies in juvenile animals should be considered."* Current use of "should be considered" could be misconstrued as meaning "should be done" . Juvenile toxicity studies are not justified in all cases merely because the major organ systems listed are target organs in adults animals or humans. Suggest rewording "should be considered **on a case by case basis"**	Comment taken into account
4.2 Clinical aspects And Preclinical aspects	In principle it is considered useful to provide greater guidance on which aspects may increase of decrease the requirement for juvenile toxicity studies, recommend bullet point lists are made modified as indicated, to provide direction in decision making. Text provided is intended as an example and does not match every bullet point in the draft guideline. Clinical aspects which increase requirement for juvenile animal studies: • Medicinal product for diseases predominantly / exclusively affecting paediatric patients • Increased duration of paediatric treatment • Decreased age of paediatric population • Primary PD target in organs systems with significant post-natal development • First in class etc Clinical aspects which decrease requirement for juvenile animal studies: • Medicinal product intended to treat serious or life-threatening	These comments have been taken into consideration, by restructuring the bullet points above but not by specifying by increased/decreased concern.

	paediatriac diseases • Extensive adult safety and efficacy data etc Non-clinical aspects which increase requirement for juvenile animal studies • Adverse and / or irreversible effects in target organs with significant post-natal development • Low safety margins for serious or irreversible effects in adult animal studies in relation to adult human exposure etc Non-clinical aspects which decrease requirement for juvenile animal studies • Extensive safety data from existing animal studies • Pre & post natal studies show sufficient exposure of pre-weaning animals • Juvenile animal data from a medicinal product of a similar chemical structure and / or the same pharmacological class etc	
Nonclinical aspects bullet 6	"*Pre- and postnatal toxicity studies show sufficient exposure of the pre-weaning animals*". Clarify what is meant by "sufficient" exposure. These data will only be relevant relative to the intended therapeutic concentration. Pre- and postnatal toxicity studies show sufficient exposure of the pre-weaning animals **vs the expected therapeutic concentration**	Comment taken into account
New section 4.2.3	See later comments, in section 4.3.6, which state that the content of the section "pre- and postnatal reproduction" refer to considerations which occur prior to the decision to conduct juvenile animal toxicity studies. Therefore these comment should be presented here, i.e. earlier in the guideline. **Move section "Influence of Pre & post natal reproduction studies" to here**	Comment taken into account
	4.2 Key Elements for the Need for Juvenile Animal Studies Major functional differences exist between human neonates/infants and	

	adults. The development of the major systems[1)] is age dependent, e.g.: • Nervous system: Development up to adulthood • Reproductive system: Development up to adulthood • Pulmonary system: Development up to two years old • Immune system: Development up to 12 years old • Renal system: Development up to one year of age It should be appreciated that the age ranges given above only apply to general development and not applicable to all endpoints related to that organ system. This should be taken into account in the design of the program and the individual studies. If any of the major functional systems are shown to be potential targets, either from human or from nonclinical studies, studies in juvenile animals should be considered. The following points should be considered when assessing the need for and design of juvenile animal studies. It should be noted that this is not an exhaustive list and the points are not ranked in order of importance. 1) As the major system, musculoskeletal and gastrointestinal systems should be added in the list to be consistent with the descriptions at later chapters 4.3.1 and 4.3.6. To objectivize, relevant references may need to be cited.	Organs have been added. The inclusion of references is not agreed as it might reduce relevant literature search by the sponsors.
	To be added: liver: biotransformation (a.o.CYP450) enzymes: Development up to 6 months and in some cases up to one year of age.	Comment taken into account
	Include a table of the paediatric age groups (noting that other criteria may be used) or refer to those defined elsewhere.	Not considered necessary, definition available in other guidelines/legislation
Section 4.3 Study Design **4.3.1 Duration**		
1st paragraph	Duration & age of animals at initiation of study: this section would benefit from greater guidance. Add tables giving broad guidelines of major organ developments ages comparing rat, dog & human For consistency it is proposed EMEA consider tables currently in the	Not endorsed. The inclusion of such information / references is not agreed as it might reduce relevant literature search by the sponsors.

