25 April 2017
EMA/256626/2017 Corr.*

Overview of comments received by EMA on the draft Addendum of the 'ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population' (EMA/CPMP/ICH/2711/1999)

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

Stakeholder no.	Name of organisation or individual
1	Denise Sturdy on behalf of Duke Clinical Research Institute
2	Les Laboratoires Servier
3	EFPIA
4	Neonatal and Paediatric Pharmacists Group (NPPG), submitted by Anna Burgess, NPPG Information Officer
5	ACRO (Association of Clinical Research Organizations)
6	Apotex Inc.
7	Professor Dr. med. Karin Kraft (President), Gesellschaft für Phytotherapie e.V. (GPT)
8	Dr. Ian M. Vasicka, M.D, EUCROF - Paediatric Working Group
9	TEDDY European Network of Excellence for Paediatric Clinical Research
10	Dr. Martine Dehlinger-Kremer, European CRO Federation, EUCROF
11	Prof. Dick Tibboel, Chair of section Pharmacology of ESPNIC, Dr. Paula Pokorna, Vice Chair of section Pharmacology of ESPNIC, Prof. Karel Allegaert, Neonatologist / Clinical Pharmacologist, Prof. John van den Anker, Neonatologist / Clinical Pharmacologist, Section Pharmacology of ESPNIC and Intensive Care Erasmus MC – Sophia Children's Hospital
12	International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium)

Please note that comments will be sent to the **ICH E11 EWG** for consideration in the context of Step 3 of the ICH process.

* New comments received added

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1. General comments – overview

Stakeholder no.	General comment (if any)
1	The document only very briefly mentions the potential utility of biomarkers, without expanding on any recommendations about biomarkers, e.g., their validity. Guidance on this topic would be beneficial as the use of biomarkers is an increasingly significant part of clinical investigations. guidance on this topic.
3	EFPIA welcome the revision of the ICHE11 guideline. We have identified the following main issues that would warrant more discussion and/or clarification: • **Paediatric oncology:** it is suggested to add some introductory wording to highlight that approaches to paediatric research may differ between therapeutic areas (e.g. for oncology). This will broaden the document's applicability to these patients (i.e., paediatric oncology patients: bigger differences in disease manifestation in paediatric subpopulations versus adults in certain cancers or combination therapy approach often used). • **Planning of paediatric development:** In section 5 the guideline states that planning a drug development program for children should not start when the adult program finishes. But it doesn't give general guidance of when the paediatric program could begin. Some further clarification of the timing of paediatric development would be helpful. • **Extrapolation and labelling:** the guidance speaks of extrapolation in various ways. There may be instances in which labelling in paediatrics can be supported by extrapolation on PK only. If this is the case, it would be helpful for further guidance on the types of data that would enable such a scenario • **Extrapolation between adults and children:** It would be helpful to have further guidance or examples of the appropriateness of assuming translatable disease state and/or drug disposition between adults and children since these assumptions set the basis for study design and the registration approach. • **MID3/Modelling & Simulation:** The current draft addendum is too high level with respect to the use of extrapolation /modelling and simulation (section 5.1.2) and doesn't contain technical details or context. In order to provide the necessary context and background with respect to which M&S approaches to consider, the current addendum should therefore refer to the MID3 (Model-Informed Drug Discovery and Development) framework and the associated publication on good practices. These practices point out how the M&S approach should be detailed (assumptions /sensitivity analysis), linked in cycles of learning & confirming and documented (plans/reports) to inform both extrapolation and decision-making in paediatric development.

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	Examples of application of MID3 framework to paediatric development are also provided in the supporting documentation of the publication and in associated presentations at EMA paediatric extrapolation workshop: *Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation. The EFPIA MID3 Workgroup. CPT: Pharmacometrics & Systems Pharmacology. March 2016* http://onlinelibrary.wiley.com/doi/10.1002/psp4.12049/full • **M&S section using a question format:** It would help if the section was also using a question format similar to the one used for extrapolation; this would ensure consistency in approaches. • **Developing future ICH guidelines:** EFPIA would welcome the drafting of a specific guideline that could provide more technical guidance, e.g. on extrapolation, on MID3 and on paediatric formulations. In addition, EFPIA have specific comments on the text as detailed in section 2 below.
4	The ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population is a welcomed contribution towards supporting the industry in developing medicines for children. The Neonatal and Paediatric Pharmacy Group (NPPG) welcomes the opportunity to respond to the public consultation and supports the development of this addendum in light of advances in paediatric drug development. NPPG supports the publication of these guidelines. Consideration has been given to the practical barriers regarding the difficulties of setting up and recruiting participants in paediatric clinical trials, including the importance of palatability, risk of excipients, ethical issues, and cultural differences.
5	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre- clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world, including 57,000 in Europe, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft ICH E11 Addendum on clinical investigation of medicinal products in the paediatric

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	population. ACRO considers this to be a comprehensive and well-considered document that provides high level guidance on the implementation of important approaches in paediatric drug development. In particular, ACRO welcomes: • The acknowledgement that a common scientific approach, not common regional requirements, is at the cornerstone of efficient paediatric drug development and timely delivery of safe and effective medicines for children. • The recognition that extrapolation and modeling and simulation techniques have a role to play in minimising both the exposure of paediatric populations to clinical trials and the risks to individuals of trial participation, and guidance on the establishment of appropriate frameworks for the use of these techniques. • The acknowledgement that maturity, and not chronological age, serves better as an adequate categorical determinant to define developmental subgroups in paediatric studies. Additionally, ACRO recommends that, with regard to maturity, it would be useful for the guideline to make a clear distinction between physiological maturity as a determinant to define developmental subgroups (as noted in the draft guideline) and mental maturity/competency, again rather than chronological age, as a determinant of the appropriate materials to be used to obtain the assent of trial participants. ACRO recognizes, however, that the replacement of age groups with levels of maturity would be more difficult to determine and there would need to be a mechanism for consistent assessment of this across investigators in any individual clinical trial. Because the draft guideline issued for comment by the European Medicines Agency (EMA) was reformatted from the original ICH draft -- resulting in changes to the line numbers -- ACRO has included both the “ICH” (meaning the original ICH draft guideline) line numbers and the “EMA” (meaning the reformatted document published by the EMA) line numbers so that ACRO’s comments may be linked back to either draft document.
7	We appreciate the intension to create an addendum to the current ICH-E11-guideline, particularly the enhancement of the topic *Extrapolation* (line 59 and chapter 5.1.1.). In consequence from this extrapolation idea in general, we suggest to consider a NIS-based extrapolation-approach as one out of several design options. For details, see below.
9	The relevance of this addendum to update and complement the original document is acknowledged, because of scientific, technological, ethical and regulatory advancements. Specific guidance documents focused on each mentioned aspects are also relevant and should be read in conjunction with the proposed addendum.

