22 February 2019
EMA/139606/2019

Comments received during the Public Consultation on 'Concept paper on the need for revision of the guideline on the investigation of medicinal products in the term and preterm neonate' (EMA/PDCO/362462/2016)

Comments from:

Stakeholder Number (SN)	Name of organisation or individual
1	Brian Smith, MD, MPH, MHS; Samuel L. Katz Professor of Pediatrics, Division of Neonatal-Perinatal Medicine, Duke University Medical Center, Duke Clinical Research Institute Christoph Hornik, MD, MPH; Associate Professor of Pediatrics, Pediatrics-Critical Care Medicine, Duke University Medical Center, Duke Clinical Research Institute Kanecia Zimmerman, MD, MPH; Assistant Professor of Pediatrics, Division of Pediatric Critical Care Medicine, Duke Children's Hospital, Duke Clinical Research Institute
2	Prof Dr Tony Nunn Member of European Paediatric Formulation Initiative (EuPFI).
3	Chiesi Farmaceutici S.p.A. (Italy)
4	EFPIA
5	Gilead Sciences International Ltd
6	Vaccines Europe
7	International Neonatal Consortium (INC)
8	EFGCP, European Forum For Good Clinical Practice
9	European CRO Federation, EUCROF

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2019. Reproduction is authorised provided the source is acknowledged.

1. General comments

SN	General comment (if any)	Outcome (if applicable)
3	Chiesi Farmaceutici S.p.A. (Chiesi) welcomes this document as useful tool and driver to develop new treatments for term and preterm neonates, or to add the neonatal indication in existing drugs for other ages; as known, this is an area of major interest for Chiesi. Chiesi agrees on the Problem Statement definition. The guideline should be globally aligned among EMA and other worldwide Regulatory Agencies, avoiding any conflicting instructions. Chiesi underlines, when possible, the need to include in the revised guideline any reference to already existing data/information through e.g. searchable website – repository/archives of "solutions" occurred at Paediatric Investigation Plan (PIP) assessment relating to methodological issues, as data recordings, invasive measurements avoidance, applicable endpoints, informed consent process etc… The opportunity to access and share the amount of data so far collected by the Paediatric Committee will allow to define an adequate plan.	The comment is generally accepted. An update of the neonatal guideline taking into account guidelines and recommendations by other competent authorities and scientific organisations (e.g. FDA, INC) is one of the aims of the current revision. Another aim is to update the guideline with recently obtained data and achievements in the neonatology field. Experience gained through the review of neonatal PIPs will be taken into account when preparing the guideline; but it is highlighted that the ability to directly share previous discussions is limited by data confidentiality.
4	EFPIA welcomes the possibility to comment on this very relevant concept paper. Since the current guideline already provides a solid foundation for drug development in this special population, it is hoped that any revision will simply build on the current content with new approaches, such as the use of high quality real world evidence (e.g., historic comparators). Consider covering the following items in the updated guideline: Drug-drug interaction studies: due to scarcity of certain drug combinations in neonatal use, there is a need to identify potential risk in small numbers of patients. It would also be helpful to include a list of potential drug-drug interactions that do not warrant a warning for use in neonates.	The comments by EFPIA are acknowledged – please also see the response above. In addition, it is also planned to involve all relevant EMA committees and working parties, as well as patient organisations and organisations of healthcare professionals. The draft guideline will be released for public consultation with all stakeholders, including industry and academia.

SN	General comment (if any)	Outcome (if applicable)
	An item for neonatal registries (methods and uses as well as the e-HR implementation) could be considered. An item for use of biological compounds (e.g.: monoclonal antibodies) in this target population could be considered. It is mentioned in the introduction of the document that input will be sought from relevant working parties, committees and experts. We would welcome mentioning the importance of collaboration between authorities, industry and academia on this topic. It is recommended to establish specialized working groups to develop standardized and specific short- and long-term endpoints for different diseases and medical conditions in neonates (preterm/term). Guidance how to adequately asses neonatal pharmacovigilance data for this vulnerable and heterogeneous population with multiple confounding factors (Ward, Benjamin et al. 2017). It is recommended to stress the importance of collaboration with nurses, nutritionists, parent etc. under the protocol development. Finally, it is recommended that following the revision of the guideline on the investigation of medicinal products in the term and preterm neonate, further global harmonisation is sought via subsequent update of ICH E11 (R1).	However, it should be noted that the guideline itself is not intended to provide highly detailed recommendations on designing neonatal trials. The purpose of the Neonatal guideline is to provide clear basic recommendations for drug development in term and preterm neonates, leaving flexibility to amend the study design according to individual situation. The need for global alignment is acknowledged. Regarding the remaining points, Point 5 is considered covered under several points of the concept paper (e.g. B, G, J, L, N) as appropriate and will be considered during the preparation of the guideline. Point 7 is considered covered under point B of the concept paper and will be considered during the preparation of the guideline. Pharmacovigilance in the paediatric population is covered in the Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016).