	FDA guideline.	
1st paragraph	Duration of treatment of the intended paediatric population should be considered when selecting the duration of dosing in juvenile animals. Modify sentence to: "The duration of the dosing period in juvenile animal studies, and the age of the animals at the initiation of dosing, will depend the age and **the duration of exposure** of the intended paediatric population, taking into consideration the developing organ system(s) that are likely to be affected by the medicinal product."	Comment taken into account
2nd paragraph	"*When adverse reactions are expected on systems with a long development period, e.g. brain development, bone growth, immune function etc, animals should be investigated up to reaching adulthood (approximately up to 13 weeks in rats and 9 months in Beagle dogs).*" The proposed text change represents wording, consistent with the intent of the guidance (e.g., evaluate the developing system during the period in which it has not been fully evaluated in standard safety studies). "When adverse reaction are expected on systems with a long treatment period, e.g. brain development, bone growth, immune function etc. animals should be investigated up to **at minimum, the age of the animal in which standard toxicology studies specifically address the potential action on the system in question. The decision on study duration should be scientifically justified.**"	We do not agree. It may be important to follow effects that may have been induced early but are not expressed until adulthood.
	We consider that the juvenile toxicity study should be used as a bridge between treatment of animals as newborns or juveniles and the conventional start of rodent toxicity studies at about 6 weeks of age. It should not be necessary to continue direct treatment for a prolonged period of time, although monitoring of normal development/recovery following the cessation of treatment may be necessary to track the significance of changes which may be induced by treatment during the early development of organ systems. It may also be necessary to continue the study for long enough to assess reproductive function in animals exposed to the test material as juveniles.	This has been addressed in the revised guideline
	The duration of the dosing period in juvenile animal studies, and the age of the animals at the initiation of dosing, will depend on the developing	

	organ system(s) that are likely to be affected by the medicinal product, taking the age of the intended paediatric population into consideration. When adverse reactions are expected on systems with a long development period, e.g. brain development, bone growth, immune function etc, animals should be investigated up to reaching adulthood (approximately up to 13 weeks in rats and 9 months in Beagle dogs). [2,3)] When adverse reactions are expected only in an organ system with a relatively short critical period of development (e.g. kidneys, lungs), then the study might be confined to that particular period of development. 1) This title should be "Duration and Age", because the major subjects in this chapter are these two factors, and in addition age is one of the essential factors to be considered in juvenile animal study design. 2) Like in adult animal studies, the duration of dosing period in juvenile animal studies should be delineated in conjunction with that of clinical study in this paragraph. 3) We would like to recommend a supplemental description of the period that each of individual organs reach their maximal development with citation of supportive references.	1) Endorsed 2) revised to take comment into account 3) not endorsed,
	The paragraph does not only discuss the duration of a study, but also the time point of initiation of a study. This is, however, not very explicit, and better guidance might be given.	Covered by the first paragraph
4.3.1 1st paragraph	Duration of treatment in the pediatric population should be considered when selecting the duration of dosing in juvenile animals "The duration of the dosing period in juvenile animal studies, and the age of the animals at the initiation of dosing, will depend on the developing organ system(s) that are likely to be affected by the medicinal product, taking the age and **the duration of exposure** of the intended paediatric population into consideration."	Comment taken into account
4.3.1	It may be helpful to note that maturation endpoints are sometimes investigated as the animal reaches adulthood even when treatment duration is limited to a younger age range.	Not endorsed