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11	I miss guidance on 'perceived needs' within the pediatric population. I miss a focused text on pharmacological product development for 'pediatric diseases', including re-purposing, but perhaps this is out of scope for this exercise ? Overall ? What's our main concern as academia ? If we try to have a look to all failed (and about the fail) FP7 programs, why do they fail ? It seems that recruitment is the major issue, and the need for valid biomarkers in my opinion. What's our opinion on how to solve this and how this 'document' can be helpful to do this ? Recruitment (6.1. feasibility related) Can this be solved by 'pediatric trial center' building capacity (cf IMI), perhaps, but pragmatic approaches are needed (eg success of neurosis study) Valid biomarkers (6.2. outcome related) Is this an academic task that should be stimulated ? There is a need for the option of extrapolation for drugs with a clear PD marker and proven equal mechanism of action in adults and children. Important is a more structured communication between EMA and FDA to prevent doublures. This is important that in case of multicentre studies approval by the IRB of the lead PI is also accepted by other centres without extensive re-evaluation by other IRB's of other institutions. Under some circumstances the usual approach to divide the patients in age classifications starting from 12-18 years. In this way reaching the youngest age groups usually takes 5-10 years which is not of benefit for the most vulnerable children, including newborns.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
41	3	'*the foreseeable risks to which a paediatric participant would be exposed must be low*' **Comments:** Legal and ethical frameworks might differ across countries where the trails are conducted. In addition, special considerations must be met with regard to risk in paediatric studies. These often require a discussion between the regulatory agency and the sponsor. The wording should be flexible to allow these special considerations. **Proposed change:** the foreseeable risks to which a paediatric participant would be exposed ~~must~~ ***should be*** low
42-65	8	**Comments:** Scope and objective of the ICH E11 guideline addendum (R1) The purpose of this document is to serve as a supplement to the ICH E11 Guideline established in 2000 and as stated is not meant to alter the original guidelines but simply to update in light of new developments with pediatric drug research within the past 16 years, including a discussion on a common scientific approach taking into consideration various regional and national settings as well their respective regulatory agencies, i.e. the document should be a harmonized addendum which is supplemental in nature and up to date. Concepts such as extrapolation of data across pediatric and adult populations as well as modeling and simulation (M+S) are also given consideration; however, should be carefully applied since significant differences in medical physiology exist among various ages, genetic backgrounds, heights and weights, etc. i.e."A child is not a little man." The same applies to modeling as data from a model must be carefully interpreted since what is found might not always apply in-vivo, given the many variables-metabolic, pharmacodynamic, pharmacokinetic, genetic, environmental , psychological that can have an a signifcant effect in children. In general, the aims of the addendum to serve as an update to the original document are clearly stated and an important development given the many technological, scientific developments of the human genome, genetic analysis, (pharmacogenetics) understanding of metabolic disorders, cf DNA, etc. within the past 10 years, which makes this

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		addendum important for pediatric drug development.
42-65	10	**Comments:** Scope and objective of the ICH E11 guideline addendum (R1) This harmonized addendum is a great step forward to reduce substantial differences among regions for the acceptance of global pediatric data and thus contribute to timely access of new medicines to children.
43	3	*'Experimental interventions or procedures that present greater than low risk must offer sufficient prospect of clinical benefit'* **Comments:** see above **Proposed change:** "Experimental interventions or procedures that present greater than low risk ~~**must**~~ ***should offer*** sufficient prospect of clinical benefit".
44	3	*'This addendum does not alter the scope of the original guideline. ICH E11 (2000), including the present addendum (R1) is not intended to be comprehensive; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and pediatric societies, provide additional detail*.' **Comments:** The guidance acknowledges that E11 is not intended to be comprehensive and other guidances/documents from HA's, WHO and paediatric societies may provide additional details. Such an acknowledgement might detract from its utilization/adoption. Suggest adding "but complement;" after "not intended to be comprehensive". **Proposed change:** … the present addendum (R1) is not intended to be comprehensive ***but to complement***; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and paediatric societies,

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		provide additional detail.
45	3	'*Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments*'. **Comments:** see above **Proposed change:** Likewise, the balance of risk and anticipated clinical benefit ~~must~~ ***should be*** at least comparable to the available alternative treatments.
51 - 53 ICH 10 – 13	5	**Comments:** The clarification of the interpretation of the word "should" is particularly useful.
59 ICH 52	5	**Comment:** The statement indicates that information regarding the study is provided at time of enrolment. Therefore, it would be helpful also to provide clarity on the information that should be provided prior to enrolment to support the informed consent/assent process. **Proposed change:** Add a statement to clarify the information that should be provided prior to enrolment to support the informed consent/assent process.
62	3	*'A fundamental principle of drug development is the public availability of objective and unbiased clinical study results (…)'* **Comments:** Legal requirements across regions might differ which needs to be considered in the document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: A ~~**fundamental**~~ **recommended** principle of drug development is the public availability of objective and unbiased clinical study results (...).
66 - 100 ICH 27 – 64	5	**Comments:** ACRO recommends including a statement in the section on Ethical Considerations (section2) that paediatric trials with an "only placebo" arm are usually not accepted. All subjects participating in paediatric studies should be treated with active substance(s) (e.g. investigational product versus available standard of care, cross over studies, etc.). **Proposed change:** Add the following statement: "Paediatric trials with an "only placebo" arm are usually not accepted. All subjects participating in paediatric studies should be treated with active substance(s) (e.g. investigational product versus available standard of care, cross over studies, etc.)."
66-100	8	**Comments:** Ethical considerations: IRB and ethical committees are responsible for the approval or disapproval of research protocols and proposals, and hence, play a very important role in determining whether scientific work in pediatric drug development will be conducted at all. Such committees should be composed of members from various professional and ethnic backgrounds. Ethicists, physicians, lawyers, philosophers, school teachers, could provide a broad social, moral, and ethical perspective necessary to approve or disapprove pediatric drug development. In line 74, the concept of a "pediatric public health need" should be specifically defined and supported by clinical evidence from scientific publications, or other demographic-geographic references; when considering enrollment of children in clinical studies. Furthermore, the balance of risks and benefits must also be clearly defined as to what constitutes low risk or anticipated clinical benefit. Again, ethical committees should be involved as well as pediatricians across a wide range of sub-specialties, such as pediatric oncology, dermatology, gynecology, psychiatry as these disciplines are very specific and the impact on children can be well assess only be specialists in these particular disciples. Existing scientific data must be analyzed and assessed in order to draw proper conclusions regarding risk to

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		children and clinical benefit. In regards, to child assent in line 90, this is a very important area that requires careful legal, ethical, and moral consideration. For proper “assent” the child must be fully aware and comprehend the nature of the research he/she will be participating in. Of course, this will vary with age groups and cognitive development, however, assent must come from the “own free will” of the child and devoid of any external parental influences or coercion that might be derived from own personal or financial gain. All efforts must be made, preferably by a child psychologist or pediatrician to ensure that there is full understanding on the part of the child to participate in the research and what will be required of him or her irrespective if the work is considered to be of minimal or low risk to the child. First, the child should be addressed and then the parent, and then both should give agree to participate; if this is not possible, then the work should not be conducted irrespective of the potential clinical benefit it may have. Line 91,92 is important in that lack of expression should not be considered as assent. This process must be confidential and conducted within an established legal framework with oversight.
66-100	10	**Comments:** Ethical considerations In line 74, the concept of a “pediatric public health need” might be defined more precisely.
Section 2	11	**Comments:** A clear shift from ‘individual potential benefit’ to potential benefit for the population’. This a very reasonable, but important, shift in the ethics related framework applied and facilitates the conductance of clinical pharmacological studies in childhood. DSMB is not mentioned as a tool to further secure the safety of children included in studies.
74	3	‘*What is the medical need in one or more paediatric populations that the drug could address*?’ **Comments:** We need to understand the context of what is meant by “medical need”. Please clarify.

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74-77	3	'*When clinical studies are required to obtain information relevant to the use of a medicinal product, such studies should be conducted in paediatric populations having the disease or condition for which the investigational product is intended, unless an exception is justified*.' **Comments:** Clarify what 'an exception is justified' is referring to. Is this a waiver not to do a clinical study or not to conduct the study in children with the disease or condition?
77-80	3	*'Without a prospect of clinical benefit from an experimental intervention or procedure, the foreseeable risks to which a paediatric participant would be exposed must be low. The burden of a procedure or an intended intervention should also be minimized. Experimental interventions or procedures that present greater than low risk must offer a sufficient prospect of clinical benefit to justify exposure of a paediatric population to such risk'.* **Comments:** In the paediatric oncology setting there may not be many or any approved treatment options and the only prospect for clinical benefit might be from an experimental intervention or procedure. Under such circumstances it may not be possible for there to be low foreseeable risks. Additionally text should cover phase 1 studies of drugs for serious medical conditions with unmet medical need where the short duration of exposure to the IP inherent in many of these studies is unlikely to result in significant benefit to the study subject during the study, but could result in future clinical benefit to the study subject or patients with the same condition who would benefit from the generation of PK and PD data on the drug allowing it to proceed into safety and efficacy evaluation. Therefore revised lines 79-81 are proposed. **Proposed change:** Without a prospect of clinical benefit from an experimental intervention or procedure, the foreseeable risks to which a paediatric participant would be exposed ~~should~~ ***must*** be low. The burden of a procedure or an intended intervention should also be minimized ***with due consideration to the benefit/risk to the paediatric patient and to the paediatric population that is being studied***. Experimental interventions or procedures that present greater than low risk ~~must~~ ***should*** offer a sufficient prospect of ***present or future*** clinical benefit to justify exposure of a paediatric

