Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

# Reflections on the methodological issues associated with the CHMP guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

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# Contents

- 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 evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)

- Adopted by CHMP 15 December 2011
- Came into effect 15 December 2012
- Section 4.2 Clinical studies

# Section 4.2 Clinical studies

- Analysis populations – “With few exceptions (e.g. in urinary tract infections) it is not required that the primary analysis should be confined to the subset of patients with at least one acceptable baseline pathogen. … clinical primary endpoint it is suggested that the all-treated and clinically-evaluable populations… are co-primary. In studies with a microbiological primary endpoint it is suggested that the co-primary analysis populations should be all-treated with a pathogen and microbiologically-evaluable.”

# Section 4.2.1.4 Major (Pivotal) Studies

- “It is preferred that 2 pivotal studies of efficacy are performed for each clinical indication sought. If a single study is proposed the CHMP guidance on submission of a single pivotal study apply. It is preferred that investigate sites in the study in each clinical indication are geographically dispersed and that protocols should plan for secondary analyses of efficacy by country and/or region. It is not required that confirmatory clinical studies should include investigate sites located within the EU but the sponsor should provide a rationale to support the relevance of the efficacy data to EU patients”

# Section 4.2.1.4.1 Non-inferiority studies

- “In a valid non-inferiority study against an active comparative treatment:
  - There must be confidence that the test antibacterial agent would have demonstrated superior efficacy to placebo if such a study had actually been performed.
  - The study design should minimise the possibility of reaching a false conclusion of non-inferiority.”

## Section 4.2.1.4.1 Non-inferiority studies

- “Selection of the non-inferiority margin (delta)
- The selection of the non-inferiority margin must be tailored to the indication under study taking into consideration the need to indirectly demonstrate superiority of the test agent to placebo and to assess the relative efficacy between the test agent and the active comparator. The final choice of the non-inferiority margin should take into account clinical judgement regarding how large a difference between the test and reference treatments could be considered clinically important in each type of infection. Historical data are often used to estimate the no-treatment effect but the relevance of these data to current medical practice may be questionable. Sponsors are encouraged to explore alternative and emerging methods for estimating the no-treatment effect (e.g. using pharmacometric-based approaches)”.

## Section 4.2.1.4.2 Superiority studies

- Explains situations when non-inferiority studies are not acceptable.
- Gives preference to conducting 3 arm studies (placebo, test and reference).
- Option for delayed therapy in the placebo group after a fixed number of days on placebo with no improvement.

## Section 4.2.1.4.3 Alternative study designs

- Not feasible to conduct at least one adequately powered randomised and controlled clinical trial to support an indication.
- “Even when small numbers of patients are expected to be enrolled it is always preferred that a randomised and controlled clinical study is conducted rather than an uncontrolled study or a comparison with external or historical controls.”
- “The justification for a randomised study planned with a lower than standard levels of statistical power must include comment on the prevalence of the infection and on the statistical performance characteristics of the trial (e.g. Type I and II errors to investigate an effect size of interest).”

## Section 4.2.1.4.3 Alternative study designs

- “If it is agreed between the sponsor and EU Regulators than an uncontrolled study cannot be avoided, every attempt should be made to generate a precise and unbiased estimate of efficacy in a clearly defined patient population in order to facilitate the interpretation of the data. Where possible, the number of patients recruited should be sufficient to exclude unacceptably low cure rates from the 95% 2-sided confidence interval estimating the response rate. The minimum acceptable cure rate should be defined prospectively based on currently available treatments and experience.”

## Section 4.2.1.4.3 Alternative study designs

- “On occasion there may be a rationale for employing a flexible (e.g. adaptive) study design. In these cases it is essential that the study design is developed in conjunction with EU Regulators and that agreement is reached on the mode of primary analysis of outcomes, including the primary patient population.”

# Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013)

- Additional advice requested by CHMP on:
  - Patient selection criteria
  - Primary endpoints
  - Indications for which superiority or non-inferiority study designs would be expected
  - Suggestions for non-inferiority margins
- Adopted by CHMP on 24 October 2013
- Came into effect on 1 May 2014

# 3.2 Indications for which non-inferiority study designs are acceptable a) Non-inferiority margins

- Sponsors should note the suggested non-inferiority margins are applicable whether two pivotal studies are conducted or a single pivotal study is proposed. If a single pivotal study is proposed the sponsor should give consideration to pre-defining a smaller level of significance than is usual in such studies (e.g. 0.01 rather than 0.05). However, if a single randomised controlled pivotal study is conducted as part of the development of the types of antibacterial agents discussed in section 3.4 a level of significance of 0.05 could be acceptable subject to justification.
- Sponsors may wish to propose alternative non-inferiority margins to those suggested (e.g. based on emerging methods for estimating the placebo effect). These proposals will be given due consideration according to the strength of supportive evidence.

# 3.2 Indications for which non-inferiority study designs are acceptable

- Skin and soft tissue infections. -10% NI margin, primary endpoint = Test of cure (TOC) approx 7-14 days after the last day of treatment.
- Community-acquired pneumonia. -10% NI margin, primary endpoint = TOC approx 5-10 days after the last day of treatment.

# 3.2 Indications for which non-inferiority study designs are acceptable

- Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). -12.5% NI margin, primary endpoint = TOC approx 7-14 days after the last possible day of treatment. All-cause mortality secondary endpoint.
- Intra-abdominal infection (IAI). -12.5% NI margin, primary endpoint = TOC approx 7-14 days after the last possible day of treatment.
- Urinary-tract infection (UTI). -10% NI margin, primary endpoint = microbiological success rate (TOC approx 7 days after the last possible day of treatment). Microbiological success defined as $< 1x10^3$ CFU/mL

# 3.3 Indications for which superiority study designs could be required

- Why?
  - High spontaneous resolution rate
  - Low likelihood that the clinical picture is due to a bacterial infection
  - Include
    - Acute bacterial maxillary sinusitis (ABS)
    - Acute bacterial exacerbations of chronic bronchitis (ABECB)
    - Acute otitis media (AOM)
    - Superficial skin infections (e.g. impetigo and minor wounds).
  - Clinical benefit cannot be assessed with confidence in a non-inferiority study

# Acute otitis media

- Superiority trial required however placebo controlled trial not required in children aged from 6 months to 3 years. Non-inferiority trial versus oral amoxicillin-clavulanate acceptable. NI margin should be less than -10%.

# Inhalational antibacterial regimens in non cystic fibrosis patients

- Superiority over placebo is required.
- If trying to prevent bacterial exacerbations an appropriate primary endpoint could be time to exacerbations assessed over 12 months after completion of an initial or first course of the test agent (depending on the regimen under evaluation).

# Conclusion

- Guideline and Addendum provide more specific guidance on the development of products indicated for the treatment of bacterial infections then in previous version.
- However due to the complexities of clinical development in this area it will normally still be necessary to check the planned clinical development for a number of indications is deemed appropriate by regulators.
- Without prior interaction with regulators this can lead to difficulties for example can a study in one infection be considered supportive/pivotal to the use of the product in another indication?

# Any questions?

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