EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# EMA updates and perspectives

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# Antibacterial agents targeting unmet needs

Range of possible clinical programmes depending on

- Properties of the agent (e.g. very limited or broader spectrum)
- Aim to claim standard infection type-specific indication(s) as well as a pathogen-specific indication for patients with limited treatment options or only seek the latter claim

for any of:

- New antibacterial agents of new class
- New antibacterial agents of known class with novel spectrum
- New or known drug plus new protective agent (new BLI/ new BL/new BLI known BL/new BLI)

# Pathogen-specific indication

Section 4.1:

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

If there is any doubt about drug penetration (e.g. into urine or ELF) the indication could also be qualified by the infection type(s) as most relevant to the pathogen and for which there is evidence that it would be effective, e.g.

*Treatment of HAP/VAP due to {some types of pathogens} in patients with limited treatment options.*

# Other possible approaches to indications for agents addressing unmet needs

To claim a standard infection type-specific indication e.g.

*Complicated urinary tract infections*

The indication sought must be supported by at least one trial that meets all CHMP requirements (patient population, NI margin etc) for an infection type-specific and unqualified indication

PLUS

*Infections due to {some types of pathogens} in patients with limited treatment options.*

# Eligibility for limited development programme (I)

- ✓ Provisionally based on in-vitro microbiology and nonclinical efficacy (*in vitro* and/or *in vivo*)
- ✓ Human PK plasma exposures thought likely to be needed are achievable and can be tolerated
- ✓ PK-PD and PTA initially using healthy subject and later repeated using target patient PK data

# Eligibility for limited development programme (II)

## New drug of new class:

- ✓ Demonstrate mode of action is unlikely to be affected by existing mechanisms of resistance
- ✓ Assess risk of cross-resistance, including non-drug-specific mechanisms (efflux, porin)

## New drug of known class:

- ✓ Demonstrate activity likely against organisms that are resistant to other agents in same class
- ✓ Understand the mechanism(s) and frequency of resistance to the new drug

# Eligibility for limited development programme (III)

- ✓ Describe the target pathogen(s)
- ✓ Establish that there is (still) an unmet need
- ✓ There is no stated limit on the number of new agents that cover a similar resistant pathogen range since it is recognised that having several options available is valuable
- ✓ There are some pathogens that at present are not considered an unmet need (PRP; MRSA)

# Requirements for granting an approval based on a limited development programme

## Core elements

- Extensive microbiology investigations
- Clinical pharmacology data sufficient to support use in the target patient population
- Strong PK-PD support for adequacy of the dose regimen for target patients and pathogens

## Variable elements

- Safety database proportionate to unmet need, expected benefit and observed safety profile
- Clinical efficacy data depending on the aim of the initial programme

# Aim of the initial programme

## Indication for treating specific pathogens in patients with limited treatment options

- At least one RCT in a standard indication is preferred if the spectrum allows; provides comparative safety data and the control arm provides a benchmark for efficacy

## As above plus some of the indications approved for a known beta-lactam when paired with a new BLI

- It may not be necessary to conduct a fully powered RCT to support each indication subject to adequate supporting PK-PD analyses
- Depends on strong PK-PD for inhibitor regimen

# PK-PD aspects for further discussion

- Handling of heterogeneity in the PDTs derived from different in vitro – in vivo models, different labs and across tested strains
- Approaches for selecting the PDT to be carried on for PTA assessment
- Consideration of the type of infection targeted and suitability of the non-clinical model
- If product developed for pneumonia, penetration in the lungs has to be factored into the dose selection

# Evidence of activity against target MDR pathogens

- Addendum* suggests that at least some clinical data should be provided for target MDR pathogens but could be uncontrolled
- Also suggests that a mixed infection study confined to or enriched for target MDR pathogens could suffice for approval in some cases or could be supplementary to infection specific RCT(s); preferably randomised but not powered for NI
- In reality, CHMP advice has in most cases directed applicants to infection-specific RCTs as the main evidence for approval
- Adjustment of the current recommendations is expected in the forthcoming revision to the Addendum.

- **EMA/CHMP/351889/2013** Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [to be revised and combined with core GL during 2018]

# On-going harmonisation efforts
# FDA-EMA-PMDA meeting in Vienna April 2017

- Areas were identified where a move to convergence was agreed.

- Some aspects of clinical development programs for drugs intended to treat patients infected with multi-drug resistant bacteria were agreed.

- Areas were identified where currently differences remain, e.g. primary endpoint for CAP. Further scientific discussion and sharing of information may help to achieve convergence in those areas.

CURRENT DIFFERENCES DO NOT PREVENT AN EMA-FDA AGREED SINGLE DEVELOPMENT PLAN

# On-going harmonisation efforts
# FDA-EMA-PMDA meeting in Vienna April 2017

EMA, PMDA, and FDA will be working to update guidance documents to reflect the agreed areas of convergence.

