EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antimicrobial drug development

Role and importance of the regulatory requirements

Session on antimicrobial resistance EMA Working Parties with PCWP/HCPWP joint meeting

Presented by Dr. Mair Powell 19 September 2017
Rapporteur for CHMP guidelines discussed

Responsibilities of regulators

- To provide written guidance for sponsors on the data that would be required to support specific indications for use
- To provide scientific advice to sponsors during the drug development process, including issues that are not covered in written guidance or are covered only briefly
- To conduct the assessment of the dossier and assess the benefit-risk relationship to determine the indications granted
- To ensure that the prescribing information for the physician (the SmPC) accurately reflects the evidence
- To ensure that the patient information reflects the SmPC

Issues not within responsibilities of regulators

- Involvement in sponsor decisions to select or deselect certain candidates for further development
- Strategic decisions on direction of development driven by what else is licensed or is known to be in development
- Guidance on first-line vs. second- or third-line treatments for specific types of infections
- Stewardship; since 1997 the indications for all antibacterial agents are followed by a standard sentence:

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

Importance of regulatory guidance

- Guidelines for antimicrobial drug development are prepared by the Infectious Disease Working Party
- Guidelines assist sponsors in estimating the time lines for developmental stages and the attendant costs
- The existence of guidance may eliminate or reduce the need to seek scientific advice from regulators
- No guideline can cover every possible scenario that may arise
- Direct interaction with EU regulators is available via individual agencies and via the CHMP's Scientific Advice Working Party

CHMP Guidelines of most relevance

- **CPMP/EWP/559/95 Rev 2 (2011)** Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections
- **EMA/CHMP/351889/2013** Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections
- **EMA/CHMP/594085/2015** Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products
- Others cover anti-TB, antifungal and antiviral agents

CHMP Guidelines of most relevance

Draft

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

Expected release for consultation end of 2017

CPMP/EWP/559/95 Rev 2 (2011)
Main topics covered

- Microbiological and nonclinical efficacy assessments
- Clinical studies of the treatment of bacterial infections
- Clinical studies of the prophylaxis of bacterial infections
- Clinical studies in children and adolescents
- Evaluation of safety
- Considerations for the SmPC that are specific to antibacterial agents, such as how to present the microbiology data and describe what is known about mechanisms of resistance

EMA/CHMP/351889/2013 (Addendum)
Topics covered

- Trial designs to support indications for treatment of common types of infection (e.g. community or hospital-acquired pneumonia, urinary tract infections)
- Circumstances in which limited clinical data* may be accepted to support approval; specifically agents to address multidrug-resistant bacteria for which there may be few remaining treatment options

* Limited clinical data in this setting means a reduction in the clinical safety and efficacy data that would usually be required before first approval

Eligibility for approval based on a reduced clinical development programme

Acceptance of a proposal for a limited clinical development programme is based on the ability of the new agent to address an unmet need.

For example:

- A new drug in a new class, so that antibacterial activity is not affected by bacterial resistance to most/all licensed drugs
- A new drug of an existing class that has been designed to withstand resistance to other drugs in the same class
- A combination of a new or licensed antibacterial agent with a new protective agent against bacterial resistance (e.g. a new inhibitor that protects a licensed drug from inactivation by bacterial enzymes)

Type of reduced clinical programme

Clinical programmes will be influenced by:

- Antibacterial activity of the agent

  Agents with a wide spectrum could be evaluated for treatment of several types of common infections

  Agents with a very narrow spectrum may be evaluated for treatment only in one type of infection and, perhaps, only when the pathogen can be identified by a rapid diagnostic test before enrolment into a study

- The sponsor's aim to obtain infection type-specific indication(s) or only a pathogen-specific indication for patients with limited treatment options

Pathogen-specific indication

Section 4.1 Indications:

Treatment of infections due to {some types of pathogens} in patients with limited treatment options.

[+/- any infection-specific indications that are supported]

Section 4.2 Posology:

It is recommended that {drug name} should be used to treat infections due to aerobic Gram-negative organisms in adult patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section 4.4)

EXAMPLE: New drug active vs. many aerobic Gram-negative bacteria - I

- Randomised trial in one site-specific infection
- Select patients based on clinical diagnosis; trial does not seek to enroll patients infected with highly resistant organisms so it is possible to use a single comparative regimen
- If the sponsor wishes to claim an indication for use in this type of infection, the trial must meet the usual requirements for supporting standard indications for use
- If the sponsor wishes to claim only a pathogen-specific indication the trial may be relatively small

EXAMPLE: New drug active vs. many aerobic Gram-negative bacteria - II

- The randomised trial in a site-specific infection type provides information to support the safety and efficacy of the agent when used at the proposed dose regimen
- Sponsors are also encouraged to obtain at least some clinical data on using the agent to treat infections due to highly resistant organisms in a small randomised or uncontrolled trial
- These will likely be few in number; the expectation of efficacy of the agent against target highly resistant organisms is based on pharmacokinetic-pharmacodynamic (PK-PD) analyses