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		population to such risk.
77-81	4	**Comments:** We agree with the statement that “Without a prospect of clinical benefit from an experimental intervention or procedure, the foreseeable risks to which a paediatric participant would be exposed must be low.” However, it is critical that the assessment of risk is not focused solely on the experimental interventional or procedure, but inclusive of all trial-related activities (e.g. frequency of blood sampling, scans) required of the patients.
77 – 84 ICH 37 - 47	5	**Comments:** When the draft guideline refers to clinical benefit, it is not clear whether this means a potential clinical benefit for the target paediatric population in general or for the specific individual participating in the clinical trial. Also, use of the term “low” in relation to the risks to which a paediatric trial subject may be exposed is inadequate, especially in situations where the trial subject may not receive direct benefit and the risks should be minimal. ACRO therefore recommends that the guideline should include a statement to clarify that when a clinical trial does not offer the prospect of direct benefit to the minor, there should be the prospect of some benefit for the population represented by the minor, and that such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition. Additionally, ACRO recommends that the guideline should state explicitly that in the risk-benefit ratio the benefits should clearly predominate. **Proposed change:** Add the following statement: “When a clinical trial does not offer the prospect of direct benefit to the minor, there should be the prospect of some benefit for the population represented by the minor, and that such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition. The benefit expected from the trial should be identified in the protocol.” Additionally, add the following statement: “The benefits should clearly predominate in the risk-benefit ratio.”
82	3	*‘Are specific juvenile animal studies needed?’*

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		Comments: ICH S11 is not ready to be referenced – but can we put some language here that nudges readers of this document to know that there is (or will be) a more specific place to go for information on juvenile animal studies. **Proposed change:** include reference to ICH S11with "* under discussion"
82-83	3	*'Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments'.* **Comments:** Suggest rewording to reflect that the goal is to improve paediatric care and clinical benefit, through improved efficacy or lessening risks when compared with other available treatments. A reworded sentence is thus proposed. **Proposed change:** Likewise the ***goal is to improve paediatric care by either improving efficacy or lessening the risk when compared with*** ~~balance of risk and anticipated clinical benefit must be at least comparable to~~ the available alternative treatments ~~(if any).~~
90 – 92 ICH 53 – 55	5	**Comments:** For clarity, ACRO recommends adding to this text that it is the responsibility of the investigator to make an assessment based on medical training/favoured approach on the most appropriate assent information to be used, based on the competency/maturity of the minor. If this is accepted, then Investigators need to be made aware that they will need to justify the assessment to regulatory inspectors and in the event of litigation. Additionally, given the caution regarding interpretation of absence of objection as assent, ACRO recommends that the document should contain a clear position regarding dissent. **Proposed change:** Add a statement to confirm that it is the responsibility of the investigator to make an assessment based on medical

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		training/favoured approach on the most appropriate assent information to be used, based on the competency/maturity of the minor. The Investigator must be able to justify the assessment of maturity such that third parties, such as inspectors, can be satisfied that the information the child received was appropriate Additionally, add the following statement: “Dissent by a child must be respected to the extent required by relevant legislation.”
91-92	9	**Comments:** DISSENT- A definition for DISSENT is missing in the glossary. **Proposed change:** To add dissent definition in the glossary: Dissent means the expression of the minor’s will not to participate
92-93	3	**Comments:** Reassessing the assent of a child should not be required for trials in which the child is treated for less than 1 year. For trials of longer duration the protocol should contain a justification on whether or not reassent would be required based on age of children, disease state etc., as the requirement to obtain assent multiple times may not be feasible once the treatment phase has ended. **Proposed change:** ***For trials with a treatment duration of more than 1 year, the protocol should contain a justification on whether or not reassessment of the child’s assent is required, depending on i.e. the age of the child, disease state etc***.
93 – 95 ICH 58 – 59	5	**Comments:** It is ACRO’s view that the statement “During clinical studies there may be a requirement for obtaining adequate informed consent from paediatric participants once a child reaches the age of legal consent” is not sufficiently strong with regard to the legal requirement to obtain the trial participant’s informed consent when he/she reaches the age of legal consent, and suggests replacing the text as recommended below.

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		ACRO also notes that most paediatric trials are conducted at specialist centres, which may entail a full day's travel to reach, and it would be inappropriate to require the patient to make an additional visit on reaching the age of consent simply for the purpose of providing consent as an adult. Consequently, we recommend that the guideline should draw attention to situations in which obtaining consent in a conventional manner on the child's birthday may be impracticable, and advise investigators to create provision for e-consent, remote consent, or conditional prospective consent, e.g., using wording to indicate that the child's consent will take effect upon a date in the future. **Proposed change:** Replace the current text with "As soon as a minor becomes legally competent to give informed consent during the course of the trial, no trial-related procedures, including continued dosing of the investigational product, may be performed until informed consent is provided by the trial subject. The consent of the parents/legally designated representative lapses upon attainment of legal competency by the former minor." Additionally, the guideline should draw attention to situations in which obtaining consent in a conventional manner on the child's birthday may be impracticable, and advise investigators to create provision for e-consent, remote consent, or conditional prospective consent, e.g., using wording to indicate that the child's consent will take effect upon a date in the future.
95 – 96 ICH 59 – 60	5	**Comments:** Data privacy legislation in various countries prohibits collection of date of birth by the sponsor, therefore responsibility for ensuring consent is taken at the appropriate time must reside with the investigator. ACRO recommends adding a statement to make this clear. Additionally, in view of the clarification of the meaning of "should" stated earlier in the guideline, ACRO suggests that here the word should be replaced by "must" as compliance with data privacy regulations is not optional. **Proposed change:** Add a sentence as follows: "The Investigator is responsible for ensuring that consent is taken when required." Additionally, revise the sentence to read "Local regulations related to confidentiality and privacy of paediatric participants must be followed."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
101-129	8	**Comments:** Commonality of scientific approach for pediatric drug development: As stated earlier, the multiregional, cultural, regulatory factors that exist within various regions require a common approach: Once again the medical need must be clearly defined and established according to current scientific evidence of high impact, as well as the demographics of the population to be studied. Such variables will inevitably exist across national boundaries including genetic factors, when defining the pediatric population. The population can be defined according to age, height, weight, BMI, medical history, family history, genetic and metabolic disorders, diseases, infections, immunizations, etc. Regular discussions should be held among stakeholders from various regions to insure that a common approach is being followed and in the event that certain differences arise, then measures should be taken to rectify such differences and allow for a more unified approach.
101-129	10	**Comments:** Commonality of scientific approach for pediatric drug development Discussions among stakeholders from various regions could help to achieving a common approach.
104-106	3	**'***Multiregional paediatric drug development programs face specific challenges due to regional differences in paediatric regulatory requirements, operational practicalities, and cultural expectations*.' **Comments:** There could also be regional differences in Standard of Care **Proposed change:** Multiregional paediatric drug development programs face specific challenges due to regional differences in paediatric regulatory requirements, operational practicalities, ***Standard of Care*** and cultural expectations.

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107-109	3	**'**Thus, timely and efficient drug development requires a common scientific approach for which the following key questions should be addressed'. **Comments:** ICH E11's acknowledgement that regional differences might limit the ability of health authorities to align on regulatory processes provides an opportunity for ICH to foster good regulatory practise via the encouragement of paediatric clusters such as that established in the paediatric oncology space. **Comments:** Terminology – The terms "addressed" and "discussed" are both used to discuss lists of questions. These questions are not applicable to all products and have been caveated with "should be". One suggestion is to change these to "considered", which would align it with the message that these are points to think about. **Proposed change:** Thus, timely and efficient drug development requires a common scientific approach ***and multiregional alignment of Health Authorities on proposed paediatric development plans*** for which the following key questions should be ~~addressed~~ ***considered.***
110 ICH 74 – 75	5	**Comments:** The question "What is the medical need in one or more paediatric populations that the drug could address?" may result in a potential conflict between the planned guideline and current regulatory requirements in the USA and EU. According to the latter, all applications for marketing approval for new medicines have to include the results of studies as described in an agreed paediatric investigation or development plan, unless the medicine is exempt because of a deferral or waiver. In practice, this means there must be a paediatric investigation or development plan for all drugs approved for adult use if the condition occurs in children. However, if, for example, three drugs of the same class are already approved for paediatric use, can a medical need for a fourth drug of the same class be justified? **Proposed change:** Align the text with current US and EU regulatory requirements.