4.3.3 Species	Because timing of postnatal development varies markedly across species and organs, it can be a key factor in species selection. "Factors that need to be considered **… and comparative developmental status of organs of concern."**	Comment taken into account
4.3.4 PK/TK 3 paragraph	*"Such detailed data [ADME] will only be necessary if (based on in vitro data, scientific rationale etc) it is anticipated that the pharmacokinetic and toxicokinetic characteristics of the juvenile animal model(s) are comparable to the human situation at the stage of development so that the data can be used in efficacy and/or safety evaluation."* This could be misinterpreted to literally mean extra data is needed when animal model(s) show good PK comparability to humans, when in fact such additional characterization might only be helpful when it has not been possible to attain clinically-relevant systemic exposure in animals. "Such detailed data will only be necessary if **systemic exposure the juvenile animal model(s) is inadequate relative to the human situation at the stage of development."**	The purpose of this paragraph is slightly different than indicated in the comment. The paragraph has been revised
4.3.5 , 1st paragraph	*"The primary purpose of juvenile animal studies is to assess whether young animals are more sensitive to a reaction of a medicinal product than adult animals, and to identify reactions on developing organs."* "The primary purpose of juvenile animal studies is to assess whether young animals **react differently to** a medicinal product **compared to** adult animals, and to identify reactions on developing organs."(young animals may be less sensitive and therefore a nonclinical toxicity might be less concerning for the clinical studies)	Comment taken into account
4.3.5 , 1st paragraph	In the interest of reducing the numbers of animals used in toxicology testing, we appreciate the recognition that an intermediate dose might not be necessary in some cases.	Comment noted
4.3.5 , 2nd paragraph	Comparability depends on exposure rather than administered dose "Moreover, in order to bridge the juvenile animal data to the existing adult animal data, a **dose with comparable systemic exposure**, **…"**	Comment taken into account

4.3.6 Endpoints	In selected cases, endpoints of pharmacological activity in juvenile animals could be relevant.	Comment taken into account
4.3.6	*"To differentiate long-term effects on developmental organs from acute effects, it might be appropriate to measure certain endpoints immediately before the first administration of the medicinal product."* That would not provide testing at the same age, and it does not address the salient question of whether a postnatal developmental toxicity is the result of acute or extended exposure. "Juvenile animal studies often include dosing over the greater proportion of the species' postnatal development, and when effects are identified, additional studies may be useful to test if the toxicity can or cannot be produced with more acute treatment, when clinically relevant."	Accepted.
4.3.6 Neurotoxicity Assessment	*"… cause for concern for … neuroendocrine system balance."* is unclear as a "trigger." It is suggested this could be omitted here and covered in the context of the organs potentially affected, e.g., concern for adrenal, thyroid or reproductive organ toxicities.	This comment is not agreed. No change.
4.3.6. Immunotoxicity Assessment 3rd paragraph	The suggestion that an immunotoxicity study should include functional assays such as T-cell dependent antibody response, host resistance and cell-mediated immunity creates the need for an extremely comprehensive evaluation that might not be warranted. It would be more appropriate to use a tiered approach that is similar to what is typically done for adult animals (re ICHS8). "Histopathology should be included as well as function assays, **which should be conducted on a case-by-case basis according to a tiered approach.**"	Comment taken into account – reference to ICH S8 has been made.
4.3.6. Immunotoxicity Assessment 3rd paragraph	*"A study should be based on immune assays already validated, …"* Some immunological assays are considered useful but may not be "validated" by everyone's definition. "A study should be based on immune assays **already accepted for use in adult animal toxicology studies.**"	Comment taken into account

4.3.2 Route of Administration		
1st paragraph	The draft guideline provides the opportunity to use alternate routes of administration than the preferred clinical route as long as differences in exposure and distribution between the clinical route and alternate route are small. Simply stating that a "small difference is acceptable" does not allow for a clear decision path. It is recommended that more discussion on decision-making parameters is added in the final guideline.	Paragraph has been reworded.
	Although this section covers practical difficulties of some routes of administration it is suggested that the phrase ".. small differences in exposure and distribution due to route may be of little significance." could be modified to "…the relevance of small differences in exposure and distribution due to route should be consider in the context of this objective".	Paragraph has been reworded.
4.3.3 Species		
	Other important factors for consideration in the selection of the appropriate species are comparative developmental status of major organs of concern and species sensitivity to a particular toxicity. Guidance on comparative developmental timing correlates for human (infant), rat, and dog would be appreciated. As an alternative, provide appropriate references. Modify sentence to: "Factors that need to be considered when choosing the appropriate species include the pharmacodynamic, pharmacokinetic and toxicological properties of the medicinal product, **comparative developmental status of the major organs of concern between juvenile animals and paediatric patients, sensitivity of the species,** and the feasibility of conducting the study".	The inclusion of such information / references is not agreed as it might reduce relevant literature search by the sponsors Comment taken into account
	The juvenile animal species should be appropriate for evaluating toxicity in endpoints relevant for the intended paediatric population. With respect to repeat dose toxicity studies, rats and dogs are	

