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Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements

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This addendum complements the Guideline on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2).

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

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Executive summary

This addendum to the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) has been developed to provide specific guidance on paediatric clinical development programmes that are required to support the authorisation of antibacterial agents for treatment of infectious diseases in paediatric patients.

This Addendum provides guidance on clinical data requirements to support the approval of an antibacterial agent to treat infectious diseases in paediatric patients, both when extrapolation of efficacy from adults (source population) to paediatric patients (target population) is possible, and when this is not the case.

An extrapolation of the efficacy of an antibacterial agent across age ranges is considered possible for the majority of infectious diseases (see section 6.1) but there are a few exceptions (see section 6.2).

The safety profile will primarily be driven by the dose of, and the systemic exposure to, the antibacterial agent. For the most part, a similar safety profile is expected in adults and paediatric subjects when the paediatric dose regimens achieve similar systemic exposures to those in adults, supporting an extrapolation of safety from adults to paediatric subjects.

Safety data may need to be generated in the paediatric population or in specific age subsets if there are emerging concerns from the available non-clinical and/or adult clinical data that are especially relevant to the paediatric population (e.g., age-specific adverse effects such as those of fluoroquinolones). In these instances, the need to adequately document safety in children has implications for the size of the pre-approval paediatric safety database.

In many circumstances, only paediatric pharmacokinetic studies will be needed. Depending on the study population, the test antibacterial agent could be administered alone, as adjunctive therapy or on top of an effective antibacterial regimen. Timing of the paediatric pharmacokinetics studies in relation to the availability of safety and efficacy data in adults should be considered and adequately justified in terms of the study population that will be enrolled and how the test antibacterial agent will be administered.

Any uncertainties related to the extrapolation of safety and/or efficacy between age groups at the time of seeking approval for use in children should be discussed in the application dossier. An extrapolation concept needs to be developed, the elements of which and their role in the extrapolation exercise should be detailed in an extrapolation plan. Depending on the amount of data planned or actually generated in the paediatric population, mitigation measures to deal with uncertainty and risk should be proposed, e.g., post-marketing measures to collect safety data in the paediatric population if the paediatric indication is only based on pharmacokinetic studies.

1. Introduction (background)

The *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 2) and the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CHMP/351889/2013) provide guidance that is mainly focussed on adult clinical development programmes.

CPMP/EWP/558/95 rev 2 (Section 4.2.3.*Studies in children and adolescents)* states that it may be reasonable to extrapolate efficacy data obtained in adults to paediatric patients provided that sufficient

pharmacokinetic and safety data have been generated with the intended dose regimen(s) in paediatric patients. The same section recognises that some types of infectious disease occur almost exclusively in children so that a demonstration of efficacy can be obtained only in the paediatric age range that is affected. Details of these situations and the extent of the paediatric data that may be expected are not addressed.

This guideline considers the various situations that could apply and the paediatric data that should be generated for approval of antibacterial agents in the paediatric population, including whether pharmacokinetic data in a limited number of paediatric subjects may suffice to grant a paediatric indication.

2. Scope

This Addendum provides guidance on clinical data requirements to support the approval of an antibacterial agent to treat infectious diseases in paediatric patients when:

Extrapolation of efficacy against an infectious disease from adults to paediatric patients is possible based on similar pathophysiology of the infectious disease and a spectrum of activity of the antibacterial agent that includes pathogens relevant across the target age groups. This situation applies to the majority of infectious diseases that occur both in adults and in one or more paediatric age sub-groups.

Extrapolation of efficacy against an infectious disease from adults to paediatric patients is not possible because the infectious disease occurs only or predominantly in paediatric patients (e.g. impetigo and otitis media)and/or there are differences between age groups in the nature or course of the infectious disease leading to different response to treatment (e.g. streptococcal pharyngitis).

The considerations for extrapolation of safety from adults to paediatric subjects are addressed, taking into account any age-related safety concerns from the available non-clinical and/or adult clinical data.