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110-121	3	**Comments:** Though acknowledged in lines 139 to 140 ('*Depending on the condition and treatment, it may be justifiable to include paediatric subpopulations in adult studies or adult subpopulations in paediatric studies*'), the following consideration should be in this section: '*Can some paediatric data be generated by broadening the eligibility criteria for age to include adolescent patients once the recommended phase 2 dose in adults has been established*.' Reference is made to the ASCO/FOCR/ASCO initiative to modernize eligibility criteria for clinical trials and the FDA publication in Clinical Cancer Research 'Chuk et al. Enrolling adolescents in disease/target-appropriate adult oncology clinical trials of investigational agents DOI: 10.1158/1078-0432.CCR-16-1367 Published 25 October 2016.' **Proposed change:** Add the following question: ***Can the eligibility criteria in the adult clinical development program be broadened to include paediatric patients?***
113-115	1	**Comments:** neonatal period for premature infants is defined in this document as expected date of delivery plus 27 days. This is not the standard definition. The standard definition of neonatal period for premature infants is the period from birth to 28 days of age. **Proposed change:** revise definition to "the period from birth to 28 days of age."
113-115	12	**Comments:** Include M&S data as existing knowledge, which can be used to identify knowledge gaps prior to conducting any pediatric clinical trials
117	6	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Should placebo controlled studies be considered or deemed unethical? **Proposed change:** Additional clarity is requested.
119	3	'*8. Are there different formulations/dosage forms that will be needed for specific paediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of paediatric patients in different subgroups?*' **Comments:** An age appropriate drug delivery system may also be crucial for paediatric drug development **Proposed change:** 8. Are there different formulations/dosage forms, ***delivery device that*** will be needed for specific paediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of paediatric patients in different subgroups?
119-121	3	**Comments:** It is important to consider also if there any new drug-drug interaction studies that might be needed in view of paediatric-specific concomitant drug administration for the disease or condition. **Proposed change:** Add a new question ***9. Are there new drug-drug interaction studies that will be needed to be conducted in view of paediatric-specific concomitant drug administration for the disease or condition?***
122	11	**Comments:** I anticipated also to read something on parents and/or patient organisations (eg ICAN) ?
122 – 123	5	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
ICH 88 – 90		ACRO recommends including in this section of text a statement similar to that proposed by the European Commission's expert group on clinical trials in their proposed recommendations on Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors: "A 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended." **Proposed change:** Add the statement "A staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended."
123	3	**Comments:** Along with scientific requirements, the question on feasibility must also be addressed (ref chapter 6.1 on line 266 and onwards). It is of no use to initiate a scientifically highly interesting investigation if impossible to find the suitable patients in reality. **Proposed change:** Consider adding a specific question.
126 etc:	11	**Comments:** I agree, but within the current regulatory framework, we have to respect these local regulations obviously. There is however a task for the academia (e.g. Dutch decision on recruitment of special populations, including children, psychiatric and geriatric patients) to make the local authorities aware of such issues. **Comment:** Why not add that a rationale should also be provided to use a stepwise age-driven recruitment strategy within the age-related subcategories since this delays recruitment and knowledge building in neonates and infancy (so the stepwise age driven approach by default should be omitted).

Line no.	Stakeholder no.	Comment and rationale; proposed changes
127-129	3	**Comments:** The guideline states '*Therefore, a common scientific approach, not common regional requirements, is at the cornerstone of efficient paediatric drug development and timely delivery of safe and effective medicines for children.'* *Differences in regional requirements are one of the biggest challenges in paediatric drug development. The guidance should be more specific on how common scientific approach could be achieved*.' **Comments:** Confusing statement. Please rephrase to clarify the statement "a common scientific approach, not common regional requirements" Some examples would be useful.
130-148	8	**Comments:** Age classification and pediatric subgroups, including neonates: Pediatric age classifications are divided among a range of ages such as early, middle, and late adolescents or periods corresponding with emotional, physical and social development such as preschool, school aged, adolescence, covering a range of ages such as from 2 to 5 years, 6-12 years, 13-18 years, etc. corresponding to a group of children undergoing a similar rate of growth, development, metabolism, and vulnerability to various illnesses. Such categories should be used as reference for inclusion of children in clinical trials but should not be the main criteria for inclusion or exclusion of subjects for pediatric drug development. More specific criteria must be used in reference to metabolism, physiology, existing pathology, and study end points must be clearly defined. In essence, chronological age should serve as guide with more specific criteria as defined in the existing ICH E11 document. In regards to the neonatal population, the period of development in which birth occurs must be clearly defined, i.e. early preterm labor, preterm labor, late preterm labor, term, post term, according to number of weeks in utero as well as birth weight; VLBW, LBW, and over 3500g. Gestational diabetes, IUGR, etc. Depending on the period in which the child is born, and the degree of maturation achieved, i.e. lung, brain, etc. and the degree of neonatal care needed, specific criteria must be established accordingly. In general this concept is stated in lines 141-148 of the ICH E11, however, the specific periods of birth should be defined as well as how the deliveries were managed, i.e. spontaneous

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		or C-Section, use of corticoids, tocolytics, antibiotics, etc. as such variables are significant.
130-148	10	**Comments:** Age classification and pediatric subgroups, including neonates In respect to the neonatal population, the period of development in which birth occurs is important. How the deliveries were managed, i.e., spontaneous or C-Section, use of corticoids, tocolytics, etc. are important variables as well.
132	12	**Comments:** Please consider referring back to the original ICH E11 age classifications and specify the new terms in the R1 and state if the current E11 age definitions can still be applied.
134-136	3	*'Physiological development and maturity of organs, pathophysiology of disease or condition, and the pharmacology of the investigational product are factors to be considered'.* **Comments:** It would be beneficial to add '**natural history'** of disease or condition and '**available / established treatment options**' as an additional factors to consider **Proposed Change:** Physiological development and maturity of organs, pathophysiology ***and natural history*** of disease or condition, ***available / established treatment options***, and the pharmacology of the investigational product are factors to be considered.
136	3	**Comments:** The statement that division into subgroups may be arbitrary and limits paediatric drug development should be made stronger and state that subgroups are only required when there is a scientific rationale to do so. A sentence is thus proposed to be added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: …in paediatric studies. ***<u>For each indication and each trial there should be a rationale on whether or not the trial population should be divided in chronological age groups. Division in chronological age groups should only be done when scientifically justified.</u>*** Further the arbitrary division of paediatric subgroups…
136-139	12	*'Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study.'* **Comment and rationale:** though it is agreed that the division in chronological age groups may sometimes arbitrary and not necessary it seems applicable in the vast majority of cases that pediatric patients <1 year and especially neonates are deviating most from adult conditions. **Proposed change:** "Further, the arbitrary division of pediatric subgroups by chronological age **in patients older than 1 year**……"
139-140	9	**Comments:** It must be better highlighting that the inclusion of paediatric subpopulations in adult studies or adult subpopulation in paediatric studies is not the rule, but an exception and has to be properly justified (e.g. in the case of rare diseases). The reasoning should take into account also study features (different from condition and treatment), e.g. endpoints and procedures.
141-143	3	**'***Advances in medical care have led to better survival of high risk newborn infants, especially preterm newborn infants, which makes drug development research in newborn infants or "neonates" increasingly important*.' **Comments:** Neonate research may not be relevant for all conditions