SN	General comment (if any)	Outcome (if applicable)
6	Vaccines Europe welcomes the opportunity to provide comments on EMA's 'concept paper on the need for revision of the guideline on the investigation of medicinal products in the term and preterm neonate' The general comments provided below pertain to vaccine trials: The numerous classification systems developed around preterm birth should be considered. Depending on the cause of prematurity and the method of nomenclature/classification, the effect on the maturity of the immune system and response to vaccines will have an impact on various safety and efficacy parameters assessed in vaccine trials. Consideration of special parameters for this age group may be needed and not what is frequently recorded for local and systematic AEs. E.g. skin changes, redness, temperature. Attention to normal laboratory values and clinical measurements should be used in adverse event reporting which are very variable in this age group. Special attention should be given to safety monitoring: Preterm infants are likely to develop many immune-mediated diseases as compared to other paediatric age groups. How would this impact/adapt collection of safety information in the long and short term? This should be updated with reference to exclusion of certain more vulnerable syndromes/symptoms or justification for participation of very vulnerable individuals. Against backdrop of concurrent/intercurrent medical conditions common in preterm neonates. This may also bias or skew adverse event reporting. Given the scope of terms used to define preterm and neonatal period and the spectrum of characteristics of children in this age group, justification based on stratification of risk factors and baseline characteristics *vs*. seriousness and uniqueness have to be considered for timing of development of medicinal products. Further guidance on first data required for conditions exclusively found in neonates is deserved. The need for trials being carried out in this vulnerable age group should be clarified. Advances in technology and life support in early life e.g. neonatal intensive care units care protocols may affect the expected immune responses to vaccine products. This vulnerable age group may require revised expectations in immune response profile. Routes of administration do not reflect the differences between vaccines and drug administration in common practice. If a formulation is significantly changed during development for neonatal use, comparison of bioavailability may be required. Update to the blood sampling: since this age-group has a small blood volume and yet this would be a key	The comments by Vaccine Europe are acknowledged and will be considered during the Guideline revision, unless already covered in other relevant Guidelines. It is generally agreed that there is a need for specifically tailored recommendations for defining and reporting adverse events in neonates. Special attention will be paid to requirements for short- and long-term safety monitoring.

SN	General comment (if any)	Outcome (if applicable)
	feature of vaccine trials for example, a more concise guideline on acceptable volumes/limits/timelines for the different age categories should be included. Suggest providing minimum recommended follow up time for long term safety follow up. Could registries be considered as a mandatory requirement for some trials? Harmonization of adverse event and case definitions for adverse events, in particular for those of special interest in the preterm and neonatal period would be appreciated. Because this special population will have fewer studies and limited study size, this will make the data more globally applicable. Neurodevelopmental disorders post vaccination- adverse event of special interest literature states a link between this and vaccination in preterm and neonates. This should be considered. Contamination of neonatal units following shedding or excretion of vaccine components in neonatal units e.g for some oral vaccines. This should be considered.	
7	INC applauds EMA for taking on this critical effort to improve the development and evaluation of medical products in term and preterm neonates. The advances in the field in the decade since the last guideline was prepared, together with innovations in regulatory science, can serve to optimize the design and execution of neonatal trials. INC agrees that each of the issues listed in the Discussion section (3a-3n) merit consideration and updating. Additional suggestions for topics that would benefit from inclusion in the updated guidance include the following: Considerations for biologic compounds (e.g. monoclonal antibodies) should be part of the discussion of sections 3d-3f. Considerations on the evolution of digital technology (e.g. wearable devices and sensors) to provide clinical outcome assessments and biomarkers for neonatal trials Considerations on the use of electronic health records and other sources of 'real world data' to inform regulatory decision-making. Standards and measurements to use in the assessment of neonates born to mothers who have been exposed to pharmaceuticals and biologics during the pregnancy. We recognize that perinatology may not be within the scope of the planned guidance.	The comments by INC are acknowledged and will be considered during the guideline revision process. Recommendation to pay specific attention to perinatal and foetal medicine as a part of neonatal medicine is supported and will be further discussed as appropriate; however in utero drug exposure due to treatment of the mother is outside the scope of the guideline.

SN	General comment (if any)	Outcome (if applicable)
8	EFGCP welcomes the update of the guideline. EFGCP has reviewed the Concept paper. The Concept paper document is very straight forward and focused and there is actually nothing really to comment on. Nothing disrupting has been identified.	The comment by EFGCP is acknowledged.
9	Additional points that we would see as benefiting from being addressed are safety in neonatal trials and how to achieve good reporting of relevant AEs/SAEs without over burdening the neonatologist. The use of registries for long-term follow-up particularly with the influx of advanced therapies may also benefit from being mentioned. We welcome the update of the guideline.	The comments are acknowledged (see also responses to comments above).

2. Specific comments on text

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3a		**According to the current Guideline neonates are the group of children from birth up to and including the age of 27 days, including term and preterm neonates. This should be re-discussed ~~vised~~ taking into account most recent and commonly utilised classification system based on postmenstrual age (PMA) more specifically addressing enzyme and organ system development and maturation in preterm neonates. ~~In accordance with the most precise modern definition the neonatal age for preterm neonates is considered the age period up to 44 full weeks of PMA.~~**	
3. Discussion (on the problem statement). *Paragraph a)* Lines 36-41	3	*Comment:* Chiesi agrees on this statement. At the same time, ontogeny changes according to the metabolic pathway of interest, so some flexibility in the definition of the subgroups should be warranted	The purpose of the planned revision is to align the definitions of the neonatal age group and subgroups with the recently published guidelines (e.g. ICH E11, INC). Updated definitions of the neonatal age group should more correctly reflect the actual maturation of enzymes and organ systems reflecting specific maturation-related PK and PD alterations. However, it is noted that divergence from defined subgroups is always possible if scientifically justified.
3.(a)	4	Comment 1: The definition of neonatal age as 44 full weeks of PMA is crucial for preterm and term neonates. Full-term neonates have been considered as a homogeneous group, however high neonatal morbidity of early-term neonates compared with term neonates has been reported (Sengupta, Carrion et al. 2013). Preterm neonates are usually classified	Comment 1 has been acknowledged and will be considered during the guideline revision (see also response above). Comment 2 is acknowledged. In general