For the majority of antibacterial agents, a similar safety profile is expected in adults and paediatric subjects when the paediatric dose regimens achieve similar systemic exposures to those in adults, supporting an extrapolation of safety from adults to paediatric subjects. Safety data may need to be generated in the paediatric population or in specific age subsets if there are emerging concerns from the available non-clinical and/or adult clinical data that are especially relevant to the paediatric population (e.g., age-specific adverse effects such as those of fluoroquinolones). In these instances, the need to adequately document safety in children has implications for the size of the pre-approval paediatric safety database.

This addendum considers antibacterial agents that are administered by parenteral, oral or topical routes (i.e. direct application to skin, mucous membranes or conjunctivae). It does not address the clinical development of inhaled antibacterial agents (e.g. those intended for treatment of lung infections in children with cystic fibrosis).

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, as well as Regulation (EC) No 1901/2006, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2).
- Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008)
- 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 use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015).
- ICH E11 and ICH E11 addendum R1: Guideline on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99).
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum).

4. Patient selection

4.1 Pharmacokinetic studies

Pharmacokinetic studies with antibacterial agents are usually performed in paediatric subjects with suspected or confirmed bacterial infections. It is recommended that when the test antibacterial agent is intended to be used for the treatment of the underlying infectious disease in multiple dose pharmacokinetic studies, age-appropriate internationally-agreed diagnostic criteria for specific infectious diseases (such as those developed and published by professional bodies) are used for paediatric patient selection. The paediatric pharmacokinetic data may be obtained in patients with one or a limited range of the infectious diseases for which use of the antibacterial agent is proposed, taking into account whether pharmacokinetic differences were observed in adults depending on the site of the infection. It is recommended that pharmacokinetic data are obtained from at least some paediatric patients with evidence of severe systemic illness, if applicable to the indications proposed.

It may not be necessary to obtain pharmacokinetic data from all age subgroups in which use is to be proposed. In some circumstances, modelling and simulation of adult data may be sufficient to support dosing recommendations for certain age subgroups (e.g., adolescent subjects). On other hand, pharmacokinetic data will need to be generated in neonates in almost all cases owing to the rapid developmental changes in absorption, distribution, metabolism and excretion.

Unless there are suspected or identified safety concerns, pharmacokinetic studies may be conducted in parallel in paediatric age subgroups for which no age and maturation-related differences in drug disposition are expected. If there are age subgroups in which such differences are expected, these should be studied later on in the development programme in a staged fashion.

In term and preterm neonates it may be difficult or impossible to determine the primary site of infection. In this population, it may be necessary to obtain pharmacokinetic data for the test antibacterial agent in patients with suspected or proven late-onset sepsis with no known primary focus who are receiving standard of care antibacterial regimens.

4.2 Efficacy studies

In the very few situations outlined in section 6.2 in which a demonstration of efficacy may or would be required in a paediatric population, any available age-appropriate internationally-agreed diagnostic criteria for specific infectious diseases (such as those developed and published by professional bodies) should be used for patient selection.

5. Assessment of efficacy

5.1 Infectious diseases for which an extrapolation of efficacy from adults to paediatric patients is possible

Whenever adult efficacy data are available an extrapolation of efficacy from adults to paediatric patients should be attempted.

The application dossier should include a discussion of the basis for the extrapolation of efficacy from adults to various paediatric age subgroups. To support the extrapolation of efficacy from adults, the paediatric programme should provide sufficient pharmacokinetic data to support the paediatric dose regimens (see section 7.1).

An extrapolation of efficacy from adults to paediatric age groups is considered possible for the majority of infectious diseases including, but not limited to the following:

- Acute bacterial skin and skin structure infection (ABSSSI)
- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI)
- Uncomplicated urinary tract infection (uUTI)
- Community-acquired pneumonia (CAP)
- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
- Pelvic inflammatory disease
- Sexually transmitted diseases (when acquired through the sexual route)
- Acute bacterial sinusitis
- Acute bacterial endocarditis. Efficacy is most likely to have been demonstrated in adults with right sided endocarditis and without prostheses whereas infective endocarditis in paediatric patients may also be due to a left sided or septal focus. Nevertheless, the causative pathogens and duration of treatment is similar and an extrapolation between age groups is possible.
- Acute bone and joint infections, exception for acute haematogenous osteomyelitis.
- Travellers' diarrhoea and *Clostridium difficile* infection
- Acute bacterial conjunctivitis (for topical formulations of antibacterial agents)

- Superficial wound infections and secondarily infected dermatoses (for agents administered topically to skin and mucous membranes), except for infected atopic dermatitis.

