13 December 2018

Submission of comments 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:

| Name of organisation or individual |
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| EFPIA |

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

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | 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:1. 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.
2. An item for neonatal registries (methods and uses as well as the e-HR implementation) could be considered.
3. An item for use of biological compounds (e.g.: monoclonal antibodies) in this target population could be considered.
4. 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.
5. 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).
6. Guidance how to adequately asses neonatal pharmacovigilance data for this vulnerable and heterogeneous population with multiple confounding factors (Ward, Benjamin et al. 2017).
7. It is recommended to stress the importance of collaboration with nurses, nutritionists, parent etc. under the protocol development.
8. 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).
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1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 3.(a)  |  | 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 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). |  |
| 3.(b)  |  | Consider including in the section:1. innovative study designs, e.g. applied in studies of rare diseases could be feasible (Allegaert, Smits et al. 2018).
2. master protocols to improve conduct of the clinical trials in this non-homogeneous and vulnerable group (Woodcock and LaVange 2017).
3. 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).
4. 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 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.”*** |  |
| 3.(c) |  | Comment: Revision of the guidance should be in line with the newly created ICH S11 Guidance on Development of Paediatric Medicines. Furthermore, consider including:1. 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.
2. 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.
3. Development of animal models with translatable designs, with focus on the extent to which they are *translatable* to human neonates should be discussed.
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| 3.(d) |  | 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.” |  |
| 3.(f)  |  | 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:1. Physiologically based PK/PD models, adjusted for body size, body weight, and age-related physiological changes (Michelet, Van Bocxlaer et al. 2018).
2. Practical examples of acceptable extrapolation are welcome and could be a useful accompaniment to the guidance.
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| 3.(h)  |  | 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). |  |
| 3.(i)  |  | 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. 1. 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).
2. 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.**
3. More recent data on developmental pharmacology should include maturation of cardiovascular receptors: effect of certain drugs (partial agonists, inverse agonists) on the stimulation of G-coupled protein receptors, GCPRs during maturation.
4. 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)”. |  |
| 3.(j) |  | 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.
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| 3.(k)  |  | 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. |  |
| 3.(l)  |  | When describing this section consider: 1. 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).
2. 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).
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Please add more rows if needed.

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.

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.

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.

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.