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
		by gestational age into groups: extremely preterm 24-<28 wk GA, very preterm:28 -<32 wk GA and moderate to late 32-<37 wk GA. When updating the definitions consider stratifying term neonates as following: *early term (37 (0/7)-38 (6/7) weeks; Term (39 0/7) – 41 (0/7) weeks.* Comment 2: When the definition is updated it should not be forgotten to revise associated documents such as the PIP Part A to reflect the revised age range for waivers applicable for paediatric subsets (current drop-down menu states: Preterm and/or term new born infants (0-27 days), Infants and toddlers (28 days to 23 months), etc). Sengupta, S., V. Carrion, J. Shelton, R. J. Wynn, R. M. Ryan, K. Singhal and S. Lakshminrusimha (2013). "Adverse neonatal outcomes associated with early-term birth." JAMA Pediatr 167(11): 1053-1059.	EMA is committed to the continuous improvement in the handling of PIP applications as agreed in the "EMA-EC action plan on paediatrics" published in October 2018, and it is highlighted that PIP Part A already at this point allows applicants to specify subsets different from ICH E11.
Discussion section 3A	7	There are two parts to this section of the guideline: 1) the definition of neonate; and 2) the definition of neonatal age for preterm neonates. Regarding the first part, there is uniform adoption of the definition published in the 2016 Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11(R1): "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. Neonates include both term and preterm newborn infants. The neonatal period for term newborn infants is defined as birth plus 27 days. The neonatal period for preterm newborn infants is defined as beginning at birth and ending at the expected date of delivery plus 27 days. As the neonatal population represents a broad maturational range, the conditions that affect this population can vary considerably. A rationale for the selection of a neonatal population in clinical studies should be provided." http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/E11-	The comment is acknowledged. The proposed definition of the neonatal age as a period of 44 full weeks of PMA does not conflict with the definition stated in the recently revised ICH E11. However, it is supported that clear definitions of the neonatal age and subgroups are needed. The text in the concept paper has been modified to reflect that the discussion of the actual wording of the definitions will take place during the guideline revision process.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
		R1EWG_Step4_Addendum_2017_0818.pdf INC has extensively discussed the definitions of preterm and term neonates as well as the need for international alignment around these definitions. INC agrees with the standardized definition of preterm neonates as any neonate born less than 37 completed weeks of gestation and the neonatal period as the first 27 days after birth (Ward et al., Pediatrics Research 81(5):692-711 (2017). These definitions are in alignment with the ICH definition (cited above) and the WHO definition of preterm birth: any birth before 37 completed weeks of gestation, or fewer than 295 days since the first day of the woman's last menstrual period (Howson et al, 2012). Regarding the statement "In accordance with the most precise modern definition the neonatal age for preterm neonates is considered the age period up to 44 full weeks of PMA", there is a need for greater clarity around the choice of 44 weeks PMA, including a rationale for that choice.	