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: …increasingly important ***for certain conditions.***
143-6	4	**Comments:** The BNF for Children 2016-17 (BNFC) defines a neonate as from 0 up to 28 days of age (or first 4 weeks of life) rather than birth plus 27 days. The definition as per BNFC removes the debate on whether the day of birth counts as day 0 or day 1.
147-148	3	'*A rationale for the selection of a neonatal population in clinical studies should be provided*'. **Comments:** This sentence is unclear. It seems like there should be a rationale for the definition of the neonatal population for each study that includes neonates. **Proposed change:** A rationale for ~~the selection of a~~ ***definition of the choice of the*** neonatal population ~~in clinical studies~~ should be provided ***for each trial that includes neonates***.
147-148	12	*"A rationale for the selection of a neonatal population in clinical studies should be provided."* **Comment and rationale:** this sentence can be unintentionally understood as discouraging sponsors to investigate neonates. **Proposed change:** As it is expected to encourage studies including neonates the section should be rephrased to: "Though studies in a neonatal population are encouraged a rationale for the selection of a neonatal population in clinical studies should be provided."
149 – 160	5	**Comment:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
ICH 118 – 150		ACRO recommends including in section 5 (Approaches to Optimize Paediatric Drug Development) the need to highlight the deviation from the normal standard of care for a patient with a specific diagnosis if a paediatric patient is to be exposed to a very different treatment pathway or regime from the standard clinical care. This is a frequent discussion point in a wide range of Industry and governing body meetings. **Proposed change:** Add a statement on the need to highlight the deviation from the normal standard of care for a patient with a specific diagnosis if a paediatric patient is to be exposed to a very different treatment pathway or regime from the standard clinical care.
149-160	8 and 10	**Comments:** Approaches to optimize pediatric drug development: This paragraph reflects the spirit of the addendum to ICH E11 and the need to establish a more uniform ethical and scientific approach that can be applied internationally taking into consideration all regulatory factors and regional differences in pediatric drug development.
150	3	**Comment:** Suggest adding a reminder on the overall objective, in line with ICH E11 (2000) **Proposed change:** "…The concepts presented in ICH E11 (2000) Section 2.4 still apply, ***with the main objective being to generate information/improve labelling on the paediatric use of medicinal products***."
151	7	**Proposed change:** Please add "… should be consulted for interventional clinical studies in contrast to non-interventional studies."
151–199	1	**Comments:** Section 5.1.1 "The Use of Extrapolation in Pediatric Drug Development" is unclear that extrapolation should only be

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		used for efficacy rather than pk/safety. The sentence at lines 152-156 says “Pediatric extrapolation is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population….” would imply that extrapolation for safety is acceptable. That has never been the case and would indicate a radical change in policy by health authorities. If the sentence intended to have a different meaning it should be revised to clarify.
157-158	2	**Proposed change:** *A non binding multidisciplinary (scientific as well as regulatory) early dialogue should be initiated in order to optimize pediatric development.*
157-158	3	**Comments:** Edits proposed below to help to clarify the meaning of ‘early’ dialogue in this context. **Proposed change:** ~~Early~~ Multi-disciplinary dialogue regarding the acceptability of such approaches with regulatory authorities is recommended ***during early phase clinical development in adults*****.**
158-160	4	**Comments:** It is suggested that the sentence “The planning for development of the drug for children should not begin when development in adults reaches its conclusion” could be written in a positive rather than negative way **Proposed change:** The planning for development of the drug for children should run parallel to the adult process
159-160	2	**Proposed change:** *When alternative treatments exist for a paediatric disease or condition, the pediatric development of a new alternative still have to consider preliminary efficacy and safety data obtained in the adult population and clinical studies in children should be deferred accordingly.*
159-160	3	*‘The planning for development of the drug for children should not begin when development in adults reaches its*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		conclusion' **Comments:** The sentence could be slightly clarified, i.e., written in a positive way. **Proposed change:** The planning for development of the drug for children should ~~not~~ begin ~~when~~ ***before*** development in adults reaches its conclusion.
159-160	12	**Comments:** *"The planning for development of the drug for children should not begin when development in adults reaches its conclusion."* Comment and rationale: this statement is imprecise as it does not provide guidance on when the planning for the pediatric drug development should begin **Proposed change:** the guidance should provide language around consideration of factors that inform on the most appropriate timing for pediatric programs. In addition, timing for the planning should also be mentioned
Section 5.1	9	**Comments:** the use of existing knowledge for paediatric drug development may also refer to off-label use. This is particularly useful in case of old medicines, that have been not duly studied in paediatrics, but with a large use in an off-label manner.
161	3	**Proposed change:** Chapter sub-numbering (5. and 5.1) probably not necessary without sub-chapter continuation (5.2. missing). Same comment applies to section 1, where there is only a 1.1. **Rational:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Readability/Structure
161-178	8	**Comments:** Use of existing knowledge in pediatric drug development: The use of existing knowledge must include an acceptance of a degree of uncertainty, that due to the rapidly evolving nature of scientific investigation and the development of new findings; existing knowledge must be continuously reassessed and evaluated for its present relevance. Certain knowledge will inevitable remain, however, depending on the period of time that has elapsed, there is always the possibility of new developments and findings. Hence, reviews of the literature, professional meetings, and consultations with reliable experts will help to insure the drug development is up to date. Once again, extrapolation of knowledge derived from the adult population must be cautiously interpreted and applied in the pediatric population and differences clearly delineated when applicable.
161-178	10	**Comments:** Use of existing knowledge in pediatric drug development Due to the rapidly evolving nature of scientific investigation and the development of new findings; existing knowledge must be continuously reassessed and evaluated for its present relevance.
163-164	3	**Comments:** Suggest amending the sentence as proposed. There are multiple monoclonal antibodies that are being developed for as many as 3-4 different indications in the same paediatric populations. Knowledge, particularly PK and safety data, from a group of children with JIA (for example) should be applicable to children with Crohn's disease in the same age range. **Proposed change:** Existing knowledge includes evidence already or concurrently generated with the drug under development in adult and paediatric populations with ~~the~~ ***similar*** ~~same~~ ***diseases or conditions***.
163-164	4	**Comments:** Evidence generated in adult and paediatric populations with **other** diseases or conditions should also be considered to