	traditionally the species of first choice. However, other species might be more appropriate in some instances.[1] Factors that need to be considered when choosing the appropriate species include the pharmacodynamic, pharmacokinetic and toxicological properties of the medicinal product and the feasibility of conducting the study. Testing of juvenile toxicity in one appropriate species using both sexes will normally be sufficient. 1) Exemplifying specific animal species would be requested.	That is such case by case decision, and will not be stated in the guideline.
4.3.4 Pharmacokinetics & Toxicokinetics		
	Section title does not mention ADME Suggest new 1st sentence to provide context. Suggest simplification of paragraphs and clarification that "population" sparse sampling methods are acceptable for TK purposes i) Amend title to: **Pharmacokinetics, Toxicokinetics and ADME** ii) New 1st sentence: "**Kinetic and ADME data can be used to support the relevance of the animal model for risk assessment**. iii) Amend 3rd sentence in 1st paragraph. "The use of methodology allowing population **pharmacokinetic / toxicokinetic** determinations may also be considered to confirm appropriate exposure levels in different treatment groups." Delete 2nd paragraph because now included in above sentence.	i) Partly taken into account ii) Not endorsed, not necessary iii) Not endorsed, as not fully agreed
	It is difficult to visualise what "… *in vitro* data …" would be a useful adjunct to determining the need for ADME investigations in the juvenile animal model. Could this be clarified? It is recognised that collection of blood samples in juvenile animals for	A sentence has been added addressing this comment.

	the purpose of toxicokinetic profiling is sometimes impractical; however, it is important to perform good toxicokinetic investigations in directly comparable animals in order to establish the relative toxicity of the test material when administered to juvenile animals in comparison with adults. It is generally possible to use satellite animals and/or build into a study provision to use excess offspring to provide individual or pooled samples, even from young rodents. Investigators should not be discouraged from considering this possibility when designing either a preliminary or main study in juvenile animals, particularly as possible inclusion of satellite animals for assessment of reversibility of potential long-term effects is mentioned in Section 4.3.6. (Endpoints).	
4.3.5 Dose Selection		
3rd paragraph, 2nd sentence	"Therefore, the high dose should be selected such that frank toxicity does not occur and it is recommended that doses in the lower part of the dose response curve established in adult animals are selected." We agree that dose levels should be selected based on exposure considerations because paediatric doses can be greater than doses given to adults in terms of mg/kg to reach optimum exposure and efficacy (growth hormones, for example). Choice of dose levels in juvenile animals should represent reasonable multiples of the expected exposure(s) in the paediatric therapeutic range. Frank toxicity is an ambiguous term, and further guidance is required in this respect, a revision is proposed. "Therefore, **dose levels** should **represent reasonable multiples of the expected exposure(s) in the paediatric therapeutic range, and where possible the high dose should achieve some identifiable toxicity (e.g. small reduction in body weight gain).**"	The term frank toxicity has been reworded.
	The draft guideline states that "…the high dose should be selected such that frank toxicity does not occur…". We are pleased to see that in its finalised Guidance for Industry	