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3b		**Greater emphasis should be placed on the importance of aspects associated with study design, identifying standard measures and/or timelines where appropriate, e.g. choice of response variables, assessment time points and observation duration and intervals, in the context to the expected and clinically relevant effects. Study design should consider possibility to differentiate between treatment effect and impact of various confounding factors typically influencing outcomes of neonatal conditions. For example, timing and criteria for neurodevelopmental outcomes, neonatal asphyxia criteria, diagnosis and monitoring of neonatal seizures, and prematurity-related conditions, etc.**	
Regarding Item 3.b)	1	Regarding Item 3.b) addressing study design, we would suggest carefully considering methods for analysing data in neonates, e.g., Bayesian designs based on priors from other pediatric populations	The comment is acknowledged. Various specialists and working groups will be involved in the guideline revision, including specialists in biostatistics. Moreover, data sharing collection in a prospective setting is supported to improve the knowledge of the neonatal diseases and to improve the design of the studies.
3. Discussion (on the problem statement). *Paragraph b)* Lines 42-49	3	*Comment:* Chiesi agrees and is confident that the revision of the guideline will facilitate future development plans. Current guideline is too general, a better defined guideline would avoid the need to frequently scientific advices to discuss acceptable efficacy endpoints.	The comment is acknowledged. Although, the purpose of the guideline is not to provide very specific and narrow recommendations, it is generally supported that clear and well defined guidance will provide better support for all interested parties.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
			However, no guideline can cover all scenarios and thus the guideline is not intended to substitute for Scientific Advice.
3.(b)	4	Consider including in the section: innovative study designs, e.g. applied in studies of rare diseases could be feasible (Allegaert, Smits et al. 2018). master protocols to improve conduct of the clinical trials in this non-homogeneous and vulnerable group (Woodcock and LaVange 2017). development of non-invasive or micro-sampling techniques, use of scavenged samples for detection of the specific biomarkers as well as the IMP for PK/PD studies in neonates. The validation of the assays for neonatal studies should be assessed early in the IMP development process, e.g. during the preclinical and early clinical studies (Phase I and II), these studies should also provide the evidence to support the use of the biomarker for the specific neonatal condition (Ward, Benjamin et al. 2017), (Bai, Barrett et al. 2013). Sampling scheme must be planned to obtain the maximum information from the minimal number of samples. The preferable collection is together with the samples collected for clinical purpose. Proposed change: "Study design should consider possibility to differentiate between treatment effect and impact of various confounding factors typically influencing outcomes of neonatal conditions. For example, timing and criteria for neurodevelopmental outcomes, neonatal asphyxia criteria, diagnosis and monitoring of neonatal seizures, and prematurity-related conditions, etc*. Additionally, alternative*	The comment is acknowledged. Innovative approaches appropriate for designing studies in neonates will be considered during the guideline revision process. Development of any study protocols is outside the scope of the guideline revision. It is agreed that one of the main principles for neonatal studies is minimising the potential burden to the patient as much as possible whilst still maintaining scientific robustness. Recommendations for minimising all types of burden to such a vulnerable population will be discussed in preparation of the revised guideline.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
		approaches including innovative study designs and master protocols (to improve conduct of the clinical trials in this non-homogeneous and vulnerable group) should be taken into account. With regard to sampling, the development of non-invasive or micro-sampling techniques and the use of scavenged samples for detection of specific biomarkers should be envisaged." Allegaert, K., A. Smits and J. N. van den Anker (2018). "Drug evaluation studies in neonates: how to overcome the current limitations." Expert Rev Clin Pharmacol 11(4): 387-396. Bai, J. P., J. S. Barrett, G. J. Burckart, B. Meibohm, H. C. Sachs and L. Yao (2013). "Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants." AAPS J 15(2): 447-454. Ward, R. M., D. Benjamin, J. S. Barrett, K. Allegaert, R. Portman, J. M. Davis and M. A. Turner (2017). "Safety, dosing, and pharmaceutical quality for studies that evaluate *medicinal products (including biological products) in neonates." Pediatr Res 81(5): 692-711.* *Woodcock, J. and L. M. LaVange (2017). "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both." N Engl J Med 377(1): 62-70.*	
Page 3 Section 3 b)	6	Comment: Considerations about vaccine clinical trials in neonates should be mentioned here. Proposed change (if any): Additional bullet(s) may be included to focus on the specific needs associated with study design, e.g.: guidance on the early assessment of potential immunological interference between maternal immunization(s) and infants' active immune response to	The comment is acknowledged. Special attention will be paid to the revision and implementation of recommendations applicable to neonatal vaccine trials, as appropriate and unless already covered in other relevant guidelines. Inclusion of the proposed additional bullet points will be further discussed during the guideline revision process.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
		pediatric vaccination (e.g. maternal immunization with vaccines containing non-toxic mutant of diphtheria toxin, CRM, as the carrier and infants' vaccines containing diphtheria toxoid) guidance on measures for long-term follow-up and monitoring of vaccine trial participants; differences versus the long-term follow-up required for drug trials participants	It is also noted that vaccination in pregnancy and the duration of safety follow-up are covered in the guideline on clinical evaluation of vaccines (currently also in revision).

Line number(s) of the relevant text	SN	Comment and rationale; proposed changes	Outcome
Section 3c		**Development of proper animal models for specific neonatal conditions (more targeted designs).**	
3. Discussion (on the problem statement). *Paragraph c)* Lines 50-50	3	*Comment:* Chiesi agrees on this statement. Indeed, some members of Chiesi R&D team are currently working on this topic within Health and Environmental Sciences Institute (HESI) network. They are contributing to the drafting of a review manuscript focused on the non-clinical models of the 6 more common NICU conditions (Bronchopulmonary dysplasia -BPD, Retinopathy of prematurity -ROP, Necrotizing enterocolitis - NEC, Neonatal abstinence syndrome -NAS, Nosocomial bacterial infection - NBI, Sepsis) with no available approved therapies. The manuscript is supposed to be published in the first half of 2019. Considering that the scenario for these animal models is always evolving, the insertion in the guideline of a reference to such scientific manuscripts and its follow-ups is suggested Chiesi believes that more detailed indications on the required animal models (or at least on the literature of reference) both for the safety and, when possible, efficacy studies could be of help. Chiesi suggests promoting the alignment among worldwide Regulatory Agencies on the requirement of what it is really needed in terms of dedicated neonatal non-clinical investigations. This session in the guideline should be revised and expanded through the insertion of adequate indications on the animal neonatal models suited for safety studies.	It is principally agreed to take into account and refer to results from ongoing scientific projects and the current literature. Ongoing discussions on paediatric development plans between regulatory bodies also include non-clinical topics and a systematic approach in order to align requirements as far as possible should be considered.

Line number(s) of the relevant text	SN	Comment and rationale; proposed changes	Outcome
3.(c)	4	Comment: Revision of the guidance should be in line with the newly created ICH S11 Guidance on Development of Paediatric Medicines. Furthermore, consider including: The animal models for most disease states affecting newborn infants, preterm or full term are already existing. To avoid a very broad statement, regarding development of proper animal models, this section should focus on unmet disease states, for which animal models are missing. Finding of adequate juvenile animal models with similar organ maturation, covering the effect of prematurity and birth, may be challenging. A fair judgement of suitability and availability of such models as well as acknowledging the current limitations should be described in this this section. Development of animal models with translatable designs, with focus on the extent to which they are *translatable* to human neonates should be discussed.	The comment is principally agreed. The level of detail, however, will depend on the availability of appropriate data and experience using the models, and developments of models specifically appropriate to the neonatal population.
3C and 3F	7	Regarding the development of animal models (section 3c) and PK/PD extrapolation (section 3f), the discussion could be informed by work presently being conducted by a Health and Environmental Sciences Institute (HESI) technical committee on issues related to neonatal drug development: http://hesiglobal.org/developmental-and-reproductive-toxicology-dart/	Agreed (see first comment in this section).