In the meantime, EMA, PMDA, and FDA will provide advice to drug developers that is consistent with the agreements reached. Prior advice on drug development is not impacted.

**NEXT MEETING PLANNED FOR OCTOBER 2017 in JAPAN**

# Examples of agreement - cUTI Primary Endpoint

| | FDA | EMA |
|---|---|---|
| **Primary endpoint** | **Combined clinical and microbiologic response (<1x10$^4$CFU/mL)** at TOC at least 5 days post completion of therapy; OR co-primary 5 days post-randomisation before PO switch and 7 days post-completion of therapy | **Microbiological response (<1x10$^3$ CFU/mL)** at TOC 7 days post-completion of therapy, regardless of whether there was an IV/PO switch (based on requirement for **≥10$^5$ CFU/mL** at baseline) |

**Agreed proposal for convergence:** Clinical response and Microbiological response with a microbiological reduction cut-off at 1x10$^3$ CFU/mL

# Examples of agreement – cUTI study population

| | FDA | EMA |
|---|---|---|
| **Population** | At least 30% patients with pyelonephritis (for an indication including pyelonephritis) | Separate trials in cUTI and pyelonephritis OR limit % with pyelonephritis and stratify |

**Agreed proposal for convergence:** instead of conducting separate trials in cUTI and pyelonephritis, include both with at least 30% cUTI patients and at least 30% pyelonephritis patients

# Examples of agreement –cIAI Study Population

| | FDA | EMA |
|---|---|---|
| **Study Population** | Diagnosis of cIAI via operative procedure planned or completed within 24 hours of first dose<br>**Limit infections originating in the appendix to <50%** | Diagnosis of IAI established during laparotomy, laparoscopy, or percutaneous drainage<br>**Limit infections originating in the appendix to <30%**<br>Stratification according to infection type; Exclude upper GI perforations unless established secondary infectious process in abdominal cavity |

**Agreed proposal for convergence :** limit infections originating in the appendix to < 50%.

Exclude upper GI perforations unless established secondary infectious process in abdominal cavity

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 to be released for consultation by end of 2017

# Paediatric addendum - Principles

- 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.
- Need to generate specific safety data to be discussed
  - if emerging concerns re. certain adverse events of particular relevance for children, assessing the agent and discussing size of safety database may be necessary.
  - Role of post-marketing measures to be discussed if only PK clinical data
- PK paediatric data needed to derive the dose that matches the exposure in adults.
  - timing of the paediatric PK study in some cases may need to wait results of confirmatory trial(s) in adults

# Extrapolation of efficacy

## Extrapolation possible

- u/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

## Extrapolation not possible

-Impetigo

-Acute otitis media

-Secondarily infected dermatoses due to atopic eczema

-Acute haematogenous osteomyelitis

# Proposed approach for paediatric drug development

- If extrapolation of efficacy is possible:
  - PK study in patients
    - Not all age groups may need to be included
    - simultaneous enrolment of all age groups above 2 years of age when there are no safety concerns
    - sequential enrolment of children under age 2 years, including neonates.
    - Single or repeated dosing as considered necessary

# Safety

- A similar safety profile is expected in adult and paediatric patients (provided that similar systemic exposure is achieved)
  - if safety concerns deemed relevant in children emerge from available non-clinical/clinical data, size of pre-approval safety database (PIP agreed with PDCO) and post-marketing measures to be discussed on a case by case basis
  - Collection and reporting of safety data by paediatric age groups

- Long-term follow-up for safety usually not needed

# Eligibility to PRIME scheme

Based on Accelerated Assessment criteria

Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation.

- Potential to address to a significant extent **an unmet medical need**
- Scientific justification, based on data and evidence available from nonclinical and clinical development

No satisfactory method or if method exists, bring a major therapeutic advantage

Introducing new methods or improving existing ones

Meaningful improvement of efficacy (impact on onset, duration, improving morbidity, mortality)

# Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines.

- **Written confirmation of PRIME eligibility** and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.

# PRIME and antibacterial agents

- So far no antibacterial agent has received PRIME designation
- Stage of development and benefit of entering into the PRIME scheme are important factors:
- Products already in advanced clinical development and for which CHMP scientific advice has already been given, might not benefit
- Products for which there is too limited evidence on the ability to address unmet needs based on microbiological data and on the suitability for human use, might be considered premature for eligibility
- In any case, lack of PRIME designation does NOT imply that the antibacterial agent is not eligible for a limited development programme

# Conclusion

- The experience gained in scientific advice and approval processes are steering the views around regulatory requirements, particularly in the context of development of agents addressing unmet needs
- The international dialogue within TATFAR and in the tripartite meetings with FDA and PMDA, will be continued in order to further explore options for convergence
- EMA guidelines will be amended to take into account these evolutions
- A draft guideline for paediatric development will be released for consultation expectedly by end of 2017
- Interaction with HTA bodies and payers will need to progress to ensure access to patients in need

EUROPEAN MEDICINES AGENCY

# Thank you for your attention

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