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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population

Agreed by Pharmacokinetic Working party	June 2016
Agreed by MSWG	September 2016
Agreed by PDCO	September 2016
Adopted by CHMP for release for consultation	21 April 2017
Start of public consultation	4 May 2017
End of consultation (deadline for comments)	31 July 2017

The proposed guideline will replace ' Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population ' (EMEA/CHMP/EWP/147013/2004).

Comments should be provided using this template. The completed comments form should be sent to PKWP@ema.europa.eu

Keywords	*children, extrapolation, dose finding, maturation, age, pharmacometrics*

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1. Introduction

The guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population was adopted by the European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP) in 2006 with the aim of aiding paediatric drug development. The Paediatric Regulation came into force in the EU in 2007. Since then the EMA Paediatric Committee (PDCO) has approved a large number of Paediatric Investigational Plans (PIPs) and an increasing number of applications for paediatric indications have been submitted to EMA and the national regulatory agencies. A revision to the guideline is therefore proposed to reflect the experience gained over the last decade and developments in science. The revision will implement the current regulatory view and provide recommendations in areas identified as important in the application of new pharmacokinetic knowledge in paediatrics, as well as general scientific advances in the area of clinical pharmacology and pharmacometrics. The revision is being done taking account of other ongoing relevant initiatives, including at International Conference on Harmonisation (ICH) and EMA level.

2. Problem statement

The paediatric pharmacokinetics guideline needs revision to implement new knowledge and to reflect the experience gained since the Paediatric Regulation came into force.

3. Discussion (on the problem statement)

The revision will mainly relate to the many considerations needed to optimise study design as well as the use of current pharmacometric modelling methods to support paediatric drug development. Furthermore, the need to consider both pharmacokinetic (PK) and pharmacodynamic (PD) for dose finding and dose selection must be further addressed. A change in the scope and title of the guideline from PK to clinical pharmacology will be introduced to reflect this.

The following topics have been identified that may be covered in the revision of the guideline:

Drug development considerations

- The role of PK and the importance of knowing the PK/PD relationship in the development.
- The importance of exposure-response modelling to support efficacy and safety.
- Considerations on the choice of appropriate methods for scaling PK from adults to children and between different paediatric subpopulations.
- Considerations on the importance of the choice of formulation to be used in paediatric dose finding studies.
- Considerations on required level of confirmation in paediatrics when existing clinical pharmacology data from adults is leveraged to the paediatric populations (e.g. in relation to PK support of specific formulations to be used in the target population, anticipated differences in drug-drug interactions or special populations such as children with hepatic or renal impairment).
- Considerations on appropriate methodologies and situations where collection of PK/PD data in children in the post-marketing setting may be needed to better monitor drug response.

Study design

- General recommendations on the design of paediatric PK and PK/PD studies.
- Dosage adaptation (during trial) with or without PK/PD run in leading to dosage optimisation.
- How and when to use individualised dosing through continuous titration based on PK, PK/PD relationships or other dose escalation approaches, e.g. for small numbers, (sub-)populations, neonates, non-responders or on loss of response.
- Update the section on paediatric age categories.
- Power of the study/analysis and setting acceptance criteria to answer the key question(s) of the study (difference in exposure between populations, relationship between clearance and body size, differences in PK/PD relationship, etc.).
- Simulation-based approaches to optimise study design (sampling times, sample size, study population including stratified inclusion, etc.).

Data analysis, modelling and presentation

- Recommendations for analyses using simple or more complex models.
- Use of prior PK and PK/PD information in the analysis and how to evaluate that it has a proper weighting in relation to new data collected.
- Clarification on the need to present results on exposure versus individual variables such as body weight, age and Body Surface Area as a basis for posology for cutoffs.

4. Recommendation

It is recommended that the CHMP guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population should be revised.

5. Proposed timetable

The Concept Paper will be released for 3 months external consultation. Following the receipt of comments, the draft Guideline will be consolidated and released for 6 months external consultation towards Q4 2018.

6. Resource requirements for preparation

The preparation will mainly involve the Pharmacokinetics Working Party (PKWP), the Paediatric Committee (PDCO) and the Modelling and Simulation Working Group (MSWG).

7. Impact assessment (anticipated)

The revision is likely to impact the design, conduction and the data analysis of PK and PK/PD studies included in applications and PIP proposals and also to advance the use of pharmacometric methodologies in paediatric drug development.

8. Interested parties

Interested parties include learned societies and academia (e.g. European Paediatric Association and others), pharmaceutical industry (e.g. European Federation of Pharmaceutical Industries and Associations (EFPIA) and others), paediatricians and other healthcare professionals and other regulatory agencies.

9. References to literature, guidelines, etc.

Not applicable.