Furthermore, it is considered that an extrapolation of efficacy across age groups is possible for antibacterial agents that are indicated for the treatment of infections due to certain bacterial species in patients with limited treatment options.

5.2 Infectious diseases for which an extrapolation of efficacy in adults to paediatric patients is not possible

A demonstration of efficacy in the target paediatric population is usually required to support the treatment of infectious diseases that occur only or mainly in the paediatric population so that efficacy trials in adults are not feasible and/or when the course of the disease and response to treatment may be different. Some examples include, but are not limited to:

- Impetigo occurs predominantly in paediatric patients aged less than 5 years so that a demonstration of efficacy in adults is not feasible.
- Infected atopic dermatitis occurs predominantly in pre-pubertal paediatric patients. It has a specific underlying pathophysiology requiring different management compared to some other superficial dermatoses. For example, efficacy against conditions such as infected psoriasis, whether this is demonstrated in adults and/or paediatric patients, does not necessarily predict efficacy in infected atopic dermatitis.
- Acute otitis media (AOM) occurs most often in children aged less than 5 years and rarely in adults.
- Acute group A streptococcal (GAS) pharyngotonsillitis can occur at any age but the eradication rate of GAS in paediatric patients with pharyngotonsillitis treated with penicillin has been reported to be lower than that in adult patients, giving uncertainty regarding the extrapolation of efficacy between age subgroups.
- Acute haematogenous osteomyelitis (AHO) has a different presentation to other forms of osteomyelitis that can occur in adults and children (e.g. due to trauma and/or around prosthetic implants) and may require a different duration of treatment.

6. Study design

6.1. Pharmacokinetic studies

Applicants should refer to the *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population* (EMEA/CHMP/EWP/147013/2004 Corrigendum).

6.1.1 Systemic administration to achieve a systemic effect

Depending on the pharmacokinetic properties of the test antibacterial agent in adults:

- If single dose pharmacokinetic data are considered adequate to select paediatric dose regimens it is recommended that the test antibacterial agent is administered to paediatric patients who are also receiving routine antibacterial therapy for their infectious disease.

- If multiple dose pharmacokinetic data are required it is usual that paediatric patients receive a full course of the test antibacterial agent for treatment of their infectious disease, either alone or as adjunctive therapy, but it is acknowledged that this may not be possible in all cases. No definitive recommendations can be provided in this respect as the appropriate design depends on the indication(s) targeted and the age group(s) that is/are being studied. Therefore, this needs to be considered on a case-by-case basis.

When the test antibacterial agent is administered with other antibacterial agents, there should be prior knowledge of the potential for drug-drug interactions to occur.

For some intravenously administered antibacterial agents for which efficacy is related to the time that plasma concentrations are above a certain threshold the adult dosing regimen may involve prolonged infusion times. Long infusion times may be problematic in some paediatric age groups and it may be appropriate to consider alternative approaches. Alternative dosing regimens using shorter infusion times may be simulated and assessed for probability of target attainment subject to consideration of the applicability across age groups of the pharmacokinetic-pharmacodynamic index and target applied to the adult data. Paediatric regimens selected in this way could then be used in pharmacokinetic studies in appropriate age subgroups.

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.

6.1.2 Topical or oral administration to achieve a local effect

In these cases, dose regimens for paediatric patients cannot be identified based on comparable plasma exposures to those in adults in whom efficacy was demonstrated.

