# The paediatric Addendum to the antibacterial agents guideline

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# Agenda

- Overview of PIPs of antibacterial agents with EMA decision and timelines (antibacterial agents authorised in adults from 2015 on)
- Clinical development programmes (past agreed PIPs vs. more recently agreed PIPs)
- Pharmacokinetic studies
- Extrapolation of efficacy
- Extrapolation of safety
- Timing of paediatric study(ies) with respect to adult development
- Conclusions

**Aims:**

- Identify which proposals in the addendum are found controversial (e.g., feasibility) and/or may need further elaboration/more detail.
- Identify areas not covered (specific for antibacterial agents and not addressed in other EMA guidelines).

# Current guidance

- Note for Guidance on evaluation of medicinal products indicated for treatment of bacterial infections = *Core Guidance* (CPMP/EWP/558/95 rev 2); *currently under revision (draft CP paper released for public consultation)*

- *Section 4.2.3 Studies in children and adolescents* considers that extrapolation of efficacy from adults to paediatric patients is possible in most cases if sufficient PK and safety data have been generated with the intended dose regimen(s) in paediatric patients

- Paediatric addendum triggered by the current situation of agreed PIPs of antibacterial agents/scientific advice

- Addendum released for consultation 6 April 2018 until 30 October 2018

# Overview agreed PIPs (June 2018)

- 30 agreed PIPs (with EMA decision)/26 different active substances
  - excluding antibacterial agents for inhalation (e.g. cystic fibrosis) and for eradication of *H pylori*
- Fourteen (14) IPs include all paediatric age subsets.
- Seventeen (17) include neonates (as 3 additional PIPs include only young children).
- Indications covered:
  - Site-specific indications: ABSSSIs (n=6), CAP (5), cUTI (5), cIAI (5), HAP/VAP (3), CDI (3), other indications
  - Pathogen-specific indications (limited therapeutic options): 3
  - None of them cover paediatric-specific indications (e.g., acute haematogenous osteomyelitis)
- Paediatric indications based on completed PIPs granted for two antibacterial agents; an additional one includes paediatric indications in children aged 2 months or older.
- Timelines: out of the 7 antibacterial agents recently authorised, only one includes a (partial) paediatric indication. The estimated date of completion of the remaining 6 PIPs ranges from 2019 to 2022.

# Paediatric clinical development plan

- Clinical development in most agreed (in the past) PIPs:
  - PK study PLUS
  - Site-specific indications: a randomised, active-comparator safety/efficacy study usually per adult indication
  - Pathogen-specific indications: no dedicated paediatric study requested unless this is the only indication sought in adult patients
  - Timing: start of PK study usually in parallel with adult phase 2

- Proposal in the paediatric addendum:
  - PK study (with careful collection of safety data) if extrapolation of efficacy and of safety is possible

# Paediatric addendum - Principles

- Paediatric PK studies and population PK modelling and simulation needed to identify the dose that achieves similar systemic exposure and PTA in adults.

- Extrapolation of efficacy from studies conducted in adults (based on similar aetiology and antibacterial spectrum of the antibacterial agent)
  - not possible if no adult studies (disease does not occur/rarely occurs in adults)→paediatric efficacy study needed.
  - pathogen-specific indications: antibacterial agents qualified by CHMP (SAWP) as addressing an unmet medical need

- Extrapolation of safety from studies conducted in adults (based on similar systemic exposure at the doses selected)

- Timing of the paediatric (PK) study(ies) with respect to adult development

  *The timing of paediatric pharmacokinetic studies needs to be carefully considered in relation to the adult data that are available, particularly when the test antibacterial agent is intended to be administered to paediatric patients as a full course of treatment for their infectious disease.*

# Paediatric PK studies

- The addendum proposes a clinical development based on PK study(ies)
  - Paediatric subjects distributed across all age ranges (adolescents)
  - Simultaneous enrolment of all age groups unless age and/or maturation related differences in drug disposition
  - Primary objective is dose-finding in the different age groups based on PK
  - Not possible in case of locally-acting antibacterial agents (PK collected to document negligible systemic exposure)
  - Prior knowledge of the potential for drug-drug interactions to occur
- In many cases a PK study that assesses PK after single (intensive sampling) and repeated (sparse) doses.

