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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE INVESTIGATION OF MEDICINAL PRODUCTS IN THE TERM AND PRETERM NEONATES (EMEA/267484/2007)

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation

Stakeholder No.	Name of Organisation or individual
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3	European Federation of Pharmaceutical Industries and Associations (EFPIA)
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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No. *(see cover page)*	**General Comment**	**Proposal**	**Outcome (if applicable)**
1	The current guideline is a well balanced and therefore potential useful document for all stakeholders involved in the use and research of medicinal products in this specific population.		
7	The EMEA neonatal guidance […] Overall, it was very well done.		
11	The document is well done, however it has to be pointed out that no references have been made to the need of including normal reference values related to the gestational age. TEDDY Experts believe that a such parameter (obtainable from the trial) would be helpful to unify criteria among researchers.	Need to include a few normal values of reference, related to gestational age	Comment acknowledged. Proposal not in the scope of the guideline.
4	The draft guideline presents a comprehensive examination of the technical difficulties inherent in clinical trials in the neonatal population. Careful consideration is given to the unique challenges presented by the heterogeneity of developmental stages in this patient population and the means to ensure collection of scientifically valid data while minimizing subject risk. Key terms are clearly defined and used consistently throughout the document.	Inclusion of some additional information about potential complications, risk factors, procedures, study design and ethical considerations would enhance the ability of investigators to incorporate the information from these guidelines into study design.	Comment acknowledged. Proposal essentially covered.
8	Comprehensive guideline for term and pre-term neonates. we can attested to the many challenges impacting the design and conduct of the trials in this paediatric population (i.e., accruing adequate patient numbers, parental consent, physiological limitations of the pre-term neonate, etc.). However, we believe the availability of safe and effective medicinal products for neonates is of significant public health benefit.		

2. SPECIFIC COMMENTS ON TEXT

Stakeholder No. *(see cover page)*	Line / section number	Comment	Proposal	Outcome
4	Line 559-588	On the other hand using the term stratification may be misleading, since these parameters cannot all be used within a study given sample size considerations. Rather, these factors should be captured for characterisation, with stratification in the analysis for the most relevant. Several additional characterisation topics (for capture in case report forms) should be included (presence and nature of congenital abnormalities; maternal medications, both antenatal and post natal, method & volume of feeding).	Please add: "-Blood transfusion -Parenteral nutrition or tube feeding. -Apgar score -congenital anomalies"	Suggestions added.
4	Lines 729-758 Line 741	The guidance document appropriately acknowledges that the evaluation of pharmacovigilance aspects in neonates is complex and that long-term follow-up of safety is a challenging task where prematurity and its sequelae complications together with pharmacological treatment and medical care are obvious confounding factors. However there is concern that it is not made clear that the sponsors of clinical trials are not expected to set up and carry out this special monitoring of clinical trials that may extend to school age which not only require specific means, tools etc but also raise a number of issues in relation to personal data protection and confidentiality. This might be envisaged only on a case-by-case basis and discussed in a Scientific Advice where appropriate.		No change.
4	Lines 427-442	Sites for iv injection can be limited in neonates and, to overcome this, "piggybacking" (separate infusion lines joining up e.g. with a Y-site device) and co-administration of intravenous medications is common practice.This is alluded to in lines 440-441 but the link with administration devices is not so clear.	Would be good if the EMEA guidance flagged the potential for serious consequences if diluents compatibility / co-administration is not explored carefully.	Aspect now addressed.
4	Lines 427-442	Adverse effects of inadvertent extravasation must be specifically considered because of the high rate of peripheral IV loss & infrequent use of i.m. administration of doses pending IV access		Section revised.
4	Lines 431-442	Routine procedures in neonatal wards should be taken into account when assessing compatibility of iv formulation. For example, 5% dextrose infusion is commonly used as a source of energy of this patient population in addition to its use as a diluent. Consequently, it is advantageous if an iv formulation that requires dilution is compatible with 5% dextrose.	Another example related to compatibility is ensuring formulations are compatible with normal saline or heparin solutions that are routinely used to flush administration lines (flushing of devices is referred to in lines 431-433 but not from perspective of formulation compatibility).	Comment acknowledged, section had been revised.
7	Lines 468-478	Comparisons of different formulations suggests that urine sampling		Section amended.