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3d		**The differences of pharmacokinetics, pharmacodynamics and dose finding in different neonatal subgroups could be updated where measurable or clinically meaningful. Limitations of PK collection should be considered as well.**	
3. Discussion (on the problem statement). *Paragraph d)* Lines 51-52	3	*Comment:* Chiesi agrees and would like to add the following topics/considerations: Modelling to predict will be very important for the paediatric plan. This updated guideline should clearly report the possibility to include extrapolation plans for neonatal product developments, according to the "Reflection paper on the use of extrapolation in the development of medicines for paediatrics" (EMA/189724/2018). Chiesi would suggest giving more details on significant reference populations. Modelling can link subgroups or simulate neglected subpopulations, but it needs anchoring on data: data from what? Older children (which age?)? Animal (juvenile) models? Molecules in the same class? Molecules with similar chemical structure? Molecules with similar physical properties? PK assessment requires blood, and neonates are infamously stingy in providing it: so Chiesi recommends that the guideline provides guidance not only on PK analysis, but also on the practicalities of PK collection. Hard to investigate fixed effects, random effects or covariates when you have only a couple of samples for neonate.	The provided comments are appreciated. Modelling and extrapolation will be considered in the guideline preparation – see point F of this concept paper. Practicalities of PK sample collection will be considered in the guideline as part of the study design under point B of the concept paper. However, for clarity the text in the concept paper has been amended.
3.(d)	4	To update the differences of pharmacokinetics, pharmacodynamics and dose finding in different neonatal subgroups would require there are specific measurable pharmacodynamics outcomes from all medications in neonates, which may not always be true. The statement, therefore, should be softened to "where measurable" and "where clinically meaningful."	Agreed. The text in the concept paper has been changed in line with the proposal.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3e		**Special attention should be paid on the rationale for dose selection in this ~~delicate~~ vulnerable age group; whether it is based on allometric scaling, body surface area (BSA) or linear scaling, it shall be properly justified. Situations when no reference PK and PKPD data are available from other age groups will also be considered.**	
In Item 3.e)	1	In Item 3.e) we suggest revising the nomenclature used to refer to a "vulnerable" population rather than a "delicate" one.	Comment agreed. The text in the Concept paper has been changed as proposed.
3. Discussion (on the problem statement). *Paragraph e)* Lines 53-55	3	*Comment:* Chiesi agrees. However, it should be noted that the whole section is about scaling the dose to neonates from reference population. No guidance is offered on best practice when no reference PK and PKPD is available from other population, i.e. when one is forced to first in human trial (FIH) in neonates	Comment agreed. The text in the Concept paper has been changed as proposed.
Page 3 Section 3 e)	6	Comment: When mentioning dose selection, may be useful to differentiate between vaccines and drugs dose selection Proposed change (if any):	Agreed that special attention will need to be paid during the guideline revision to make it clear whether a section also/only applies to vaccines.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3f		**PK/PD extrapolation, modeling and simulation approaches, supporting dose selection and extrapolation of efficacy from other age groups has evolved significantly over the last years and must be correctly addressed. Extrapolation of safety from other age groups to neonates is usually not possible, but ~~should~~ could exceptionally be considered where available evidence is supportive.**	
In Item 3.f)	1	In Item 3.f) regarding PK/PD extrapolation, we would suggest providing more specificity: population PK (and maybe PD) models should be incrementally developed and scaled from adults to other children to neonates. This may be thought of as 'in silico' preparatory work prior to conducting a neonatal trial.	These comments will be taken into consideration during the guideline revision, but do not require a change in the concept paper as details on PK/PD extrapolation will be part of the new guideline rather than this concept paper.
Regarding Item 3.f)	1	Regarding Item 3.f) on PK/PD, what role does the Agency intend PDPK modelling to have in neonatal PK trials?	These comments will be taken into consideration during the guideline revision. Please see response above.
In Item 3.f)	1	In Item 3.f) regarding PK/PD extrapolation, we suggest that evaluation of long term neurologic outcomes be strongly considered.	Long-term outcomes will be covered in the guideline (see point F of this concept paper).
3. Discussion (on the problem statement). *Paragraph f)* Lines 56-59	3	*Comment:* Chiesi agrees on this statement and specifically that safety profile needs to be established in the neonatal population Definitely a lot has been going on in modelling and simulation in the past 10 years, so this is probably the section that could be updated the most	The comment is acknowledged.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
3.(f)	4	Comment: Recognition in this section that modelling and simulation "must be correctly addressed" is very much welcomed. In light of this, it is proposed that consideration should be given to bringing "Modelling and Simulation" forward in the paper and from this section the animal models, PK/PD differences and extrapolation sections could flow. Furthermore, it is our experience that extrapolation of safety from other age groups to neonate is – in principle - possible and this must be addressed in the guidance. Furthermore, consider covering: Physiologically based PK/PD models, adjusted for body size, body weight, and age-related physiological changes (Michelet, Van Bocxlaer et al. 2018). Practical examples of acceptable extrapolation are welcome and could be a useful accompaniment to the guidance. Michelet, R., J. Van Bocxlaer, K. Allegaert and A. Vermeulen (2018). "The use of PBPK modeling across the pediatric age range using propofol as a case." J Pharmacokinet Pharmacodyn.	These comments will be taken into consideration during the guideline revision, but do not require a change in the concept paper. Practical examples of acceptable extrapolation are covered in disease-specific guidelines, while this guideline will specifically emphasize the possibilities and limitations of modelling, simulation and extrapolation in neonatal drug development.
3(f)	5	Comment: Due to the vulnerability of the neonate population, the extrapolation seems often more appropriate (if existing evidence supports). Proposed change (if any): Extrapolation of safety from other age groups to neonate ~~is usually~~ may not be possible…	Change not accepted. The current wording already covers all scenarios and the details will be carefully considered in the guideline.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
3C and 3F	7	Regarding the development of animal models (section 3c) and PK/PD extrapolation (section 3f), the discussion could be informed by work presently being conducted by a Health and Environmental Sciences Institute (HESI) technical committee on issues related to neonatal drug development: http://hesiglobal.org/developmental-and-reproductive-toxicology-dart/	It is principally agreed to take into account and refer to results from ongoing scientific projects and the current literature.
3F	7	Regarding the statement "Extrapolation of safety from other age groups to neonate is usually not possible, but should be considered where available evidence is supportive", in other FDA, EMA, and ICH Guidances it is clearly stated that safety cannot be extrapolated. If extrapolation to neonates is considered, it should be stated very clearly in the guidance under what conditions extrapolation could be considered acceptable, including in what other age group(s) it could be used and the limitations of extrapolation to that age group(s). Generally, safety information can be leveraged from other populations to support neonatal safety, but it is not possible to extrapolate safety. ICH Pediatric Extrapolation work is ongoing and should inform the EMA revision of the guideline: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11A/E11A_ConceptPaper_Final_2017_1017.pdf	The wording was updated to better highlight the limitations, which will be addressed in the guideline.