# Study population in PK studies

- Single dose PK studies: the antibacterial agent is administered to paediatric patients on top of an effective regimen for the underlying infectious disease.
- Repeated dose (PK) studies:
  - Paediatric patients may receive a full course of the test antibacterial agent for treatment of their infectious disease but this is not usually the case (restrictions imposed by, e.g., the IV line)
  - Pathogen-specific indications:
    - No need for enrichment of the paediatric study with resistant organisms
    - Including all infections types as studied in adults is not mandatory although the addendum recommends that PK data are obtained from at least some paediatric patients with evidence of severe systemic illness (e.g., only cUTI in paediatric patients while in adults HAP/VAP is assessed)
    - Including infection types not assessed in the adult study(ies) but caused by organisms within the spectrum of the antibacterial agent and in accessible infections sites may be discussed on a case-by-case basis (to increase feasibility)

# Extrapolation of efficacy

The addendum provides examples (but not an exhaustive list) of infectious diseases in which extrapolation of efficacy may or may not be possible

- **Extrapolation possible**

- uc/cUTI, cIAI, CABP, HAP/VAP, aBSSSIs, gonococcal disease, pelvic inflammatory disease (any STD)
- Acute bacterial sinusitis
- Acute bacterial endocarditis
- Acute osteomyelitis (not of haematogenous origin)
- Tavellers' diarrhoea/CDI
- Acute bacterial conjunctivitis
- Superficial wound infections and secondarily infected dermatoses (except atopic dermatitis)
- Pathogen-specific indication

- **Extrapolation not possible**

- Impetigo
- Acute otitis media
- Infected atopic dermatitis
- Acute haematogenous osteomyelitis
- Acute group A streptococcal pharyngotonsillitis

# Extrapolation of safety

- Follows the same approach as for other anti-infective agents (e.g., DAA for CHC)
- Safety in paediatric subjects is always extrapolated to a certain extent whether or not a randomised, comparative trial in paediatric subjects is performed
- Based on finding paediatric doses that achieve similar systemic exposure as in adult subjects

- Locally-acting agents: systemic exposure and tolerability in the target population

- Unless there are potential/identified safety concerns in non-clinical or clinical (adult) studies that are of particular relevance for the paediatric population
  - Off-target effects
  - New agents within an existing class vs. new agents of a new class

- Consideration to the size of the paediatric safety database pre-marketing
- Consideration to post-marketing pharmacovigilance (routine or pro-active measures)

# Extrapolation

- Transparent exercise (rather than a value judgment): an extrapolation concept should be developed the elements of which need to be detailed in a extrapolation plan.
- Uncertainties related to extrapolation of efficacy and safety should be discussed at the time of MAA; measures to deal with them proposed
- In PIPs:
  - agreed in the past, extrapolation of efficacy was implicitly assumed
  - in more recently agreed PIPs, extrapolation is made explicit and
  - usually reflected in the PIP opinion
    - A pop-PK/PD modelling and simulation study

      AND
    - An extrapolation study (detailing the source and the target populations, the studies considered etc.)

# Timing of paediatric studies

- Single dose PK studies can be started relatively soon, i.e., with adult phase 2 data or even earlier (e.g., urgent unmet need in paediatrics or new agents of an existing class with very well known safety profile)

- Multiple dose studies:
  - depends on the specific antibacterial agent (e.g. known beta-lactam/new beta-lactamase inhibitor)
  - how it is to be administered in the paediatric study (alone, in combination with adjunctive therapy, on top of an effective regimen)
  - pathogen-specific indications:
    - if paediatric patients with all types of infections (as in the adult trial) are going to be enrolled, adult efficacy data should be available unless it is a known agent.

- In many cases a single PK study assesses both single dose (intensive sampling) and multiple dose.

# Topics repeatedly discussed

- Sample size justification
- Distribution of paediatric subjects in the different age groups (usually higher numbers in the older age groups)
- Justification PK sampling schedule
- Blood volume per PK sample

- Multiple dose studies:
  - Types of infectious diseases that could be assessed for the purpose of obtaining PK and some safety data, particularly when the indication sought in adults is a pathogen-specific indication (e.g., only children with cUTI planned to be enrolled while in adults HAP/VAP is a possible indication)
  - Use of the antibacterial agent alone (or with adjunctive therapy) vs. on top of an effective regimen (feasibility in case of multiple doses questionable)
  - Intravenous agents: minimum number of doses that should or can be administered to obtain safety data

- Timelines

# Conclusions

- The paediatric addendum acknowledges that single dose PK studies may allow for extrapolation of efficacy and safety (the latter under specific conditions).
- No paediatric plans have been submitted based on single dose PK studies for the time being.
- This seems related to the antibacterial agent and to the proposed paediatric (and adult) indication
- The paediatric indication that can be granted based on the paediatric PK study(ies) will be that/those of adult patients regardless of the types of infections included in this study
- A recommendation is made that PK data are obtained from at least some paediatric patients with evidence of severe systemic illness
- Expectation is that the recommendations made in the addendum may lead to a timely completion of the clinical development of antibacterial agents for paediatric patients