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		could be used as a complete replacement for blood sampling in assessing bioavailability of a drug in neonates. This assertion is somewhat misleading in that with the exception of neonates who have indwelling bladder catheters (as this is the only way to accurately obtain quantitative specimens), urinary data would not enable accurate characterization of systemic exposure to parent drug and potentially, active metabolites.		
4	Lines 198-204		Measurement of head circumference should be added for the detection of hydrocephalus, very common complication in the premature	Suggestions were included as practical hint, although not strictly a monitoring of brain function. In any case, hydrocephalus warrants specific further measures in a clinical trial.
8	5.2 Lines 403-414	This paragraph suggests that juvenile animal data should be provided "if feasible." The guideline while acknowledging the availability of the CHMP's Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications, does not reflect the spirit of the guideline regarding the timing and utility of juvenile animal data. As stated in the guideline for nonclinical testing in juvenile animals, juvenile toxicity studies "should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group." Also in accordance with the CHMP's Guideline on the Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications, and considering the limitations in sample collection and the extreme handling vulnerability/mortality associated with neonatal laboratory animals, investigations in these young animals should be limited and focused on special safety concerns and/or concerns that might be occur due to reasonably anticipated differences in absorption, distribution, metabolism, and/or excretion in neonates. In interpreting the results of safety assessments in neonatal animals, special consideration should be given to the fact that many neonatal laboratory animals are even less developed at birth that human neonates while the rate of maturation is faster than in humans.	Recommended revision: Any reference to juvenile toxicity studies should delete the phrase "if feasible" and only reference principles consistent with the recommendations in the non-clinical testing in juvenile animals' guideline.	Comment acknowledge. Section was amended.
1	197-204, 2.2	Although we respect the methodologies suggested, no all (PET,	We therefore would like to suggest to add	Suggestions addressed and

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	Monitoring of brain function	fMRI) can be performed without additional burden for the neonate.	Near Infra Red Spectroscopy (NIRS) as an additional tool to measure in a continuous approach brain perfusion and oxygen consumption in neonates. This technique is validated, has been reported by different European centres and can be used bedside.	reference included.
4	Line 596-599	"The known complications and sequelae of prematurity (e.g. intraventricular haemorrhage [IVH], NEC, ROP, BPD) as well as survival should be evaluated at least as secondary endpoints in trials that include the neonatal population. In general, additional endpoints related to long-term physical and mental development should be considered." Indeed this information is important to follow up treatments of prematurity, both non pharmacological as well pharmacological. However due to the complexity sequelae of prematurity, in combination of non pharmacological as well as multi pharmacological treatments it will be very difficult to conclude adverse effect of the treatments on long-term physical and mental development.	Add: "Additional endpoints related to long-term physical and mental development should be considered to follow up both non pharmacological as well pharmacological treatment of prematurity. However due to the complexity, prematurity by it self, sequelae of complications of prematurity in combination of non pharmacological as well as multi pharmacological treatments it will be very difficult to conclude adverse effect of pharmacological treatments on long-term physical and mental development."	No change.
4	Lines 259-262	It should be mentioned that in premature and newborn the activity of the P450 isoenzymes system is below the adult activity.	Please change as follows: "The main pathway responsible for metabolism may be different in neonates as compared to adults. In particular, the activity of the P450 isoenzymes is well below the adult activity (app. 20% of the adult activity)."	Comment acknowledged, no change, already covered.
4	Line 649-651	Blood sampling of 3% maximum for study purposes over a 4-week period is too restrictive, especially given that it is not evidence based. A more realistic amount would be 5% over 4 weeks, unless medically unsafe, or 3% over 2 weeks.		Comment acknowledged, no change as no justification.
4	Lines 194-196	Add that the premature brain has increased risk of cerebral bleeding (subependymal and intaventricular) due to changes in blood pressure, pCO2 and stress.	Add to line 196: "Furthermore, the premature brain has increased risk of cerebral bleeding (subependymal and intraventricular haemorrhage) due to changes in blood pressure, pCO2 and stress."	Suggestions were included.
4	Lines 305-307	Necrotising enterocolitis (NEC) is a serious and frequent complication in the neonates. Methods to monitor NEC should be		Comment acknowledged.

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		added.		
4	Lines 395-397	"For conditions exclusively found in neonates, the development should primarily be made in neonates. However, also in such condition, the first studies in man should, if possible, be done in healthy adult volunteers. Sponsors should refer to ICH Guideline E11"	We suggest the following statement: "For a unique condition in neonate, like RDS, safety data can be generated in adult animals, adult humans supplemented where appropriate by information from juvenile animal."	No change as considered to be already covered.
4	Lines 440-442	Please clarify what potential incompatibilities must be studied - IV feeding solutions, ions, other drugs?? (There could be numerous other preparations that may be co-administered).	Clarification	Section had generally been amended.
4	Lines 470-472 Lines 484-485	Full PK profiles may be difficult to obtain in neonates, population kinetics may be a practical and feasible way to obtain PK. Existing physiologically based pharmacokinetic models to predict pharmacokinetic characteristics in the neonatal population may be considered if appropriate.	Add population kinetics.	Revised.
4	Line 173-174	These sentences vaguely imply that neuroproliferation / neurogenesis ceases after the 2nd trimester.	This is not the case; it is now appreciated that neurogenesis continues even after birth.	Wording clarified.
4	Lines 270-271	What do "markers of hepatic function" in the context of neonates mean?		Comment acknowledged, no change, depending on disease.
4	Lines 417-418	Whilst we will make every effort to develop an age-appropriate formulation, there may be some instances where an extemporaneous preparation is the only way to produce a formulation appropriate for neonates.	This is therefore an approach that should not be fully excluded, however a risk-benefit assessment should be carried out prior to development of such a formulation, and the quality and safety of the extemporaneous preparation should be demonstrated.	No change.
4	Lines 450-451	A sterile product does not necessarily mean that an antioxidant is not required. (In fact, an antioxidant is more likely to be needed to ensure stability of the API if certain types of sterilisation are used.)		Comment acknowledged, no change, already covered.
4	Lines 450-451	Sterile oral liquid products may be challenging to develop and the request to avoid preservatives may push pharmaceutical companies down the route of producing extremely 'simple' dosage forms such as drug substance in a single-dose vial, to be reconstituted with water prior to use.	Whilst this approach is probably suitable for use in hospitals it may not be very practical for carers in a home setting.	Comment acknowledged.
7	Lines 542-543	8 - As regards the design/conduct of "interaction studies" in neonates, they should be considered only if the technical/logistical demands of conducting the investigations in the context of		Comment acknowledged. The issue is already addressed in the guideline,