	(February 2006), the US FDA CDER has dropped its requirement that the high dose should produce frank toxicity in favour of establishment of a clear dose-response relationship for adverse effects in juvenile animals. The criteria for the high dose is now '… identifiable toxicity …' and we feel this goes a long way to addressing serious concerns over the definition of 'frank toxicity' and removes much of the apparent inconsistency between the two approaches.	Comment noted
	The primary purpose of juvenile animal studies is to assess whether young [1)] animals are more sensitive to a reaction of a medicinal product than adult animals, and to identify reactions on developing organs. Therefore, the high dose should be selected such that frank toxicity does not occur [2)] and it is recommended that doses in the lower part of the dose response curve established in adult animals are selected. The low dose should preferably result in exposure levels similar to the anticipated clinical exposure in the intended population. An intermediate dose level might not be necessary in juvenile animal studies if the differences between the low and high doses are relatively small. Moreover, in order to bridge the juvenile animal data to the existing adult animal data, a common dose, preferably in the low dose range (NOAEL or NOEL [3)]), should generally be included in the juvenile animal studies. In the absence of a NOAEL in the general toxicology studies, a dose range finding study in juvenile animals is advocated together with toxicokinetic evaluations to support dose selection. 1) If "young" is used as a synonym for the "juvenile", it should be replaced with the latter word to avoid confusion. 2) This sentence should read "a high dose should be included in testing doses such that identifiable toxicity would be expected to occur". 3) "NOEL" should be deleted, because nowadays it seems no longer available in any region of the world.	We still see a use of this term, and have therefore kept it.
	The sentence starting with "Moreover….." is a repetition of what has been stated in the first paragraph of this section. The sentence might be deleted.	It is not agreed that this is a pure repetition of previous wording, and therefore it is kept.

4.3.6 Endpoints		
Structure	Recommend revision of structure for clarity 4.3.6 Endpoints 4.3.6.1 Reproductive system toxicity assessment 4.3.6.2 Neurotoxicity assessment 4.3.6.3 Immunotoxicity assessment 4.3.6.4 Skeletal system toxicity assessment Describe the additional endpoints which are required when the skeletal system is a predicted target organ. 4.3.6.5 Nephrotoxicity assessment	Some rewording of the section has been made, but comment not taken fully into account
1st paragraph, 2nd & 3rd sentences	*"Studies should be designed to determine medicinal product reactions on the overall growth of the organ systems that develop post-natally etc"* This statement infers a more generic study design covering the growth pattern of ALL the major organ systems rather than the bespoke design described in 4.3.1 *"Studies should include, at a minimum, measurement of growth (e.g. serial measurements of crown-rump length, tibia length, growth velocity per unit time, or other appropriate indices), external indices of sexual maturation, body weight, physical signs, organ weights, and gross and microscopic examination.* Depending on study duration and expected target organs, body weight and terminal measurement of tibial length to be sufficient to detect effects on growth. More detailed and frequent assessment of crown-rump length and tibial length should be included on a case-by case basis where effects on skeletal growth are a specific concern Studies should be designed to determine **the toxic effects of the** medicinal product on the overall growth **and function** of the organ systems **of specific concern.** At a minimum, **studies should include** measurement of growth **(body weight and terminal tibial length)**,	Paragraph reworded.

	external indices of sexual maturation, physical signs. **Other endpoints for organ systems of specific concern such as** organ weights, gross and microscopic examinations, and functional effects, **should be included if an organ system of concern is considered to be at increased risk for toxicity based on the stage of development in the intended clinical population.**	These examples have been taken out.
New section 4.3.6.1	Move "*Should histopathological effects occur in male and / or female reproductive organs, than the functional consequence of this finding should be investigated"* from 3rd paragraph section 4.3.6 to new section 4.3.6.1 Reproductive system toxicity assessment **Should histopathological effects occur in male and / or female reproductive organs, then the functional consequence of this finding should be investigated**	No new section has been added, and therefore the wording has not been taken into account
Pre- & Post Natal	The information provided in this section describes considerations which should be taken into account whilst assessing the need for specific juvenile toxicity studies. It would be better placed in section 4.2, Key elements for the need for juvenile animal studies, specifically in the newly proposed section 4.2.3 **Delete this section, and move to section 4.2, specifically the newly proposed section of 4.2.3.**	Reworded according to comment
Immuno-toxicity	A study should be based on immune assays *"already validated"* Some immunological assays are considered useful and are accepted for use but may not have been internationally "validated" *"Histopathology should be included as well as functional assays such as T-Cell dependent antibody response, host resistance assay and cell-mediated immune assay"* This sentence creates the need for an extremely comprehensive evaluation that may result in evaluating unnecessary endpoints. It is recommended that the ICH S8 guideline is followed. A study should be based on immune assays **already accepted for use in adult animals.** Histopathology should be included as well as function assays, **which should be conducted according to the weight of evidence approach described in the immunotoxicology guideline (ICH S8).**	Reworded according to comment