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		optimise paediatric drug development programs.
164 – 166 ICH 135 – 137	5	**Comments:** Existing knowledge includes also retrospective clinical data and existing data from off-label use (if available), which should be included in the statement. **Proposed change:** Revise the sentence to read “Existing knowledge also integrates nonclinical data, retrospective clinical data and existing data from off-label use (if available), data about related compounds, disease pathophysiology, as well as consideration of the developmental physiology of the paediatric population or subgroup.”
165	3	**‘***Existing knowledge also integrates nonclinical data, data about related compounds, disease pathophysiology, as 166 well as consideration of the developmental physiology of the paediatric population or subgroup’*. **Comments:** Each compound should be evaluated individually; suggest adding "if appropriate” **Proposed change:** …knowledge also integrates nonclinical data, data about related compounds ***(if appropriate)***, disease pathophysiology…
166-170	3	‘*A thorough understanding of the differences between paediatric and reference populations is required relative to the pathophysiology of the disease, available biomarker/ endpoints, organ systems physiology (i.e., renal, hepatic, central nervous system, skeletal, and immune systems), as well as clinical context of therapeutics, and pharmacological behavior of the drug*’ **Comments:** Please clarify when extrapolation may be appropriate – especially in instances when there are differences in disease between the adult and paediatric populations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
168-169	12	"*Safety and risk consideration based on the existing knowledge should guide the decision whether specific mitigation, such as staggered enrolment based on age group, is necessary*." **Comment and rationale:** this statement is inexplicit. Unnecessary use of an age-staggered approaches have ethical implications as it leads to a delay in the access of the medicine to children **Proposed change:** Possibly consider adding more specific reference to expand this concept by clearly stating that agestaggered approaches are not a requirement.
175	7	**Comments:** We appreciate the current wording that additional approaches may include statistical and pharmacometric methods, i.e. they are not mandatory but just an option.
179	6	**Comments:** The guideline does not speak about extrapolation of the data from the reference product to a proposed biosimilar. **Proposed change:** The Agency should incorporate information regarding extrapolation from the reference product to a proposed biosimilar in the guideline.
179 – 224 ICH 151 – 199	5	**Comments:** ACRO recommends that the process of extrapolation should be explained in additional detail, including the development of an extrapolation plan, including the systematic synthesis of available data and agreed with the relevant regulatory authorities prior to implementation, details of the calculation of the paediatric dosage regimen resulting from the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		extrapolation, and adaptation of the extrapolation plan and any follow-ups considered necessary. **Proposed change:** Include further explanation of the extrapolation process as recommended above.
179-224	8	**Comments:** The use of extrapolation in pediatric drug development: The extrapolation of data from an adult population to a pediatric population in terms of expected results or effects has to be pursued with caution. As stated in line 185-196, significant differences exist with regards to physiology, pathophysiology, pathology, pharmacodynamics and kinetics, metabolism, biophysical parameters, that can influence the progression of disease and therapeutic response to drugs when administered to the pediatric and adult populations. Lines 205-207 are the most important in that data from adult populations may only provide some information as to safety in the pediatric population and cannot be taken with 100 percent reliability. However, by the same token, all realistic measures should be taken to avoid exposing children to unnecessary clinical trials if scientifically valid data from the adult population is available.
179-224	10	**Comments:** The use of extrapolation in pediatric drug development The extrapolation of data from an adult population to a pediatric population in terms of expected results or effects has to be pursued with caution. However, all realistic measures should be taken to avoid exposing children to unnecessary clinical trials if scientifically valid data from the adult population is available.
188-191	3	'*Where an extrapolation approach is scientifically justifiable, it should be a dynamic process that examines several factors including disease pathogenesis, criteria for disease diagnosis and classification, measures of disease progression, and pathophysiological, histopathological, and pathobiological characteristics that support the assumptions of similarity of disease and similarity of response to therapy between the paediatric and the reference populations*'. **Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		What is meant by “dynamic process” here? Please clarify. Dynamic process of various dependent process factors with different orders of magnitude can be better assessed using quantitative-system pharmacology models. The guidance, however, does not mention whether such approach is considered acceptable for assessing potential differences of disease and response to therapy.
196	6	**Comments:** Mechanism of action should be included in the list as a factor in understanding the differences between pediatric and reference populations. **Proposed change:** “A thorough understanding of the differences between pediatric and reference populations is required relative to the pathophysiology of the disease … ~~and~~ pharmacological behavior of the drug, **and mechanism of action**.”
197-200	3	*‘Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship, and prediction of an effective dose for the intended population, may be derived from existing data, published literature, expert panels and consensus documents, or previous experience with other products in the same therapeutic class.’* **Comments:** The current wording implies monotherapy treatment. Suggest adding "and regimen" to include a combination therapy approach, which is often the case in Oncology. And to also amend the sentence to reflect the fact that a different indication may be considered. **Proposed change:** Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship, and prediction of an effective dose ***and regimen*** for the intended population, may be derived from existing data, published literature, expert panels and consensus documents, or previous experience with other products in the same therapeutic class, ***or the same product directed at a different indication that can show similarity of exposure***

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and exposure-response between the paediatric and the reference population.
197-208	3	**Proposed Change:** Please also consider extrapolation from a benefit and risk point of view. Exposure response for paediatric patients shall be explored for efficacy, and safety when appropriate. If the extrapolation frame work is established, then the extrapolation shall be explored for efficacy, safety, and benefit and risk assessment. Rationale: The concept for extrapolation in the guideline seems to follow the traditional drug development process, i.e., establish efficacy first and then prove safety.
203-208	7	**Comments:** If additional clinical information is needed, it could be an option for regulatory authorities to grant a conditional marketing approval for a provisionally extrapolated age group (e.g. 8 to 11 years in age if the medicinal product holds a marketing authorization in patients of at least 12 years in age). The condition would be to perform a non-interventional clinical study (NIS) in that extrapolated age group within a distinct deadline in order to verify the benefit-risk-balance of the product in the extrapolated population in real medical life.
204-207	3	*'When efficacy in the paediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the paediatric population may be utilized; however, additional paediatric safety data are usually required'*. **Comments:** If an investigational product demonstrates that there is no major difference in efficacy, safety and dose-response in adults across regions, and the safety of paediatrics is confirmed with appropriate doses in Region A, we would like to confirm that it is not necessary to repeat a safety clinical trial in the same paediatric population in other regions. **Comments:** The text refers to 'reference population' and also refers to 'as data in adults'. Be consistent and just refer to reference population. Please revise accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: … additional paediatric safety data are usually required, as data in ~~adults~~ ***the reference population*** may only provide some information about potential safety concerns related to the use of a drug in the paediatric population.
204-208	12	*'When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as data in adults may only provide some information about potential safety concerns related to the use of a drug in the pediatric population.'* **Comment and rationale:** the need for (additional) safety data may also depend on the target of the development drug and the pediatric sub-population. While for CNS drugs safety also in adolescents will be required this may be not the case in general for a cardio-metabolic compound. **Proposed change:** the guidance should state that additional safety data may be also required depending on the target of the development drug and the pediatric sub-population.
206-208	3	**'***However, additional paediatric safety data are usually required, as data in adults may only provide some information about potential safety concerns related to the use of a drug in the paediatric population*.' **Comments:** Please elaborate on any innovative ways that safety data might be collected, when efficacy is extrapolated
206-222	12	**Comment and rationale:** although line 206 states the safety data may be required, the questions that should be discussed for extrapolation (Lines 211-222) are only applicable for efficacy claims. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the guidance should make clear whether extrapolation of safety is acceptable and if so, the questions (Lines 211 - 222) should be adapted to comprise safety aspects.
209-222	3	**Comments:** We would like to propose to add the below point in the framework of questions when extrapolation is considered in a paediatric drug development strategy. **Proposed change:** • ***Is there an approval case of related compound which the extrapolation approach has been used for in the same therapeutic area*?**
210	3	'*When extrapolation is considered in a paediatric drug development strategy, the following framework of questions should be discussed to assess what additional supportive data are needed'*. **Comments:** Terminology – The terms "addressed" and "discussed" are both used to discuss lists of questions. These questions are not applicable to all products and have been caveated with "should be". One suggestion is to change these to "considered", which would align it with the message that these are points to think about. **Proposed change:** …questions should be ~~discussed~~ ***considered*** to assess what additional supportive data are needed: .."
214	3	*'3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the paediatric population*?' **Comments:** Please add "**clinically**" before "relevant" **Proposed change:** .. in the reference populations that is ***clinically*** relevant in the paediatric population?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
218	3	*'5. What uncertainties do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the paediatric population remain?'* **Comments:** Please add '**and limitations**' after 'uncertainties' **Proposed change:** 5. What uncertainties ***and limitations*** do the existing data (e.g., clinical or historical data…
223-224	3	'*As evidence builds, the acceptability of the proposed extrapolation approach will need to be reassessed and it may be appropriate to change the extrapolation approach*.' **Comments:** It seems that the review and 'approval' of such extrapolation analyses or exercises can vary greatly depending on the individual reviewer from varying academic institutions. Are there any efforts to streamline the quality and type of review as well as the 'acceptability' of such analyses across these independent reviewers? **Proposed change:** As evidence builds, the acceptability of the proposed extrapolation approach ~~will~~ ***may*** need to be ***carefully*** reassessed ***by relevant experts, including regulatory authorities during filing review, using a consistent, streamlined scientific approach to ensure an acceptable level of quality*****,** and it may be appropriate to change the extrapolation approach.
Section 5.1.2	2	**Comments:** *Could you mention explicitly the notion of PK and PK/PD models, essential tools in order to: analyze the PK data (which is important to collect during pediatric drug development), establish the PK/PD relationship, make predictions and dose recommendations?*
225	3	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The term 'MID3' which was included in the ICHE11 concept paper has disappeared and was replaced by M&S. It would be appropriate to address the point in the addendum to ensure consistency with MID3 and the term 'MIDD' currently in use at the FDA.
225-259	8	**Comments:** 5.1.2. The use of modeling and simulation in pediatric drug development: The use of M+S in pediatric drug development can be an important tool in understanding drug interactions, pharmacokinetics, steady state concentrations, bioavailability, half life, therapeutic effects, side effects, etc. Mathematical models to calculate drug concentrations in relation to BMI can be very helpful in calculating dosages with safe therapeutic ranges, etc. In general, the section seems to be well written acknowledging both limitations and benefits of M+S.
225-259	10	**Comments:** 5.1.2. The use of modeling and simulation in pediatric drug development The use of M+S in pediatric drug development is an important tool in understanding pharmacokinetics, steady state concentrations, bioavailability, half life, therapeutic effects, side effects, etc. Mathematical models to calculate drug concentrations in relation to BMI can be very helpful in calculating dosages with safe therapeutic ranges, etc. In general, the section seems to be well written acknowledging both limitations and benefits of M+S.
231	4	**Comments:** Grammatical suggestion - "M&S is one such ~~a~~ tool that can help avoid……" **Proposed change:** "M&S is one such tool that can help avoid……"
238 – 240	5	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
ICH 214 – 216		The M&S approach is to be welcomed. However, ACRO recommends that the guideline should make clear that the strategic M&S plan needs to be discussed with, and agreed by, regulatory authorities prior to commencement, otherwise the risk exists that the M&S plan will be conducted but subsequently held to be unacceptable, which will delay the availability of a potentially valuable new treatment. Additionally, ACRO considers that the phrase “several criteria” is insufficient to describe the requirement for model building and should be replaced by “as many criteria as possible”. **Proposed change:** Revise the sentence to read “The incorporation of M&S into paediatric drug development should be based on a strategic plan established through multidisciplinary discussions, including relevant regulatory authorities, outlining objectives, methods, assumptions, deliverables and timelines.” Additionally, revise the sentence to read “When building a model, as many as possible relevant criteria should be considered…”
246-248	3	‘*In paediatrics, it is particularly critical to consider the maturation of organ systems with the understanding that data from older subgroups may not necessarily be informative for the younger subgroups*.’ **Comments:** What about the possibility of utilizing PBPK tools such as SimCYP to evaluate the impact of hepatic enzyme maturation to predict PK in paediatrics and/or potential (or lack thereof) for DDI's? **Proposed change:** ***Consider utilizing PBPK tools such as SimCYP to evaluate the impact of hepatic enzyme maturation to predict PK in paediatrics and/or the potential (or lack thereof) for drug-drug interactions*.**
247- 248	3	‘*Consideration should be given to the available centers willing to participate that have access to eligible paediatric participants*, (…)’ **Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Please insert text as proposed below. **Proposed change:** ***<u>Consideration should be given to ethical constraints in these populations that are not present in adult studies, such as the inability to collect blood samples in paediatric patients in a control arm for maintenance of double blind.</u>***
251 – 252 ICH 228 – 229	5	**Comments:** ACRO recommends that the impact of "influencing parameters" to the M&S process should be added here. **Proposed change:** Add the following statement: "As many as possible influencing parameters and co-variates, as well as their impact, should be considered in the M&S process. These parameters and/or co-variates might be known from already existing data and include but are not limited to age of subject, maturation of organs, disease types, disease severity, etc."
260-288	8	**Comments:** Practicalities in the design and execution of pediatric clinical trials: Feasibility: The importance of a pediatric clinical trial network becomes more evident in consideration of the limitations of patient size and the resources available throughout various research centers. The importance of creating awareness for parents and their children as to realistic expectations from participation in the research as to emotional and physical demands and what the expected therapeutic yield may be for patients with terminal conditions in oncology or other genetic disorders with long-term disability. Outcome assessments: Definition of pediatric endpoints for specific age and development subgroups. (Important aspect of any type of research that is conducted.)
Section 6.1	11	**Comments:** Building of research capacity (cf IMI initiative ?)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
267-281	3	**Comments:** To reduce the risk of committing to proposed paediatric development plans it is suggested that the guidance could acknowledge the utility of some form of feasibility assessment prior to presenting the proposed paediatric plan to Health Authorities. In addition, there is no recognition in the Feasibility section that one of the main feasibility issues is that every country assesses different patient populations differently (For example - age of consent). Even with the best of endeavours many studies that start with a Master Protocol often end up with country deviations due to the differences in assessments by national groups.
270-275	3	**Comments:** Registries, in addition to clinical trials, may in some circumstances be used to generate data in paediatric patients. The additional wording shown below is included to address this. **Proposed change:** When studying paediatric conditions, it may be necessary to consider implementing clinical trial operational strategies, including, but not limited to, the use of paediatric research coordinating centres, the development of master protocols for clinical trials ***or registries*** planned and conducted in a collaborative manner to evaluate multiple therapies for the same disease or condition with a single control arm, and the enhancement of paediatric clinical research networks.
275-276	3	'*These operational strategies may be challenging to implement, but may result in improved feasibility and increase timely and efficient paediatric drug development*.' **Comments:** The guidance addresses aspects of feasibility considerations but does not comment on when studies are unfeasible. For instance, if the novel therapeutic is being investigated in adults, but required to do conduct studies in an ultra-rare paediatric population, those studies may be unfeasible. Suggest adding additional guidance and perhaps epidemiologic criteria for when studies are unfeasible.