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		providing clinical care can be balanced. It should also be recognized that physiologic changes produced by normal growth and development and impacted by disease and/or its concomitant treatment often times will confound an interaction study (ie, drug-drug) by the variability expected in the patient.		where the wording was revised.
4	2	It would be helpful to mention in brief the embryonic/foetal development of organs (especially organs at risk), as it will be important for the assessment of prematurity and drug effects.	To add embryonic/foetal development as a graph or table.	Comment acknowledged. No change as publications exist and topic addressed in other guidelines.
2	2.0	"…may affect."	"…may potentially affect."	No change in meaning, not included.
2	2.0	"If possible, points in time of major developmental changes should be identified that could significantly influence drug exposure, safety and efficacy."	Sentence unclear, amend.	Sentence amended.
12	2	Premature infants born before 36 weeks pregnancy duration are after 4 weeks not covered by the guideline, although they are in fact at that moment term or even preterm infants. As such the following scope of the guideline should be formulated in order to include these infants during an appropriate time.	Insert at page 3 line 39 the following sentence: "Prematurely born children should be considered as neonates up to an postmenstrual age of 41 weeks (40 weeks and 27 days)." Change at page 3 line 57 into "neonatal period, defined as 40 weeks and 27 days (post-menstrual age). However, it …"	Comment acknowledged. The suggestion reflects in general neonatologists' medical practice and is included to refine the scope of the guideline and the definitions.
2	2	The term "drug" could be replaced by "medicinal product" or "active substance"	Check the document.	Document checked and amended.
2	2	Amend for clarity and appropriateness ("dramatic", "baby", "infant", "trial" etc)	Check the document.	Amended accordingly.
3	2.1		"Both receptors in the heart as well as the other parts of the vascular system can differ in expression, which may cause unexpected alterations involving the whole cardiovascular system."	Suggestion included.
4	2.1 Heart and lung	pCO2 is important to be checked,	transcutaneous pCO2 should be added.	Included with the other examples.
3	2.2		"Presence and distribution of drug receptors in the brain undergoes major alterations. Insensitiveness or increased sensitivity may lead to unexpected effects."	Suggestion included.
4	2.2 Central	Section 2.2 outlines the critical processes involved in neonatal	The guideline should include	Comment acknowledged,

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	nervous system (CNS)	central nervous system (CNS) development and includes a discussion of medicinal products with expected transport into the CNS or are specifically targeted to the CNS. Many products currently widely used in this population (e.g. steroids) for indications unrelated to the CNS exhibit good CNS penetration and may alter neurodevelopment.	consideration of possible CNS penetration and neuro-developmental sequelae for compounds that are not developed for primary indications involving the CNS.	already covered.
3	2.4		"Interpretation of these literature data should be done very cautiously since enzyme expression may not be related to enzyme activity of such an enzyme."	Suggestion included.
4	2.4 Liver and hepatic function Lines 248-273	Although a discussion of hepatic function and monitoring of liver function is provided, this section does not specifically refer to possible effects of medication on Vitamin K metabolism and synthesis of hepatic clotting factors.	This should be added.	The subsection was amended.
3	2.5		Reordering of factors in "Gastrointestinal absorption is influenced by". Several clarifications.	Suggestions were included.
4	2.6 Immune system Lines 308-357	Section 2.6 includes a discussion of the neonatal immune system and passive transference of maternal antibodies in colostrums and breast milk. Data suggests that neonates may derive continued benefit from passive transfer of antibodies in breast milk, though it is often difficult for these infants to continue receiving breast milk.	Incorporation of information that would promote continuing breastfeeding in this population should be considered.	Comment acknowledged, no change, beyond the scope of the guideline.
4	2.7 Body composition Lines 358-366	Discussion of total blood volume would be highly relevant to outline the risks of blood taking for PK, biomarkers, or safety.	This section should cross reference section 9.6 (633-55).	Cross-reference added.
4	2.7 Body composition Lines 359-366	Protein binding sites are low at birth and this should be mentioned. It should be added that changes in total body water are frequently a result of iatrogenic manipulations, especially in NICU.	Please add: "Protein binding sites are low in neonatal period"	Section was slightly amended.
4	3	Cross reference to existing documents is missing regarding informed consent from parents/legal guardians.		No change, covered by legal and other requirements.
7	5.1. In vitro data	Challenges exist in obtaining and maintaining primary human cell / tissue lines from fetal, neonatal and infant origin. The same is true for subcellular fractions (eg, microsomes) necessary to study drug metabolizing enzyme or transporter activity.	In that these cells, cellular fractions and/or tissues used to support in vitro studies are examined outside of their biological milieu, in vivo extrapolation must consider assumptions relevant to generalization of the data to the intact human.	The comment is acknowledged.
12	5.2	In children maturation covers both hypertrophy and differentiation	I would strongly suggest to add the	Comment acknowledged.