	Paragraph 4 states that "To differentiate long-term effects on developmental organs from acute effects, it might be appropriate to measure certain endpoints immediately before the first administration of the medicinal product." We respectfully point out that this sentence is confusing as it not clear whether " … immediately before the first administration … " refers to the start of the treatment period as a whole (i.e. first day of dosing) or it refers to pre-dose versus post-dose status (e.g. progression of clinical signs, routine haematology, blood chemistry, etc.). We suggest that this paragraph should be revised to give clearer guidance on the recommended chronology of endpoints. Many endpoints which can be assessed in older animals are not practical in the juvenile animal at Day 7, or younger, of age.	Wording has been revised
	The selection of endpoints to be monitored in a juvenile animal study is critical for assessing the reactions of a medicinal product on development and growth. Studies should be designed to determine medicinal product reactions on the overall growth of the organ systems that develop postnatally (e.g., skeletal, renal, lung, neurological, immunologic and reproductive systems). Studies should[1)] include, at a minimum, measurement of growth (e.g., serial measurements of crown-rump length, tibia length, growth velocity per unit time, or other appropriate indices), external indices of sexual maturation, body weight, physical signs, organ weights, and gross and microscopic examinations.[2,3)] Clinical pathology determinations can also be useful, but they may be limited by the technical feasibility of obtaining adequate samples for analysis, particularly in the case of juvenile rodents. Should histopathological effects occur in male and/or female reproductive organs, then the functional consequence of this finding should be investigated.[4)]	

	To differentiate long-term effects on developmental organs from acute effects, it might be appropriate to measure certain endpoints immediately before the first administration of the medicinal product. [5)] The use of in vitro models using juvenile animal tissue or specific disease models in juvenile animals could also be considered to study target organ toxicity. [6)] The inclusion of satellite groups of animals to study the reversibility or long-term consequences of potential adverse reactions should be considered. 1) The measurement items should be optional, because the study design in juvenile animals will vary depending on their target organ toxicity and other factors. Therefore, "Studies should include" would read "It is recommended that studies include". 2) It is important to add body weight as a measurement item. 3) We recommend to add specific itemizations for the "external indices" and "physical signs". 4) Since it is well recognized that the histopathological examination shows more detectability as compared to functional evaluation in toxicological assessment, "is recommended to investigate" is more suitable in the context of this guideline. 5) Should there be specific examples, supplementation of them with references in this paragraph is recommended to facilitate planning of the study. 6) This paragraph should be deleted , because there seems to be no validated model , which hampers maintaining the study in compliance with GLP resimen. Or This should be supported by some examples of specific studies.	1) not agreed 2) included 3) not agreed 4) not endorsed 5) sentence deleted 6) a possibility, to be used on a case by case basis if relevant models available; GLP does not exclude the possibility to mention in guideline
	Pre- and Postnatal Reproduction Studies Before performing a juvenile animal toxicity study, it should be considered whether a developmental toxicity issue could be addressed in a modified pre- and postnatal development study in rats. Key factors that need to be examined include, but are not restricted to, the amount of the active substance and/or relevant metabolites excreted via the milk	