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		Also, in the adult competitive space, many times there are multiple therapeutics being developed to treat the same disease. With a limited paediatric population, Sponsors are required to perform studies competing for the same population which limits feasibility. Recommend adding additional thoughts on prioritization of molecules or considerations for the Sponsors in these common circumstances.
276	7	**Comments:** The feasibility considerations in chapter 6.1 may also take into account the NIS-option mentioned above.
279-281	3	'Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study.' **Comments:** Please provide examples of possible strategies
Section 6.2	4	**Comments:** NPPG is supportive of the development and application of 'core outcome set' in paediatric clinical trials and believes that this is an important approach to optimise paediatric drug development and should be described in this section.
Section 6.2	11	**Comments:** Outcomes assessment variables in phase 3 type of studies should be clinical relevant on the overall health outcome, while for early phase studies, early available outcome variables can be considered for eg dose seeking studies ? quid safety outcome data, eg neurodevelopmental outcome.
284 – 287 ICH 263 – 267	5	**Comments:** ACRO concurs that relevant end-points and outcome measures may indeed be different for children. §3011 of the 21st Century Cures Act, just approved, allows the FDA up to 5 years to issue a report on the acceptability of drug development tools, including endpoints. The current wording in this document should be amended to indicate the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		extended timeframe. **Proposed change:** addition of a clause (in bold) to the last sentence of the paragraph as follows, "**Given that establishing the acceptability of an endpoint may take many years,** where relevant, it may be…..."
286	3	**Comments:** Age may not be the best patient attribute to determine the appropriate formulation development strategy. Disease state, developmental factors etc… may be more relevant than age. Consider adding language to clarify age is only a surrogate for determining the appropriateness of a dose form, and that other factors may drive this determination
287-288	3	**Comments:** Please elaborate on how to assess potential paediatric endpoints in adult development program. Is this recommending including a small number of paediatric subjects in the adult program to explore paediatric specific endpoints?
289 – 301 ICH 268 – 281	5	**Comments:** ACRO recommends adding guidance about relevant aspects of adaptive trial designs in section 6.3 (Long-term Clinical Aspects, Including Safety), as indicated below. **Proposed change:** Add the following statement: "Adaptive trial designs could also be considered as an appropriate method to react on new safety aspects resulting from clinical trial data. For this, interim data analyses are to be planned and to be performed to allow modification/adaptation of further study conduct (within pre-defined measures) based on new safety data."
289-301	8	**Comments:** 6.3 Long term clinical aspects, including safety All pediatric patients should be routinely followed up on a periodic basis to assess impact of whatever therapy or drug administration on basic biophysical parameters such as height, weight, growth rate, liver function, etc. in order to