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		of cellular structures. The way paragraph 5.2 is phrased, development toxicity might only address the hypertrophy item. Applicants might neglect the differentiation aspect.	following sentence at page 10 line 407. "Studies on long-term effect on maturation and normal physiological development of organs are mandatory."	The need for such data is already mentioned.
2	5.2 Animal data	Line 411-413 "…e.g. by optimising the design of such studies. Juvenile toxicity studies will be necessary if available data are insufficient, and if feasible. If not, a scientifically data based justification should be provided."	This sentence is repeated in the above paragraph of this section (5.2 Animal data) "…e.g. by optimising the design of such studies. In case of non feasibility of juvenile animal studies, a scientifically data based justification should be provided."	Suggestions slightly changed and included.
7	5.2. Animal data	Feasibility of a juvenile animal model (Line 408) must be predicated upon objective demonstration of physiologic comparability to humans in advance of their being selected for use. An example resides with the study of drug biotransformation where expression of a particular enzyme present in humans with a specific developmental known developmental profile may not be present in an animal species chosen for exploration / characterization of drug disposition.		Comment acknowledged and suggestion included.
7	6 Formulations and Route of Administration	Oral administration (lines 445-455) to neonates must also consider osmolarity of final formulation (a risk factor for NEC), avoidance of diluents/carrier liquids that have the potential to alter gastrointestinal function (eg, polyethylene glycol, sorbitol) and the preparation of oral liquid formulations which enable accurate measurement of the dose to be administered.	With regard to rectal drug administration (lines 456-457), evaluations must include an assessment of either absolute or relative bioavailability in addition to safety and efficacy.	Comment acknowledged. Section was revised taking into account the comment.
4	Section 6	Section 6 outlines formulation and route of administration choices in this population, but does not mention some alternative routes of administration in neonates including umbilical lines and inhalation (nebulizer).	A brief discussion of developmentally appropriate times to employ these routes of administration as well as potential complications should be included.	Section on formulation revised to several comments.
7	7 Dose Finding	Recent data supports that selection of an appropriate scaling factor may be dependent upon drug and/or postnatal age (eg, first 7-10 days associated with changes in physiologic adaptation to extra-uterine life that are not seen beyond this time point).	Lines 491-495: Consideration should be given to making mention of the use of allometric scaling when drug clearance is being predicted from either sparse data (or number of observations) in neonates or when it is being extrapolated downward from data in older infants.	Comment acknowledged and the section was revised.
2	7 Dose-finding	Line 481-482 “All relevant pre-clinical and clinical data in adults and children should be taken into consideration to find a safe starting…”	“All relevant pre-clinical and clinical data in adults and children (or adult and juvenile animals) should be taken into	Suggestions were included.

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			consideration to find a safe starting…"	
4	7 Dose-Finding Lines 479-495		Please emphasize the importance of a thorough evaluation of any literature or experience on previous off-label use (whether from clinical trials, epidemiological data, case series, case reports) that may give some insight into the safety, efficacy, PK or PD of the investigational drug being considered.	Comment acknowledged.
4	9.5, lines 626-628	Use of non-approved medications as comparator must be compelling as there may be ethical/legal implications for inclusion in protocols		Comment acknowledged, no changes requested.
2	8 Pharmacokinetic studies and PK/PD studies	"initial models based on rich data of a limited number of individuals"	Unclear	Sentence amended.
7	8 Pharmacokinetic Studies and PK/PD Studies	Additional considerations regarding the use and utility of population-based methods in the neonatal population are warranted. Given the dramatic and rapid physiologic changes that characterize the first month of life, the use of PK data from older infants and children to parameterize a population PK model for neonates can be problematic through the introduction of compounded variability (ie, noise from the model). Thus, when PK (and/or PK-PD) of a drug are being characterized in the neonate for the first time, it is essential that the method chosen be able to accurately determine/estimate PK parameters in a given patient. While traditional, sample-rich PK designs provide the highest quality data, physiologic limitations (eg, vascular access, small intravascular volumes, the need to consider both therapeutic and non-therapeutic phlebotomy as the PK studies are done in the context of caring for a sick neonate), their use may not be possible.	The alternative is to use population-based methods (eg, Bayesian estimation) to define, a priori, sampling schedules that are sufficient to determine patient-specific PK parameters in a reliable fashion (eg, a two-stage approach vs. use of random plasma concentrations). Validation of population-based approaches must embrace a "learn and confirm" paradigm that enables independent validation of models (eg, use of a validation data set that is distinct from the one used to construct the model). In the case of combined PK/PD models, it is necessary that an objective, physiologic (direct or biomarker) endpoint of drug effect be included. Finally, given that many neonatal PK and/or PD studies consist of relatively small numbers of subjects, consideration must be given to polymorphic gene expression that quantitatively, could be important in assessment of drug disposition and/or	Comment acknowledged. The section on PK and PK/PD studies was amended in several places.