Line number(s) of the relevant text	SN *	Comment and rationale; proposed changes	Outcome
Section 3g		**The current outcome assessment scales could be reviewed and the importance of use of validated scales, whenever possible, should be emphasized.**	
3. Discussion (on the problem statement). *Paragraph g)* Lines 60-61	3	*Comment:* Not always in neonatology the outcome assessment scales are validated even if commonly used in the clinical practice (e.g. Finnegan score for Neonatal Abstinence Syndrome - NAS). Chiesi agrees on underlining the importance to use validated scales but when it is not possible, Chiesi suggests to better indicate the way to use them or alternative and surrogate scales for regulatory purpose.	Comment agreed. The statement has been adapted to highlight that the use of validated scales may not always be possible, and alternatives will be considered in the guideline to the extent possible.

Line number(s) of the relevant text	SN *	Comment and rationale; proposed changes	Outcome
Section 3h		**Eventual differences in the manifestations of the disease among neonates (pre- through to post-term) and children should be addressed in drug development.**	
3. Discussion (on the problem statement). *Paragraph h)* Lines 62-63	3	*Comment:* Chiesi agrees on this statement and particularly for pre-term based on the gestational age, birth weight (extremely low, very low, low, adequate birth weight) and on the relationship between birth weight and gestational age (small for gestational age /adequate for gestational age/large for gestational age).	The comment is noted. No change to the concept paper is necessary but the different groups (gestational age, birth weight, and weight for age) will be considered in the guideline.
3.(h)	4	Comment: Differences should also be described in conjunction with an eventual extrapolation of exposure-response rate from studies in older children/adults (Ward, Benjamin et al. 2017). Ward, R. M., D. Benjamin, J. S. Barrett, K. Allegaert, R. Portman, J. M. Davis and M. A. Turner (2017). "Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates." Pediatr Res 81(5): 692-711.	The comment is noted. Extrapolation will be considered in the guideline (see point F of this concept paper).

Line number(s) of the relevant text	SN	Comment and rationale; proposed changes	Outcome
Section 3i		**There should be a greater focus put on organ and enzyme system maturation differences across the neonatal subgroups (such as term, preterm, extremely preterm neonates, small, appropriate and large for gestational age), including coverage of more recent data on developmental pharmacology.**	
3. Discussion (on the problem statement). *Paragraph i)* Lines 64-66	3	*Comment:* Chiesi agrees on this statement.	Comment noted.
3.(i)	4	Comment: Currently the dose selection for this very vulnerable and heterogeneous population is for most drugs based on weight rather than post conceptual age. It is therefore important, that the updated guidelines emphasize this point. Also, it is suggested that large for gestational age should also be included: all growth abnormalities can affect the pharmacology of the IMP (Ward, Benjamin et al. 2017). The immature liver function has limited consequences on the healthy term neonate. But the preterm neonates are susceptible to the immature liver function and impaired drug metabolism. The postnatal age has also been reported to have an impact on the activity of some enzymes (Ward, Benjamin et al. 2017). More details needed on dynamic changes in liver function during the neonatal period in preterm and term neonates, specifying organ and enzyme system maturation differences across the postnatal age subgroups. More recent data on developmental pharmacology should include maturation of cardiovascular receptors: effect of certain drugs (partial agonists, inverse	Both weight and age are relevant variables during dose-finding in neonatal subgroups. Therefore, immature liver function can be a serious issue not only in preterm but also in healthy term neonates. However, the proposed change is accepted. It is agreed that there should be a discussion also on receptors and neurotransmitters. Therefore, both PK and PD maturation are to be considered during the guideline preparation as implied by "organ and enzyme system maturation".