For topical agents, provided that the pharmacokinetic and physicochemical properties of the antibacterial agent and its formulation do not suggest that substantially higher systemic exposures of potential concern are at all likely to occur in paediatric patients, and subject to the nonclinical data, it may be appropriate to administer the same product (i.e. strength) to all age groups and to document that there is negligible systemic exposure (similar to that in adults) to support the extrapolation of safety. There is particular concern regarding systemic exposures that may result from topical treatments in children below 2 years of age due to the uncertainties about the age at which the skin barrier function can be considered fully mature and the age-dependent larger ratio of body surface area to body weight which all predispose to an increased systemic absorption.

For oral agents, it may be appropriate to administer the adult dose in an age de-escalating fashion unless or until there is evidence of local intolerance below which a reduced dose could be needed. Selection of an appropriate paediatric dose could then be based on factors such as drug solubility measurements in simulated intestinal fluids, estimated age-related gut volumes and physiologically-based pharmacokinetic models. Negligible systemic exposure as occurred in adults should also be documented to support the extrapolation of safety.

Acceptability and palatability (the latter when applicable) should be assessed in the pharmacokinetic studies of orally administered antibacterial agents.

6.2. Efficacy studies

Efficacy studies in the paediatric population will be needed in the very few situations in which efficacy trials cannot be conducted in adults or it cannot be assumed that efficacy in adults necessarily applies across all age groups. Some examples include, but are not limited to:

Impetigo

The high spontaneous resolution rate of impetigo makes an approval based solely on non-inferiority studies not acceptable. Placebo-controlled studies in patients with impetigo should therefore be performed. An alternative to a study against placebo is to randomise patients either to a full course of the test agent that is commenced at study entry or to commence with placebo for a specified number of days (e.g. 48-72 hours) followed by a full course of an appropriate licensed agent. Appropriate limitations should be placed on the use of adjunctive therapies, including the use of antiseptics.

In studies in impetigo the number of lesions should be counted and an estimate made of the total body surface affected. Protocols may set limitations on numbers and/or surface area, especially if treatment is topical. The protocol may designate treatment of only the single largest lesion, a specific number of lesions or all lesions present to be treated. Depending on the strategy adopted, pre-defined additional analyses may be needed by lesion number or area since untreated neighbouring lesions can affect the likelihood of clinical success at treated lesions.

It would be acceptable if the test agent was shown to be superior to placebo based on time to resolution of the infection, which could be assessed at end of treatment. Clinical resolution should also be assessed at post-therapy visits to document relapse rates. It is recommended that pathogens recovered from infections that have not resolved by end of treatment or which relapse should be investigated for production of toxins.

Infected atopic dermatitis

A non-inferiority study against a licensed systemic or topical treatment (selected to enable a double-blind study design) is considered acceptable provided that strict inclusion criteria are used. The suggested non-inferiority margin is -10%. The use of adjunctive therapies such as topical steroid treatment and the use of occlusionshould be standardised and predefined in the study protocol.

As part of the eligibility criteria, the size of the infected portion of the lesion or lesions should be predefined and in case of topical treatment the disease should be amenable for treatment by this route of administration.

Clinical success in infected atopic dermatitis should be based on the resolution of signs such as crusting, weeping/exudation, pustule formation and purulent discharge, all of which are suggestive of secondary infection. A demonstration of non-inferiority could be based on comparison of clinical success rates at a visit timed from randomisation to occur at post-therapy days 7-9. Clinical resolution should also be assessed at a later visit to document relapse rates.

Acute otitis media (AOM)

It is considered that published data support acceptance of a non-inferiority trial design provided that the patient population is aged from 6 months to 3 years, has adequately defined AOM and the comparator is specified. Nevertheless, the available data do not provide an unequivocal indication of the primary endpoint and non-inferiority margin to apply.

It is recommended that all eligible children should present with acute onset (within 48 hours) otalgia and a bulging tympanic membrane on otoscopy as a minimum. AOM may be unilateral or bilateral and

stratification is suggested. All signs and symptoms compatible with an ongoing acute infection should be documented and the use of a scoring system is recommended. The comparative regimen should be oral amoxicillin-clavulanate administered at the highest dose that is approved for treatment of AOM in this age group across the study sites and for at least 7 days.