Pharmacokinetic-pharmacodynamic analyses EMA/CHMP/594085/2015 - I

PK-PD analyses underpin the development of new antibacterial agents with potential to treat very resistant organisms

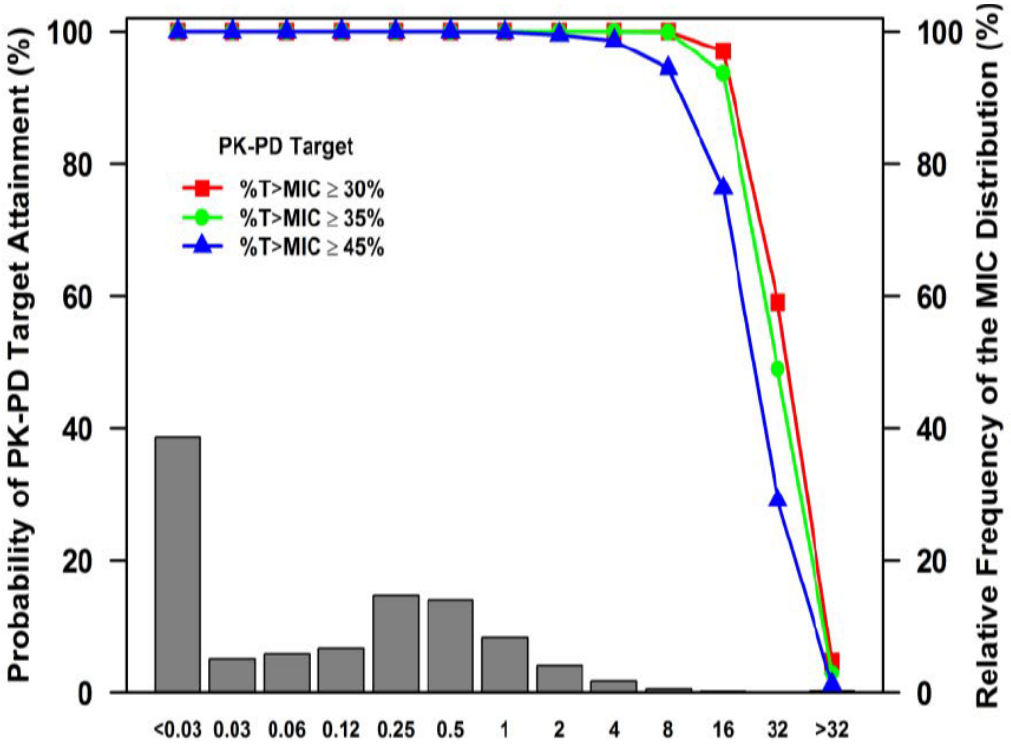
Based on the following data:

- Microbiological studies to demonstrate that the antibacterial activity of the agent is not affected by a wide range of bacterial mechanisms of resistance
- Nonclinical studies to identify the PK-PD relationship that correlates best with the antibacterial effect and to determine the target(s) that correlate(s) with bacterial killing

Pharmacokinetic-pharmacodynamic analyses EMA/CHMP/594085/2015

- Healthy subject PK data to support PK-PD analyses for selection of potentially efficacious doses
- PK data from ill infected patients who are treated with the agent at the selected potentially effective dose
- PK-PD analyses that include PK data from ill infected patients to confirm the adequacy of the dose
- Based on these same analyses, the cut-off to be applied to laboratory testing of bacterial susceptibility to the agent above which an organisms should be considered not treatable (resistant) using the recommended dose regimen is identified

Pharmacokinetic-pharmacodynamic analyses EMA/CHMP/594085/2015



Safety

- Whatever the content of the pre-licensure programme, the size of the pre-licensure safety database will be small or relatively modest in size (e.g. it may be ~300 persons)
- This type of safety database can be accepted provided that the total evidence to support benefit in patients with unmet need is very robust

AND

- The actual safety profile that is observed appears to be benign
- As always, good pharmacovigilance is essential

Paediatric guidance

- Addresses infections for which extrapolation of efficacy from adults is or is not possible

- Describes paediatric PK data and derivation of doses to support extrapolation of adult efficacy to children of different age subgroups

- Provides guidance on design of trials for paediatric-specific indications for use

New agents for TB and fungal infections

- Separate guidance has been developed regarding new agents to treat TB and serious invasive fungal infections
- The TB guidance was wholly revised last year
- The PK-PD considerations for antibacterial agents also apply in these situations
- The need for new agents to treat these infections, including multidrug-resistant organisms is recognised
- There is flexibility in the pre-licensure data requirements, which has been reflected in scientific advice

SUMMARY

- Guidance has been developed (and is to be revised during 2018) to clarify expectations for the development of antibacterial agents with potential to address an unmet need
- There is considerable flexibility regarding the content of the clinical development programme
- Programmes depend on very robust PK-PD analyses
- Pre-approval safety data will be limited
- SmPC will convey the limitations of the data and recommend use on the advice of infectious disease specialists

Thank you for your attention

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**