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Human Medicines Evaluation Division

Concept paper on the need for revision of the guideline on the investigation of medicinal products in the term and preterm neonate

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The proposed guideline will replace the guideline on the investigation of medicinal products in the term and preterm (EMEA/536810/2008)

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1. Introduction

Term and preterm neonates represent the most vulnerable subgroup of the paediatric population with the highest rate of unauthorised or off-label used medicines across the entire paediatric population.

The Guideline on the investigation of medicinal products in the term and preterm neonates was prepared during the period from 2007 to 2009 and came into effect in 2010 (EMEA/536810/2008). Considerable experience of assessing Paediatric Investigation Plans (PIP) applications covering neonatal age subset has been gained since then and it has become apparent that some essential questions arise repeatedly during the assessment of PIP applications for products intended to be investigated and used in neonates. Furthermore, in recent years there has been increasing debate about neonatal research trends and standards, suggesting that the existing guidance is not adequately addressing issues associated with the development and investigation of products in term and preterm neonates.

Therefore it seems that there is a need to update currently available guidelines regarding the non-clinical and clinical development of medicinal products in neonates in accordance with current trends in neonatal terminology, and issues encountered and experience gained during assessment of PIP applications involving the neonatal population. Input will be sought from relevant working parties, committees and experts.

2. Problem statement

Several items further detailed below warrant a discussion whether the current guideline should be revised.

The current guideline includes more general principles for conducting clinical studies in neonates. Considerable experience has been gained from the assessment of PIPs involving development of medicinal products for neonates indicating that there is a need to reflect this in updated and more specific recommendations regarding non-clinical models of neonatal conditions, models for the demonstration of efficacy of medicinal products in term and preterm neonates, evaluation of short and long term safety as well as use of available tools and biomarkers.

Furthermore, over recent years there have been an increasing awareness and discussions about neonatal research trends and standards, suggesting that the current guidance could benefit from an update in several areas to better address issues concerned with the development and investigation of products in term and preterm neonates.

A review of the guideline in order to consider new clinical developments in neonatology, to improve the quality and consistency of neonatal research, as well as avoid unnecessary studies in this highly vulnerable population seems appropriate.

3. Discussion (on the problem statement)

The following critical aspects should be discussed in the update of the guidance document:

a) 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 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.

b) 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.

c) Development of proper animal models for specific neonatal conditions (more targeted designs).

d) 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.

e) Special attention should be paid on the rationale for dose selection in this 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.

f) 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 could exceptionally be considered where available evidence is supportive.

g) The current outcome assessment scales could be reviewed and the importance of use of validated scales, whenever possible, should be emphasized.

h) Eventual differences in the manifestations of the disease among neonates (pre- through to post-term) and children should be addressed in drug development.

i) 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.

j) Consideration could be given to the development and validation of biomarkers (surrogate markers or surrogate endpoints) for disease, treatment effects and outcome evaluation, e.g. neonatal sepsis or neonatal asphyxia.

k) Consideration could also be given to trials in which neonates have been treated prenatally and the optimal use of pre- and postnatal data.

l) 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.

m) 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.

n) Overall harmonization and update of terminology and definitions is required.

o) Special attention should also be paid to the evaluation of drug safety in neonates.

4. Recommendation

It is recommended to review the Guideline on the investigation of medicinal products in the term and preterm neonates in light of the recent experience gained and to propose changes where necessary.

5. Proposed timetable

It is planned to release for consultation a draft guidance document not later than Q4 2020.

6. Resource requirements for preparation

The preparation of this guideline will involve the PDCO Neonatology Group and the PDCO with input from relevant working parties and committees. Drafts of the document will be discussed with the SAWP and other relevant WPs and committees.

7. Impact assessment (anticipated)

It is aimed that this Guideline will be helpful to achieve consensus in the evaluation of medicinal products for neonates by regulatory authorities in the European Community. It is anticipated that the revised guideline will provide guidance to pharmaceutical companies and all stakeholders such as academia, research and clinicians involved in designing, assessment and supervision of studies for medicinal products intended for use in term and preterm neonates and thus would improve quality and comparability of development programs in this population.

8. Interested parties

- Pharmaceutical industry
- Regulatory bodies
- Academia and learned societies
- Clinical trial networks (e.g. Enpr-EMA)

9. References to literature, guidelines, etc.

EMA, Guideline on the investigation of medicinal products in the term and preterm neonate, 2010

EMA, Guideline on pharmaceutical development of medicines for paediatric use, 2014

Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Rev 1, 18 September 2017

Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework, 2009 (EMEA/P/24143/2004 Rev. 1 corr.)