Line number(s) of the relevant text	SN	Comment and rationale; proposed changes	Outcome
		agonists) on the stimulation of G-coupled protein receptors, GCPRs during maturation. More discussion is needed on neurotransmitters and monitoring: potential effects of medicinal products releasing or substituting neurotransmitters in term and preterm (differentiated) on brain maturation and are there any special concerns in preterm neonates (e.g. transitory hypothyroidism). Proposed change: "There should be a greater focus put on organ and enzyme system maturation differences across the neonatal subgroups (term, preterm, extremely preterm neonates and *across birth weight subgroups* (e.g. small, *appropriate and large* for gestational age)". Ward, R. M., D. Benjamin, J. S. Barrett, K. Allegaert, R. Portman, J. M. Davis and M. A. Turner (2017). "Safety, dosing, and pharmaceutical quality for studies that evaluate *medicinal products (including biological products) in neonates."* *Pediatr Res 81(5): 692-711.*	

Line number(s) of the relevant text	SN *	Comment and rationale; proposed changes	Outcome
Section 3j		**Consideration could be given to the development and validation of biomarkers (surrogate markers or surrogate endpoints) for disease, ~~diagnosis~~ treatment effects and outcome evaluation, e.g. neonatal sepsis or neonatal asphyxia.**	
3. Discussion (on the problem statement). *Paragraph j)* Lines 67-69	3	*Comment:* Chiesi recommends focusing also on the use of translational biomarkers for guiding pre-clinical research as well as markers for providing prognostic information and stratifying infants for clinical trial enrolment.	The comment is appreciated. Translational biomarkers could be useful e.g. to guide pre-clinical research from the clinical situation and to support the use of biomarker endpoints from preclinical findings. This may be included in more the detail in the guideline. The text in the concept paper has been changed to better include both digital and translational biomarkers.
3.(j)	4	Consideration could be given to: Development and validation of biomarkers identifying the disease-related biologic activity that are not necessarily outcome measures. The evaluation of digital biomarkers.	The concept paper has been modified and more detail may be included in the guideline

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3k		**Consideration could also be given to trials in which neonates have been treated prenatally and the optimal use of pre- and postnatal data.~~the extrapolation of fetal (intra-uterine) data to preterm neonates.~~**	
3.(k)	4	Comment: The concept paper is stating that extrapolation of fetal (intra-uterine) data to preterm neonates could be considered. In view of the fact that dosing of prenatal infants is outside the scope of the guideline, this statement is confusing.	Comment agreed. The text in the concept paper requires clarification and has been re-worded.
3K	7	Regarding "Consideration could also be given to the extrapolation of fetal (intra-uterine) data to preterm neonates", significantly more data would be needed to support this concept. Presently little information is available on intra-uterine processing of drugs, and even less in known for biologics.	Comment agreed. See response above.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3l		**Specific attention should be paid to various long-term outcomes and the need for validated long-term endpoints for specific medical conditions, serving a particular interest to neonatal studies, including developmental effects.**	
3. Discussion (on the problem statement). *Paragraph l)* Lines 72-73	3	*Comment:* Chiesi agrees on this statement	Comment noted.
3.(l)	4	When describing this section consider: Long-term outcome studies to be conducted as a part of post-marketing risk management plan, and the studies should at least cover first 2 years of life (corrected gestational age). The need of a standardized and validated set of short- and long-term endpoints for specific medical conditions in preterm and term neonates, which should be developed in collaboration with relevant stakeholders (Ward, Benjamin et al. 2017). Ward, R. M., D. Benjamin, J. S. Barrett, K. Allegaert, R. Portman, J. M. Davis and M. A. Turner (2017). "Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates." Pediatr Res 81(5): 692-711.	1) These comments will be taken into consideration during the guideline revision, however do not require a change in the concept paper as long-term outcome is already covered. Details on how long term follow-up should be performed will be part of the new guideline rather than this concept paper. 2) Comment agreed. The concept paper has been amended accordingly and details on standardised and validated endpoints will be considered in the guideline.
3(l)	5	Comment: A clearer distinction between the long-term and short-term outcomes would be welcome; for instance, in the specific case of exposure to antiretrovirals (ARVs), the consideration for monitoring of neuro-developmental outcomes should be adapted to the timing of exposure and its potential impact on the neonate. A	This comment is appreciated and will be taken into account during the guideline revision.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
		unique and non-specific approach could trigger potential challenges in the long-term patient follow-up as well as patient privacy while not necessary. Proposed change (if any): Specific attention should be paid to short term outcomes in neonates who have been exposed to drugs after gestation and ~~various~~ long term outcomes ~~serving a particular interest to neonatal studies~~in neonates who have been exposed to drugs in utero, including developmental effects.	The suggested changes are not agreed as in utero drug exposure due to treatment of the mother is outside the scope of the guideline.
3L	7	Regarding "Specific attention should be paid to various long-term outcomes…", INC agrees and has developed a white paper focused on long-term cognitive outcomes (Marlow et al., Pediatric Research, in review).	This comment is appreciated and the white paper focused on long-term cognitive outcomes will be taken into account during the guideline revision.