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			effect. In these instances, investigations should explore relevant associations between genotype and phenotype.	
4	8 Pharmacokinetic studies and PK/PD studies	The discussion of the frequency of administration of multiple medications in this population mentions a number of important analyses to try to predict safety.	Addition of a reference to post-hoc analyses would be useful in determining safety from trials in which neonates received multiple medications.	No change, as already covered.
4	9	In addition, given the inherent risks of this group to the complications and sequelae of prematurity, an examination of potential study designs that would permit detection of signals above baseline is warranted.		Comment acknowledged, no change.
4	9	Given the extraordinary vulnerability of this patient population, increased guidance regarding the ethical conduct of trials in this population should be provided.	Specifically, policies that ensure the safety of the research subject should be referenced, including monitoring of safety data by an independent board.	Independent DSMB and references amended.
4	9	General comments about permissibility or caution regarding remuneration of parents/legal guardians (beyond out of pocket expenses) is missing.		No change, covered by legal and other requirements.
4	9 Special aspects of clinical trial design in neonates	Section 9 addresses the special aspects of clinical trial design in neonates and raises many important points, but fails to address some common concerns in this population. In terms of stratification criteria, prenatal drug exposure and race may both be additional important variables affecting outcome.		Suggestion included.
7	9.1 Age and further stratification criteria	In addition to gestational age (line 575), consideration should be given to examining PK and/or PD parameters for association with the continuous covariate of post-menstrual age (PMA). This provides a more robust assessment of the impact of physiologic maturation on both drug disposition and effect.		Comment acknowledged, changes made.
4	9.2	Intraventricular haemorrhage (IVH) and periventricular leukomalacia are common adverse neurological outcomes in this patient population.	The guideline would benefit from increased discussion of these outcomes.	Comment acknowledged, not in the scope of the guideline.
Task-force in Europe for Drug Development for the Young (TEDDY)	9.2	No references on specific "end points" to be used for newborn and preterm babies in clinical trial are included.	A comment on biomedical markers can be helpful since they are used to screen for potential safety-related problems, to decrease biological and genetic heterogenenicity, and to define subgroups.	Comment acknowledged, reference to pharmacodynamic markers / biomarkers added.
4	9.2 Endpoints and outcome measures	As regards, "endpoints related to long-term physical and mental development", a feasible duration of follow-up should be mentioned. The proposed duration in section 10 (lines 740-741):	Please update section 9.2 and section 10 accordingly.	Wording slightly amended.

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	Lines 596-599	"Therefore, long term monitoring for medicinal products affecting the CNS may be required (e.g., cognition assessment at school age)" means very long studies which is not feasible.		
3	9.5		Delete “Placebo use is not equivalent to absence of treatment”	Text was rephrased.
3	9.5	“placebo is often needed for scientific reasons”	“placebo is sometimes needed for scientific reasons”	Text was rephrased.
3	9.5	“standard care”	“Best standard care”	Suggestion included.
3	9.5		“Placebo should be used most often as on top of standard best care.”	Paragraph was rephrased.
3	9.5		“In all cases, its use should be assorted with measures to avoid irreversible harm, especially in serious or rapidly evolving diseases.”	Text was rephrased.
3	9.5		Add: “Local national legislations on off-label use of drugs should also be taken into consideration while planning the study.”	Comment acknowledged. Legal and other requirements in concerned countries are applicable as in other trials.
3	9.5		Add “including obtaining parental informed consent before starting the study.”	Comment acknowledged. Legal and other requirements in concerned countries are applicable as in other trials.
4	9.5	General comments regarding standard of care treatment (otherwise available to that neonate vs. global standard of care) are missing.		No change, topic already addressed.
3	9.5 Placebo and active comparator		Delete “Use of placebo in neonates is more restricted than in adults and older children”	Explanation on vulnerability added.
7	9.5 Placebo and active comparator	Throughout all of pediatrics, the most challenging period to require the inclusion of a placebo is during the first few months of life. In the sick preterm infant, accepted standards of care may be defined not on a national/professional basis but rather, on a regional or local (ie, nursery-by-nursery) basis. Adding a placebo to a standard-of-care treatment could bias the utility of this measure by obscuring its value from an experimental perspective (ie, assessment of effect / efficacy) to assess the test article against a "no effect" intervention.		The comment is acknowledged. The section on placebo was reworded to address this and other comments.
7	9.6	With respect to monitoring of actual blood loss (lines 643-648), consideration should be given to making a comment on using	An example would be to re-administer the void blood volume used to clear an	Comment acknowledged. Text revised.