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		insure maximum safety but also therapeutic effect of whatever drug may be in question. This will insure safe tolerance of the drug by monitoring potential side effects and to insure that any necessary changes in dosage regime be made to maximize safe administration.
290-318	3	*"Adult dosage forms are not always appropriate for use in the paediatric population, and if a preparation for adults is used, it may pose a safety risk. When paediatric considerations are not addressed early during the development process, the final medicinal product may require such manipulation for use in children that it increases the likelihood for inaccurate dosing and changes in stability or bioavailability. Examples of this include multiple small volume acquisitions from a vial designed for a single adult use, use of an opened adult capsule formulation or crushed tablets to administer a paediatric dose mixed with food, and breaking tablets that do not have a score line. Therefore, planning for development of age-appropriate dosage forms for paediatric populations should be incorporated into the earliest stages of product development. When manipulations of the available form are unavoidable, measures to minimize the impact on dose accuracy, stability and bioavailability must be addressed."* **Proposed change:** Planning for development of age-appropriate dosage forms for paediatric populations should be incorporated into the earliest stages of product development ***to avoid medicinal product manipulation for use in children that increases the risk of inaccurate dosing, instability or uncharacterized bioavailability***. Age-appropriate dosage forms may include paediatric formulations ***or extemporaneous formulations based on the adult dosage forms,*** such as ***crushed tablets or*** sprinkles, of ***the contents of a*** capsule contents ***on food***, ~~or crushed tablets based on the adult dosage forms,~~ ***provided that appropriate stability, potency, dose accuracy, bioavailability are demonstrated. The instructions for creating and administering the extemporaneous dosage form studied in clinical development should be communicated clearly to the caregiver and patient in formal product*** labelling. However, certain manipulations of adult dosage forms may not always be appropriate or even pose a safety risk for the paediatric population: for example, breaking tablets that do not have a score line. When paediatric formulations development is not addressed early in the development process, the final medicinal product may require such manipulation for use in children that the risk is increased of inaccurate dosing, changes in stability or bioavailability.
293-296	3	**Comments:**

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		Juvenile animal toxicity studies may not be predictive of long term safety in the paediatric population. The risk/benefit for the target product and indication must be considered when determining the need to conduct such studies. Registries, in addition to clinical trials, may in some circumstances be used to generate data in paediatric patients. The additional wording shown below is included to address this. **Proposed change:** Planned collection of safety data in nonclinical studies, adult clinical studies regardless of dose or indication, ***registries,*** or data from other sources (e.g., M&S), ~~should~~ ***may*** serve to improve the design of paediatric studies and pharmacovigilance activities to address specific paediatric safety concerns.
294-301	3	**Comments:** There is no mention of the use of long-term clinical registries for collecting adequate safety data in children particularly in the long-term safety concerns around a) cognitive development; b) linear growth; c) bone density; d) fertility; e) effect on immune function. This was part of solutions discussed at an FDA workshop in 2016. Section 6.3 could acknowledge the utility of registries and real world data as the basis for evaluating the long-term clinical aspects. It is thus proposed to add a specific sentence. **Proposed change:** Add a sentence at the end of the paragraph ***acknowledging the potential utility of registries for the long-term follow-up of paediatric patients.***
296	7	**Comments:** The Long-term clinical aspects in chapter 6.3 may also take into account the NIS-option mentioned above.
299	3	**Comments:** Regular follow-up measurements seem to be requested for all paediatric trials. This is not feasible and poses a disproportionate burden on industry. There should be a limit to how long follow up can normally be requested and for

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		which effects this can be requested. **Proposed change:** Make section more specific
Section 7	4	**Comments:** It is encouraged to see an expanded section on paediatric formulations which is an important element in paediatric drug development. However, considering the availability of the “guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012)” which provides a more comprehensive discussion on this topic, the information snippets presented here would therefore appear incomplete. **Proposed change:** A general reference to “guideline on pharmaceutical development of medicines for paediatric use”?
302-330	8	**Comments:** 7.Pediatric formulations: Age appropriate pediatric formulation should be used. Short and longer acting preparations should be used with care and under appropriate conditions. Bioavailability and distribution should be assessed and insure that proper dosages are being administered. Limitation on maximal daily dosages, i.e.per day need to be followed as well. 7.1. Dosage and administration: The ability to administer longer acting preparations in certain settings should be established with clinical oversight in the event of adverse drug reactions. Such patients should be continuously monitored in order to avoid adverse events, of course, this is continent of the specifics of the study, however, in general there should be some form of continuous oversight in place preferably by a medical professional or nurse practitioner able to properly respond if necessary. Technology used to deliver small dosages can also be utilized with oversight. The concept of a steady state or target therapeutic dose can also be applied here taking into consideration drug half-

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		life, metabolism, liver function, etc.
302-330	10	**Comments:** 7. Pediatric formulations 7.1. Dosage and administration: The ability to administer longer acting preparations in certain settings should be established with clinical oversight in the event of adverse drug reactions.
314-315	3	**Proposed change:** Administration of crushed tablets mixed with food is also mentioned in chapter 7.3 Palatability and acceptability (line 349-350). Therefore, we recommend administration of crushed tablets be discussed only in one location (in chapter 7.3). In connection with the potential use of the adult dosage form only the aspect of inaccurate dosing should be discussed. The guidance should also state that the attribute(s) of taste/palatability are directed toward the risk of adherence. The determination of acceptability or palatability can be made with a determination on risk to adherence issues as opposed to taste alone. **Rationale:** Clarification/Readability/Scope
315	3	**Proposed change:** It is important that in case tablets without a functional score must be split for paediatric dosing purposes, dose accuracy cannot be assured. **Rationale:** It is not at all considered acceptable to break tablets that do not have a functional score line.

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317-318	3	'*When manipulations of the available form are unavoidable, measures to minimize the impact on dose accuracy, stability and bioavailability must be addressed*.' **Proposed change:** Please consider moving this line up so before the sentence referring to planning for development of age-appropriate dosage forms (line 315-316). **Rationale:** Clarification/Readability
319 – 330 ICH 301 – 314	5	**Comments:** ACRO recommends that, in section 7.1 (Dosage and Administration), a statement should be added to explain that pharmacodynamic and pharmacokinetic data should be considered when establishing the dosing regimen (dependent on age /maturity). **Proposed change:** Add the following statement: "Pharmacodynamic and pharmacokinetic data should be considered when establishing the dosing regimen (dependent on age /maturity)."
321	3	'*In order to achieve the targeted drug exposure, more than one dosage form of the active pharmaceutical ingredient (API) or its strength may be needed to cover the range of paediatric populations intended to receive the medicinal product.*' **Comments:** Proposed change for consistency. **Proposed change:** … more than one dosage form of the active pharmaceutical ingredient (API) or ~~its~~ strength may be needed to cover the range of…

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329 - 330	3	**Comments:** Consider avoidance of possible dosing errors with formulations e.g. prefilled syringes/auto injectors, guides etc. **Proposed change:** Such approaches could include clearly marked administration devices designed for accurate measurement of the smallest dose volume and dose increments. ***Prefilled syringes or auto injectors could also be considered.***
334 ICH 318	5	**Comments:** Given the comments earlier in the guideline about the importance of maturity rather than age, ACRO recommends that the phrase “paediatric age group” should be replaced by “maturity”. **Proposed change:** Replace “paediatric age group” with “maturity”.
		ACRO thanks the Agency for this opportunity to comment on **ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population, Step 2b (EMA/CPMP/ICH/2711/1999).**
340	6	**Comments:** When selecting excipients, the potential to generate antibodies should also be considered. **Proposed change:** “When selecting excipients, one should always consider the potential impact on absorption and bioavailability of the active ingredient **and the potential to generate antibodies.**”
Section 7.3	9	**Comments:** a reference to the need to address patients’ compliance when planning the development of new paediatric formulations can be added in the paragraph
356-378	8 and 10	**Comments:**

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		7.4 Neonates: Consultation with a neonatal specialist concerning additional aspects in neonatal care and drug administration should be sought to insure proper oversight and management. 8. Glossary: Concepts were addressed earlier in this document and should be referred to for further reference.
361-363	3	**'***When developing a parenteral dosage form, compatibility with other commonly administered parenteral medicines or parenteral nutrition should also be investigated, as intravenous access is often limited in this population*.' **Comments:** The request to test compatibility of a parenteral dosage form with other commonly administered parenteral medicines or parenteral nutrition is not feasible because of the very broad range of parenteral medicines or parenteral nutrition being used globally in neonatal care.