Line number(s) of the relevant text	SN *	Comment and rationale; proposed change	Outcome
Section 3m		**Particular focus should be given to update of neonatal formulation issues in relation to the recent Paediatric Quality Guideline (2014), the recent addendum to ICH E11, excipient labelling documents and specifically addressing challenges with excipients. Neonatal specific challenges that might impact dose delivery and absorption, such as food effect and enteral tubes, should be considered. Neonatal specific aspects of assessing product acceptability to patient and carers should be covered.**	
3. Discussion (on the problem statement). *Paragraph m)* Lines 74-76	3	*Comment:* Chiesi suggests stressing the importance of having and how to handle at regulatory purposes shared infos on the paediatric formulation and excipients including reference to existing excipients databases (e.g. European Paediatric Formulation Initiative -EuPFI databases).	Comment partly agreed: How to handle and share information on paediatric formulations and excipients are not neonatal specific issues, but no less important in neonates. The comment on reference to existing excipient databases is considered covered by the current text and will be included in the guideline text.
Focusing on 3.m)	2	Particular focus should be given to update of neonatal formulation issues in relation to the recent Paediatric Quality Guideline (2014), excipient labelling and specifically addressing challenges with excipients. Strongly agree. The current neonatal guideline has good information on the problems with formulations for neonates but says little about the way in which the formulations and dosage forms should be investigated during clinical trials. In particular there should be information on methods of assessing acceptability of the product to both neonate and carers charged with administration. For example, a) how	Comments overall agreed. The text in the concept paper has been amended in line with the comments, unless the issues are considered already covered by the current concept paper wording.

Line number(s) of the relevant text	SN *	Comment and rationale; proposed change	Outcome
		should the acceptability of oral mini-tablets be investigated to ensure that the entire dose is administered and that there are no adverse effects (e.g. choking) from the selected dosage form?; b) can the volume of an IV injection be administered with sufficient accuracy and, if dilution is required to achieve the required dose, can this be done in a safe and timely manner? Outcome measures relating to formulations and neonates will often be observational by the carer, requiring well designed and tested methodologies and tools. I agree that the current Paediatric Quality Guideline should be taken into account but it says little about neonates. The recent ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION E11 (R1) should also be taken into account. The revised guideline should take into account advice given to PDCO on quality and clinical pharmaceutics aspects of PIP applications and any information derived from key binding elements of PIP decisions and completion of PIPs. Some of these issues would include accuracy of dose measurement and appropriate devices for dose delivery; lack of evidence of safety of excipients and extrapolation from information relating to infants and children; the need to study stability of IV drugs in dextrose as well as saline solutions; methods of risk reduction relating to formulations including avoiding ten times dose errors; status of minitablets and other formulations in relation to acceptability to regulators etc. The recent revision of the EC excipient labelling guidance is important but was never intended to be directly about pharmaceutical development. Of equal or greater importance are the EMA reviews which support the labelling guidance and these should be taken into account. Developers need to know which	

Line number(s) of the relevant text	SN *	Comment and rationale; proposed change	Outcome
		excipients to avoid and what are acceptable intake levels of excipients for neonates. How might risk assessment be applied to the selection of excipients? Biopharmaceutical aspects require more attention. Neonates may be in a state of (almost) continuous enteral nutrition and may also have drugs administered via enteral tubes. Both are examples of the need to assess effects on dose delivery and absorption.	

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Section 3n		**Overall harmonization and update of terminology and definitions is required.**	
3. Discussion (on the problem statement). *Paragraph n)* Lines 77-77	3	*Comment:* Chiesi agrees on this statement.	Comment noted.
3N	7	Regarding "Overall harmonization and update of terminology and definitions is required", INC agrees. The field will not advance until standardization is enforced. INC began by developing needed terminology for neonatal adverse events, and is now expanding that effort to fill remaining terminology gaps for regulatory submission of neonatal trials. Standardized terminology is also needed for regulators to draw on the extensive amounts of data from electronic health records. The guidance is an opportunity for EMA to express support for standardizing and sharing data as well as establishing resources such as neonatal databases that include data on observational and intervention studies, electronic health information, and information on standardized methods.	The comment has been acknowledged. During the guideline revision process neonatal terms and definitions will be updated in line with the latest available updates and based on comments from all interested parties.

Line number(s) of the relevant text	SN*	Comment and rationale; proposed changes	Outcome
Proposals for further sections		**3.o. Special attention should also be paid to the evaluation of drug safety in neonates.**	
Proposal for addition	3	Chiesi would like to suggest the following additional topics to be considered: o) to consider that a clinical trial conduct can be improved by the development of master protocols made available by the Regulatory Agencies and the use of selection criteria to optimize quality and performance of participating neonatal units p) to consider that the assessment of drug efficacy can be improved by developing valid case definitions, core outcome sets and standardized reporting. q) To provide guidance on how to limit unnecessary clinical data collection particularly in Neonatal Intensive Care Unit - NICU (e.g. defining standard concomitant medications, reference ranges for laboratory findings according to gestational age). r) Drug safety evaluation can be improved by validation of laboratory reference values, and by the development of Adverse Drug Reaction - ADR algorithms specific to neonates / time points for collecting adverse events – pre-dose and post-dose / better definition of seriousness criteria. s) To make more flexible the parents informed consent process allowing the signature at the time of treatment.	o) The development of such protocols is outside the scope of the guideline (see response in section B). p) This is already considered covered by other points of the concept paper (e.g. B, G, H, J, L, N). q) This is already considered covered under Point B. In general, the guideline will focus on the need for standardised approaches and relevant recommendations where appropriate, but is out of the scope pf this guideline to deliver highly specified recommendations (e.g. specific reference levels for lab tests). r) Comment agreed. Improvement of safety evaluation is one of the goals of the guideline revision and the development of an ADR reporting algorithm specifically adjusted to the neonatal population will be considered. Point O has been added to the concept paper. s) Comment not agreed. The informed consent process outside the scope of this guideline.

* SN – Stakeholder Number