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		methods that minimize blood loss.	intravascular catheter used for blood sampling. Some caution in this process is warranted, especially if heparin is used as a "flush" solution to maintain patency of the indwelling vascular device/line used to accomplish repeated blood sampling for PK studies.	
3	9.6		Several clarifications and extensions.	Suggestions were included.
7	9.6 Blood sampling	The potential for therapeutic transfusion (lines 634-637) to alter PK results must be recognized, especially when transfusion is required during the conduct of a given study. In addition to blood that likely has an origin from an adult donor, the administration of plasma expanders (eg, human serum albumin) has the potential to produce dynamic changes in intravascular volume and also, to alter the protein binding of highly bound drugs.		Comment acknowledged. Suggestions implemented in section 8.
7	9.6 Blood sampling	Outside of microanalytical methods, there is really no proven "substitute" for determining plasma drug concentrations. Other potential methods cited (lines 638-642) have significant limitations and few (if any) have been validated in the neonate. Until such time that they are proven as acceptable "alternatives" for blood sampling, it is probably premature to hold them out as an avenue for assessing PK.		Comment acknowledged. Section revised.
3	9.7 Study Analysis	Replace full section by suggestion.	"As in any clinical trial the statistical analysis should be carefully planned in advance, taking into account the limited amount of data that may be available with this patient population. Concepts outlined in the Guideline on Clinical Trials in Small Populations should be taken into consideration when planning the analysis."	Comment acknowledged and changes included.
7	9.7 Study analysis	In this section, it appears reasonable to re-emphasize the importance of normalizing PK parameters so that they might be "corrected" for differences in body size, a surrogate for developmental status (ie, larger neonates being generally more physiologically "mature" than smaller neonates).	An example would be "normalizing" apparent plasma clearance and volume of distribution for weight (eg, ml/hr/kg and L/kg, respectively). As well, when assessing systemic drug exposure in studies where fixed doses of a drug are used, relevant PK parameters (AUC,	Comment acknowledged. Section had been amended subsequent to this and other comments.

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			Cmax, Cmin) should be normalized for both body size and dose (eg, mg/L*hr per 1 mg/kg for AUC and mg/L per 1 mg/kg for Cmax or Cmin) so as to permit accurate exploration of associations between age (PCA, GA, PMA) and drug disposition.	
3	9.8		Registers for long-term follow-up should be implemented whenever possible.	Suggestions were included.
7	9.8 Pain and distress	The points raised in this section with respect to the physiologic consequences of pain while well taken, might be re-considered in the context of a guidance. For example, with the possible exception of transcutaneous oxygen saturation determinations, the other methods described (lines 694-697) are rarely assessed as continuous "variables" in the context of rendering clinical care.	While they can be valuable in the context of episodic assessment, caution should be used in implying (through a guidance) that these measures may constitute required safety assessments for the conduct of a given clinical trial.	Comment acknowledged.
4	9.9	The long-term monitoring of the neurodevelopment of research subjects is extremely important, but the guidelines in this area are vague.		Comment acknowledged, no change, already addressed.
4	9.9 Safety Lines 708-717	Reference should be made specifically to use age/gestation appropriate laboratory reference ranges		Suggestions were included.
7	9.9 Safety monitoring	The phrase "…blood safety monitoring" (line 712) is a bit confusing.	Perhaps it is better to state "When there are no biochemical correlates that have been established to reflect drug safety…."	Sentence amended.
7	9.9 Safety monitoring	The same would be true for evaluations of auditory function and EEG. As well, given the complexity of sick neonates and the morbidity associated with the condition and its treatments, it must be recognized that it is difficult (if not impossible) to dissect out effect(s) from a given experimental drug to those generally associated with the care of the patient and their condition.	As regards the assessment of trial participants (lines 719-728), the recommendation of specific evaluations should be "indexed" to the type of study being conducted. For example, it would not be expected that results from a neurodevelopmental test conducted before and after a short-term PK study would yield any meaningful results with respect to interpretation of drug safety.	Comment acknowledged.
3	10		Include “post-marketing experience if available”	Suggestions were included.
3	8, 9.1		Several clarifications and extensions.	Suggestions were included.
4	Line 51	"arise from the following conditions"	no "conditions" are specified	Corrected.
4	Line 170	A caveat for unreflected addition of blood analyses needs to be	Blood volume requirements for laboratory	No change, already

