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3 Committee for Human Medicinal Products (CHMP)

4 Concept paper on an addendum to the guideline on the 5 evaluation of medicinal products indicated for treatment 6 of bacterial infections (CPMP/EWP/558/95 rev 2) to 7 address paediatric-specific clinical data requirements

8 Draft

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Agreed by the Infectious Diseases Working Party (IDWP)	February 2016
Adopted by the CHMP	01 April 2016
Start of public consultation	20 April 2016
End of consultation (deadline for comments)	31 July 2016

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Keywords	Antibacterial agents, paediatric population, paediatric bacterial infections, extrapolation of efficacy, paediatric study designs, timing paediatric studies

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1. Introduction

This Concept Paper proposes the development of an addendum to the Guideline on the Evaluation of New Anti-bacterial Medicinal Products (CPMP/EWP/558/95 Rev 2) to address the clinical development of antibacterial medicinal products for use in the paediatric population.

In accordance with the EU paediatric regulation (EC No 1901/2006), as amended, for all medicinal products a paediatric investigation plan (PIP) should be submitted upon completion of pharmacokinetic studies in adult patients in order to ensure a timely and appropriate development programme in the paediatric population. At this stage of the clinical development of a new antibacterial agent, the sponsor will be aware of the spectrum of activity and will have a provisional plan for the indications that will be sought at the time of first approval. Whilst it is very unusual that use in the paediatric population is proposed in the initial application dossier, the indications for use approved in adults are commonly extended to younger patients during the post-marketing period. Some new agents may also be suitable for treatment of infections that occur mainly or only in certain paediatric age sub-groups.

2. Problem statement

Section 4.2.3 (*Studies in children and adolescents*) of CPMP/EWP/558/95 Rev 2 covers the general approaches to the development of antibacterial agents in the paediatric population. The available guidance on antibacterial drug development does not discuss the extent of the paediatric development programme that might be considered appropriate in various situations such as:

i. Situations in which the types of infection to be treated have common aetiology and pathogenesis across age groups: in this context, extrapolation of efficacy from adults to children is generally accepted provided that dosing regimens matching the adult drug exposure that has been shown to be efficacious have been identified in the different paediatric age groups.

ii. Situations in which the infections to be treated are not or rarely encountered in adults, as efficacy should be demonstrated in the paediatric age groups or otherwise justified (e.g., if feasibility issues would prevent the conduct of fully powered studies).

iii. Situations in which the antibacterial agent has undergone very limited clinical development in adults (e.g. when the new agent has a clear potential to address an unmet need) as special considerations may be needed for the paediatric clinical programme.

iv. Situations in which the new antibacterial agent exerts its action at a body surface and is minimally absorbed as it is not possible to derive paediatric doses based on comparable PK to adults. In these instances there should be some special considerations for the paediatric development programme.

3. Discussion (on the problem statement)

In recent years, reflecting activity in development of new antibacterial agents, numerous PIPs have been proposed. Given that the current guidance does not provide an adequate framework for determining the appropriate content of the paediatric development programme, there is a need to consider the critical factors that should be taken into account when considering suitable and feasible programmes in the situations identified in section 2, in particular:

- Clinical data to be obtained in each of the situations mentioned in section 2 in relation to:

- The extent at which (full or partial) extrapolation of efficacy from adults to children can be applicable.
- Need for dedicated PK studies across all paediatric age groups prior to efficacy and safety studies.
- Efficacy and safety study design: primary study objectives and endpoints (safety or efficacy), powered versus unpowered, comparative versus uncontrolled, number of comparators (in case comparative studies are needed).

- Timing of the paediatric studies in relation to the clinical development programme in adults leading to first approval

4. Recommendation

The Infectious Disease Working Party recommends drafting an addendum to the Note for Guidance on Evaluation of New Anti-bacterial Medicinal Products (CPMP/EWP/558/95 Rev 2) to incorporate guidance on the above matters related to paediatric development programmes for antibacterial agents that do not unnecessarily delay availability of new agents for the paediatric population.

5. Proposed timetable

First draft of the Paediatric Addendum to be released for consultation by end of 1Q 2017.

Finalisation by end of 4Q 2017.

6. Resource requirements for preparation

The resources needed for this addendum relate to IDWP members who will develop the draft addendum and proceed to develop a final version after the consultation period. The PDCO will be consulted during the development of the draft and final guidance.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- The paediatric development of antibacterial agents for use in indications for which there are no well-established clinical data requirements and/or for which there are potential problems surrounding the feasibility of performing studies.
- The paediatric development of antibacterial agents for which the more usual approaches to clinical development are unsuitable because of their specific properties (e.g. very limited spectra of antibacterial activity).
- The content of CHMP scientific advice.

8. Interested parties

- European Society for Paediatric Infectious Diseases (ESPID)
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
- EFPIA

9. References to literature, guidelines, etc.

- Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);
- Guideline on clinical trials in small populations (CHMP/EWP/83561/2005);
- Role of Pharmacokinetics in the development of medicinal products in the Paediatric Population (CHMP/EWP/147013/2004);
- Draft Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (EMA/CHMP/594085/2015)
- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2);
- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013);
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008);
- Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012);