The EU Regulatory Framework for New Antibacterial Agents

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Specific guidelines to be discussed

- CPMP/EWP/558/95 Rev 2 January 2012
- "Core" guidance document

- Addendum adopted October 2013
- Indication-specific guidance; Unmet need

- CPMP/EWP/2655/99 adopted July 2000
- PK/PD Points to Consider; revision in 2014

(EMA/CHMP/EWP/14377/2008 TB will not be discussed)

Impetus for revision and additional guidance

Core guidance revised 2011-2012

- To address issues that had arisen since the adoption of Rev 1 (Applications; CHMP SA)

- To state EU position due to new FDA requirements (endpoints; NI margins; selection criteria)

Addendum developed 2012-2013

- To provide additional details on study designs for major indications (no details in core guidance)

- To provide options for clinical development of antibacterial agents to address unmet need

Important features of core guidance

- If the PK/PD analyses are convincing it may be possible to completely omit clinical dose-finding studies

- A single pivotal study may be acceptable to support an indication

- Adult efficacy data in some indications can be extrapolated to children

- Guidance for SmPC sections most pertinent to antibacterial agents

- Simplified section 5.1 on microbiology, resistance mechanisms, pathogens treated in clinical trials, others expected to be susceptible

Important features of core guidance

- Re rare infections/pathogens (e.g. some MDR pathogens) efficacy data can be collected in standard RCTs and/or separate targeted studies

- Studies that enrol patients with well-documented infections regardless of which body site(s) is/are affected may be the only way forward

- When only limited data can be obtained randomised study designs preferred but may not need to be powered for inferential testing

- Minimum number of treated cases to support a specific claim for treating certain MDR pathogens to be judged on a case by case basis

Addendum

- Clinical development programme for antibacterial agents with potential to address unmet need; especially MDR pathogens when there are few therapeutic options

- Specific guidance covering the five major indications for which non-inferiority studies are acceptable

- Indications for which a superiority study is needed

- Indications for which study design may be problematic and/or requires some special considerations

Development specific for MDR pathogens

- Eligibility criteria for accepting limited clinical development

  - New drug in new class (new target)

  - New drug of existing class with novel spectrum

  - New or known drug of existing class coupled with new protective agent (beta-lactam/beta-lactamase inhibitor)

- Range of possible clinical programmes depending on

  - Properties of the agent (e.g. limited or broader spectrum)

  - Aims for the SmPC (e.g. specific indication + unmet need or only a claim for use in circumstances of unmet need)

Development specific for MDR pathogens

- Critical to conduct an extensive microbiology and PK/PD programme to fully document expectations for the product:

  - Support the dose regimen to be tested
  - Support plans for regimen adjustment in patient subsets
  - Support anticipated efficacy against "target" MDR pathogens
  - Identify any types of infection in which it should not be used or may need a different regimen (e.g. surfactant binding, ELF penetration)
  - Confirm the regimen using PK data from patients and conducting exposure-response analyses during the clinical studies

Development specific for MDR pathogens

EXAMPLE: New drug new class active vs. *P. aeruginosa* only

- Randomised study in one indication (e.g. HAP/VAP)

- For HAP/VAP indication should have standard alpha

- Otherwise may not be powered for formal inferential testing

- Monotherapy not possible; control therapy may be "BAT"

- Enrol as many target MDR organisms as possible; supplement (if needed) with uncontrolled data; discuss number to aim for

- Use (experimental) RDTs to enrich enrolment

Development specific for MDR pathogens

EXAMPLE: New BL/BLI combination active vs. MDR enterobacteria

- Randomised study in mixed infection types

- Exclude infections likely to need different regimens and/or where PK is lacking (e.g. osteomyelitis, meningitis)

- Not powered for formal inferential testing

- Monotherapy may or may not be possible

- Control therapy will need to be flexible (e.g. "BAT")

- Enrol as many target MDR organisms as possible

- Use (experimental) RDTs to enrich enrolment

Development specific for MDR pathogens

Section 4.1:

For the treatment of infections due to {some types of pathogens} in patients with limited treatment options. See 4.4 and 5.1.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Section 4.2:

It is recommended that {agent name} should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Development specific for MDR pathogens

There will need to be flexibility regarding the type of approval according to:

- What **has been** done pre-approval

- What the Company **plans to do** post-approval

- What **can be done** post-approval

The properties of the agent should be the main driver

Further evidence of safety and efficacy when using the recommended dose regimen to treat target pathogens may come from an observational study of case series

Major indications - general features

- 24 hours of prior antibacterial therapy allowed

- Clinical and/or microbiological primary endpoints

- Primary endpoint at post-treatment TOC visit

- Non-inferiority margins have taken into account ability to differentiate treatment vs. placebo and likely feasibility

- Alternative NI margin proposals will be judged on merit

- If a single study is proposed consider pre-defining a smaller level of significance (e.g. 0.01 rather than 0.05).

Major indications - general features

- Major patient selection criteria have been proposed for 5 major infection types, HAP/VAP, CAP, UTI, IAI, SSTI

- Kept to minimum to enhance broad acceptability of the patient population treated across regulatory agencies

- Use the same clinical development programme to satisfy multiple regulatory authorities

- Pre-define separate strategies for the statistical analyses (e.g. primary endpoints, time points) to meet requirements of various regulatory authorities

SUMMARY

- CPMP/EWP/558/95 Rev 1 introduced elements of flexibility into antibacterial drug development

- CPMP/EWP/558/95 Rev 2 builds on and expands on several issues that have a large impact on development

- Addendum reiterates the EU position on several important matters but still permits use of a single global development programme

- Provision is made for acceptance of limited development programmes for agents that can address unmet need