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		implemented, even the analysis of the rather small samples for blood gases imposes stress and blood loss to the neonates.	assessments and the corresponding stress for the neonates needs to be carefully considered.	addressed in another section.
4	Line 173	Please mention gestational age in weeks.		Suggestion included.
11	Line 180	Not only drugs interfering with glutamate neurotransmissions may have impact on the development of CNS, but several more neurotransmitter systems are involved, therefore, the impact of drugs is much more general.	Generalize from glutamic acid to other neurotransmitters.	Comment acknowledged, guideline already reads “glutamic acid and other neurotransmitters”.
6	Line 191	2.2 Central nervous system (CNS): bilirubin metabolism	Include compounds interacting with the UGT1A1 enzyme or the hepatic uptake transporter OATP2 and/or the efflux transporter MRP2.	Examples included.
4	Line 197	Consider to mention the fact that monitoring of CNS side effects is more difficult in this population due both to CNS immaturity (e.g., seizures are difficult to recognize because they rarely manifest obvious tonic-clonic movements) and because of the severely ill, debilitated and perhaps sedated/paralysed state of potential subjects.		Suggestions were included.
4	Line 220	Stratification is always necessary.		Paragraph had been revised.
4	Lines 265	"If feasible, the applicant is encouraged to perform studies investigating drug metabolism in vitro in neonatal hepatic material (microsomes, hepatocytes etc.)": this is very difficult in practice even in adult.		Comment acknowledged, no change requested.
10	Line 273; Gastro-intestinal system	Altered blood flow during illness might influence drug clearance for low and high extraction systems in the liver. If PK is changed in sick neonates investigators should look at blood flow measurement in the liver, which is possible, but not standard. If PK is different suggesting changed absorption in neonates, altered blood flow should be considered as cause of delayed maturation of enzymes and transporters. During parenteral nutrition or starvation mucosal enzymes, microvillus height, transporters are diminished due to decreased blood flow only, this forms the background for minimal enteral feeding in sick neonates to keep the gut functioning.		Comment acknowledged. Suggestion included as potentially explanatory information, with potential need for systematic assessment.
4	Line 304	If partial parenteral nutrition is given, the gastrointestinal absorption may be influenced by the type and degree of enteral nutrition.	Add to line 304 in the end: "If partial parenteral nutrition is given, the gastrointestinal absorption may be influenced by the type and degree of enteral nutrition".	Suggestion addressed.

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6	Line 307	2.5 Gastrointestinal tract: hyperosmolality of oral formulations has been linked to increased incidence of NEC.		Section amended.
11	Line 402	A commentary on cord and placenta in clinical trial in newborn could also be useful. Need of a commentary on cord and placenta, there is real doubt on utility.	Ask for inform consent and get samples or anatomical pieces in order to study afterwards.	Comment acknowledged, however, not in the scope of guideline and remaining subject to prior informed consent.
4	Line 423	"Prescribing software"	? "prescribing hardware"	Amended.
4	Line 427	“In general, the IV route will normally be used in clinically unstable term and preterm neonates.” However, not for all situations.	Please add "in most cases" instead of "normally".	Section was revised.
4	Line 436	Specification of requirement (pH adjusted, isotonic etc) missing.		Wording amended.
7	Line 445	Reference to extravascular administration routes should make mention of intrapulmonary drug instillation.		Comment acknowledged and section revised.
6	Line 448	Formulation and route of administration	When administered through nasogastric tube, the viscosity should be suitable for easy extrusion and rinsing of tubing. Accuracy of enteral dosing and potential loss of drug through adsorption to tubing should be investigated.	Section was revised.
5	Line 450	To be exact, a preservative is a natural or more often synthetic chemical added to pharmaceutical products to retard spoilage, whether from microbial growth, or undesirable chemical changes. Anti-microbial preservatives function by inhibiting the growth of bacteria and fungi, and antioxidants inhibit the oxidation process within the preparation. Hence antioxidants are not directly linked with microbial contamination prevention and the preparation of a sterile dosage form does not necessarily avoid the use of an antioxidant.	Maybe the text should clarify that, in order to avoid undesirable antioxidant, single use oral dosage forms prepared under nitrogen and kept protected from atmospheric influence so that they are less likely to degrade could be used if it is what is intended.	Comment acknowledged. Section on formulation amended.
5	L 451	“feeding tube”	It should be suggested that compatibility of commonly used polymer types and preparation is established before use.	Comment acknowledged. Section revised.
5	Line 451 “a sterile product should be considered”	It is to be noted that no oral preparation is sterile. Hence this tends to suggest that a parenteral product will be used orally off license or unlicensed. In that case the composition of the parenteral product should be scrutinised for absence of undesirable excipients and the salt of the active ingredient that may require dose adaptation.	Maybe the text should clarify (if it is the intention) that, in order to avoid undesirable excipients, sterilised single use oral dosage forms should rather be used if necessary e.g. oral electrolyte solutions (no antimicrobial preservative) are sterilised for neonates and have a validated shelf life of 7 days in use when	Comment acknowledged. Section on formulation amended.