Clinical success should require resolution of abnormalities on repeat otoscopy (in both ears if AOM was bilateral) and resolution of otalgia. There should also be resolution of signs and symptoms of an ongoing acute infectious process that were present at baseline. A demonstration of non-inferiority could be based on comparison of clinical success rates at a visit timed from randomisation to occur at 1-2 days post-therapy. There should also be a comparison of sustained success rates at approximately 14-21 days post-randomisation, depending on the length of treatment and timing of the TOC visit.

At the current time an approval for treatment of AOM in other age groups and in populations that do not meet these diagnostic criteria is not possible based on non-inferiority studies.

Acute group A streptococcal (GAS) pharyngotonsillitis

A non-inferiority study against amoxicillin or phenoxymethylpenicillin is considered acceptable.

Eligible subjects should have an acute onset sore throat and a positive rapid antigen detection test (RADT) for GAS. The clinical criteria and/or clinical scoring systems used in the patient selection criteria should be appropriately justified and documented. A pharyngeal specimen should be obtained for culture confirmation of GAS pharyngotonsillitis and only those patients with a positive baseline culture should be eligible for the primary analysis.

The primary endpoint should be the microbiological eradication rate based on cultures obtained at the test-of-cure visit, usually 5–7 days post-therapy. Sponsors are advised to discuss the non-inferiority margin that might be acceptable in the age subgroup to be enrolled with EU Competent Authorities but in all cases it is recommended that it must not exceed 10%. A follow-up visit occurring at approximately 38 to 45 days post-randomisation should be planned to assess relapses and any complications of the infection.

Acute haematogenous osteomyelitis (AHO)

In AHO, a non-inferiority trial is acceptable. Nevertheless, the available data do not provide an unequivocal indication of the non-inferiority margin to apply. For this reason, it is recommended that the pre-defined non-inferiority margin is discussed with EU Competent Authorities. Comparative antibacterial regimens should be selected to cover the most likely pathogens based on local experience of AHO cases, the age of the child and early microbiological findings (e.g. Gram’s stain and/or a rapid diagnostic test).

The primary endpoint can be based on a measure of clinical improvement from baseline in pain, inflammation, and (limb) function on day 8-post randomisation. However, this should be supported by the rate of clinical cure judged at an appropriate time point (e.g. 21-35 days after end of therapy) which should be very high (usually above 95%). It is strongly recommended that an independent Data Adjudication Committee unaware of treatment assignments is appointed to assign clinical outcomes to be used in primary and secondary analyses.

Patients should be followed for 6 months from study entry for relapse. Evolution to chronic osteomyelitis or relapse occurs usually within this timeframe with late relapses being exceptional.

7. Safety aspects

The safety profile will primarily be driven by the dose of, and the systemic exposure to, the antibacterial agent. For the most part, a similar safety profile is expected in adults and paediatric subjects when the paediatric dose regimens achieve similar systemic exposures to those in adults, supporting an extrapolation of safety from adults to the paediatric population.

Safety data may need to be generated in the paediatric population or in specific age subsets if there are emerging concerns from the available non-clinical and/or adult clinical data that are especially relevant to the paediatric population (e.g., age-specific adverse effects such as those of fluoroquinolones). In these instances, the need to adequately document safety in children has implications for the size of the pre-approval paediatric safety database that should be addressed in the paediatric investigation plan.

Any uncertainties related to extrapolation of safety at the time of seeking approval for use in children should be discussed in the application dossier and appropriate post-marketing measures should be proposed to collect safety data in the paediatric population, particularly when the size of the pre-approval safety database is very limited.

Safety data should be described for the overall paediatric population and, if the number of subjects allow it (e.g. if a demonstration of efficacy in paediatric patients is required), by age sub-groups.

Long-term follow-up for safety is usually not needed for antibacterial agents that are administered for a limited period. However, the duration of follow-up for safety may need to be longer than usual if signals of concern have been shown in juvenile animals that would not preclude paediatric development but raise issues that cannot be addressed by further nonclinical studies or by the adult safety data. The exact duration of follow-up in these situations should be decided on a case-by-case basis.

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