	and resulting plasma exposure of the pups, which organs under development that will be exposed during the pre-weaning period, physical development[2)] and histopathological investigations. [1)] When a pre- and postnatal study is also being used to address a specific aspect of juvenile toxicity, such a study should be extended to include appropriate developmental endpoints. If specific developmental endpoints cannot be assessed within the context of pre- and postnatal studies, additional juvenile animal studies will be required. 1) Itemized description would be preferable to avoid confusion and/or mislead resulted from long sentences. 2) "Physical development" seems to be the synonym for the "physical signs". If this is the case, the same wording is recommended to avoid confusion or further explanation.	1) Not considered necessary 2) Not agreed
	Neurotoxicity Assessment Neurotoxicity studies are only required if the chemical/pharmacological class of compound or previous studies in humans or animals gives cause for concern for the developing nervous system or influences for neuroendocrine system balance. For developmental neurotoxicity assessments, where possible validated methods[1] should be used to monitor key functional domains of the central nervous system, including, but not restricted to, assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, and learning and memory. 1) It is recommended that specific methods are inserted as examples (water-maze, open-field FOB and others).	Not agreed
	Immunotoxicity Assessment Immunotoxicity studies are only required if the chemical/pharmacological class of compound or previous studies in humans or animals gives cause for concern for the developing immune system.	

	Pre- and postnatal exposure can potentially result in all types of immunotoxicity in the offspring, e.g. immune suppression, hypersensitivity, allergy and autoimmune disease.[1] A study should be based on immune assays already validated, but the experimental design should be flexible. Histopathology should be included as well as functional assays such as T-cell dependent antibody response, host resistance assay and cell-mediated immune assay. This paragraph should be deleted: this seems incompatible with the immediate foregoing paragraph and furthermore the definition of the period "pre- and postnatal exposure" is too extended and vague.	Agreed
	Clinical "*pathology*" should be: Clinical chemistry. Histopathological effects are mentioned in the next line. The sentence on "*To differentiate long-term effects on developmental organs from acute effects, it might be appropriate to measure certain endpoints immediately before the first administration of the drug*" is not fully clear. On the one hand these endpoint should be measured then also after the first administration, but in that case the sentence is redundant. On the other hand apparently it is needed to differentiate between long-term effects and acute toxic effects. It might be sufficient just to mention this, instead of giving a solution that is not clear. Pre- and postnatal reproduction toxicity studies. This paragraph apparently is meant to bridge the gap between the reproduction toxicity studies (S5A and B) and the juvenile toxicity studies, also with respect to determination of exposure. It is not fully clear what the guidance is when the exposure via the milk is too low, and whether or not the drug under study should be given in addition to the milk gift, etc. (GW). Neurotoxicity assessment The inclusion of social behaviour (playing behaviour in the post-weaning period) should be considered. Immunotoxicity Assessment From an immunotoxicological point of view the approach is acceptable.	Covered by the first paragraph, and more detailed guidance is not considered appropriate in a guideline. Accepted

	As with the discussion on the ICH guidance document immunotoxicity studies are only required if causes for concern are present. We agree.	
1 paragraph Schering-Plough	The standard measurements of growth should be clarified and are also dependent on the animal model used. In the rat, this should be body weight. The ICH guidance on the "Detection of Toxicity To Reproduction for Medicinal Products" (ICH 5a) discusses pre- and postnatal developmental toxicity studies which includes neonatal evaluations from birth to sexual maturity (Stages E and F of the reproductive process). These guidances indicates that neonatal body weight is the "best indicator of physical development" (Section 4.1.2., Note 21).	All examples have been taken out.
Section 4.4 Timing of Toxicological Studies in Relation to Clinical Development		
Paragraph 2	*"Studies in juvenile animal, if considered necessary, should be available before the initiation of trials in paediatric populations."* In many cases, a single dose pharmacokinetic studies in children can be safely conducted based on existing adult animal & human data. *"Pharmacokinetic data should also be evaluated before the proposed paediatric clinical trials(s)"* This sentence is ambiguous, alternative wording is proposed	Not agreed for inclusion in this guideline, awaiting ICH M3 Pharmacokinetic data **from humans and animals (including juvenile animals if performed)** should also be evaluated before the proposed paediatric clinical trial(s)" agreed
4.4 2nd paragraph	**"Studies in juvenile animal, if considered necessary, should be available before the initiation of trials in *paediatric populations."*** In many cases, a single dose pharmacokinetic studies in children can be safely conducted based on existing adult animal & human data. "Studies in juvenile animals, if considered necessary, should be available before the initiation **of multiple dose efficacy and safety** trials in paediatric populations."	Not agreed