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			stored at 2-8 degrees. These may be or not be the same formulation as the parenteral product and not simply mean to use parenterals off label. E.g.: Vit K is available as a sterile solution for injection or for oral use (licensed).	
4	2.3 Kidney and renal function, lines 216, 237	VLBW categorization misleading in this context as maturity related and not weight related changes of GFR dominate the issue of nephrogenesis.	Replace VLBW with relevant GA of less than 34 weeks.	Suggestion included.
10	Line 491	BSA is not related to drug dosing, but kg bodyweight is with an exponential figure multiplied with body weight, frequently necessary for neonates compared to expressed for weight in older children.		Comment acknowledged. BSA may correlate well with pharmacokinetic parameters and should be tested for such an association. Disadvantages of BSA for dosing are already mentioned.
9	Line 536	The ability to effectively analyze all concomitantly used drugs in neonates in the ICU in population PK studies is essentially untenable. There are multiple agents used for multiple durations which would make this analysis challenging and possibly infeasible. Known or potential interactions should be considered as stated in lines 534 and 535.	Removal of the sentence: "Concomitantly used drugs should be included in the population pharmacokinetic analysis."	Comment acknowledged, but not agreed.
4	Line 543	It should be specified whether the interaction studies should be performed in adults or neonates.		Already stated, wording amended.
8	9.1, lines 559ff.	This paragraph suggests that stratification of the population should be considered, and it mentions a broad range of factors to take into account. Although these are all valid points, in practice it will be very difficult to implement any stratification strategy in (prospective) studies in neonates. Our experience confirms that enrollment of neonates per se is extremely difficult for various factors (i.e., consent, protocol adherence in view of disease/mortality etc). Stratification will further limit enrollment into the study. Furthermore, the number of patients to be enrolled will usually be small and subsequent analysis		Comment acknowledged.

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		per stratified group will seldom lead to statistically sound (valid) conclusions.		
10	Line 278, 303	Motility instead of mobility		Corrected
4	Line 585 Line 586-587		Please add theophylline. In addition to incubator care, also include infant warming devices.	Included.
8	9.2 lines 589ff.	This paragraph suggests including outcome of well-known/expected complications and/or death as secondary endpoints. Also, end-points for long-term physical and mental development should be considered. Again, the number of patients in the study cohort(s) will most probably be too small to draw any conclusions on the morbidity/mortality outcome. Hence we suggest restricting this recommendation to potentially life-threatening diseases/conditions. As for the long-term developmental issues (also mentioned in Paragraph 10, which even suggests cognition assessments at school age), such a requirement will be very difficult to implement and (again) not that meaningful in view of the small numbers of patients to be included in studies.	We suggest restricting this to those drugs where impact on (long-term) development can be expected because of mechanism of action, pharmacology and/or prior knowledge of related compounds.	Not changed.
11	Line 599	Need to define in general terms, the criteria of exclusion, e.g. degree of cerebral injury, neonatal asphyxia, NEC degrees, DBP (except related studies).	Include in clinical trial design the definition of grades of SNC injuries	Comment acknowledged, not within the scope of this guideline.
8	9.3 line 600ff.	We expect major problems with obtaining informed consent for PG sampling in neonates. Hence, we would expect only a very low number of samples for testing.	Pharmacogenetic (PG) testing in neonates should only be considered if there is significant and clinically relevant evidence from adult data and/or data from older children warranting such testing.	Comment acknowledged. Section and requirements clarified.
4	9.3 Pharmacogenetic Line 603	Pharmacogenetics sampling might be restricted by limitation of blood sampling in the neonate.		Section clarified with respect to applicable requirements.
11	Line 654	Need to forbid, especially in premature children, any study that demands follow-up or extractions of blood even though it is observational (not using Medicinal Products). This is for avoiding any excess of visits or extractions.	To define the whole amount of blood to be taken at the beginning of study and in each visit.	No change, not in the scope of the guideline. Guideline already has requirements for blood sampling.
4	Line 655	The SIS unit is mL and not ml.		As per the 8th edition 2006 of the Bureau International des Poids et Mesures' "The

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				International System of Units (SI)", both "l" and "L" are allowed.
4	Line 717	Add statement regarding an independent Data Safety and Monitoring Board	The safety parameters and, if applicable, trial stopping rules should be defined prior to initiation of clinical investigation. An independent Data Safety and Monitoring Board may be established to review safety and efficacy data on a pre-planned basis and to advise on trial continuation.	Comment considered elsewhere in the document.
11	Line 728	Specially in premature children, need of a commitment from part of the researchers not to increase the number of visits in the follow-up.	To strictly determine the necessary number of visits and distribution and ensure the utility of the long term follow up.	No change, already covered.
11	Line 729	Need to not repeat studies, though they are observational, if they do not provide any benefits for the child. The first aim must be maintaining the health of the newborn child.	European database including neonatal studies to be accessible to the neonatal Centers	Comment acknowledged. Clinical trials in EudraCT will also be made public.
8	10 line 729ff.	We agree with the assessment that prospective studies on the long-term effects of medicinal products used in neonates will be very difficult to conduct and of limited value due to the small number of patients to be enrolled (in studies conducted as part of regulatory approval).	Instead, we would propose to pursue the appropriate pharmacovigilance approaches and/or initiate pharmacoepidemiological studies, preferably based on a European (rather than country-specific and/or industrial) platform.	No changes.
5	Lines 435-6, 449	'provided it is practical (not too small) to withdraw and that the dose remains accurate and reproducible.'	It would be helpful if the guidance would specify as well what is seen as a maximum acceptable volume.	Comment acknowledged. Section had been revised.