



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antibiotic drug resistance the EMA perspective

New developments in drug regulation, Pretoria, SA
8th September 2015



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Antimicrobial resistance

- growing European and global health problem;
- MDR bacteria in the EU are associated with 25 000 extra deaths and about 1.5 billion euros extra economic burden per year;
- EMA and its EU and international partners involved in initiatives attempting to limit the development of antimicrobial resistance.



Recent evolutions of the EU regulatory standards for approval of new antibacterials (I)

- **2012: core guidance revised**
 - 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);





Recent evolutions of the EU regulatory standards for approval of new antibacterials (II)

- 2013: **addendum to the guideline developed**
 - 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;





Addendum: 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).



Addendum: development specific for MDR pathogens (II)

- ❑ The type of development will depend on:
 - ❖ what ***has been*** done pre-approval;
 - ❖ what the applicant ***plans to do*** post-approval;
 - ❖ what ***can be done*** post-approval.
- ❑ Main driver: properties of the antibiotic;
- ❑ 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.



Addendum: development specific for MDR pathogens (III)

- ❑ 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.

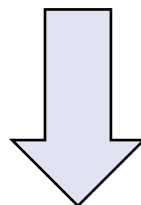


Addendum: development specific for MDR pathogens

- Example 1: **a new drug active on MDR Enterobacteriaceae**

- a single standard NI pivotal study in HAP/VAP (or IAI)

- An "all comers" study with MDR/XDR cases from different site of infection either single arm or vs. Best Available Therapy (BAT)



Indications potentially granted:

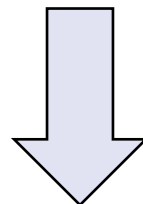
"For the treatment of infections due to Enterobacteriaceae in patients with limited options"



Addendum: development specific for MDR pathogens

- Example 2: **the same new drug for MDR Enterobacteriaceae**

-An “all comers” randomised study with MDR/XDR cases from HAP/VAP, IAI, cUTI, bacteremia vs. Best Available Therapy (BAT). Cure as Primary Endpoint. No inferential testing, but exploratory analysis for superiority at least with some secondary endpoints. Enrich with RDTs



Indication potentially granted:

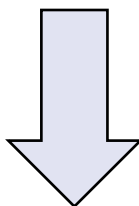
“For the treatment of infections due to Enterobacteriaceae in patients with limited options”



Addendum: development specific for MDR pathogens

- Example 3: **a new drug with antibacterial spectrum limited to single species, e.g. *Pseudomonas aeruginosa***

-A randomised study in HAP/VAP caused by *P. aeruginosa* in combination with another active agent vs. Best Available combination Therapy. Cure as Primary Endpoint. Exploratory analysis for superiority at least for MDR/XDR cases. Enrich with RDTs



Indication potentially granted:

*"For the treatment of HAP/VAP due to *Pseudomonas aeruginosa* in patients with limited options"*



Addendum: major indications - general features

- ❑ 24 hours of prior antibacterial therapy allowed;
- ❑ Clinical and/or microbiological primary endpoints at post-treatment TOC visit;
- ❑ Non-inferiority margins have taken into account ability to differentiate treatment vs. placebo and likely feasibility;
- ❑ 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.



Addendum: major indications - general features (II)

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



Addendum: prophylaxis and eradication of carriage

- ❑ Comparative studies expected for prophylaxis when role of antibacterial agents in defined circumstances is established;
- ❑ Placebo-controlled studies needed if the role of prophylaxis is not established;
- ❑ Eradication of carriage: microbiological primary endpoint only if the clinical benefit of the eradication is well-established and widely recommended, e.g. pre-operative MRSA nasal carriage.




WHAT NEXT?....

WE NEED TO TEST THE PATHWAYS!

- ❑ Approx 20 medicinal products for treatment of bacterial infections came for CHMP Scientific Advice since 2013
- ❑ More CHMP SA in this field in the last 2 years than in the previous 18 years
- ❑ At least one third of them possibly targeting unmet needs related to AMR
- ❑ HTA or FDA parallel advice used on just few cases
- ❑ Need to discuss further with HTAs as access to patients is the ultimate goal



On-going harmonization efforts

- ❑ TATFAR (Trans-Atlantic Task Force on Antimicrobial Resistance); 
 - provides an excellent tool to foster discussion between EMA and FDA in the area of antibacterial drugs development.
- ❑ Pilot interaction on development plans for antibiotics:
 - new development plans (scientific advice stage) are mutually discussed between FDA and EMA on a monthly basis.
- ❑ Information sharing on upcoming policies and options to foster antibacterial agents development



WHAT NEXT?....

Opportunities for further harmonization

Differences in evidence requirements between regulators

- Endpoints
- NI margins
- Superiority vs. NI trials
- Allowance of prior therapy
- Primary Population



Support to EU funded activities for AMR

☐ Participation in the advisory board of:

☐ IMI: COMBACTE



☐ FP7: AIDA



☐ Participation in the stakeholders board:

☐ IMI: DRIVE-AB





WHAT NEXT?....

PK/PD of antibacterial agents

- ❑ Ongoing conversion of “Points to consider on PK/PD in the development of antibacterial medicinal products (CPMP/EWP/2655/99)” into a comprehensive guideline on PK/PD investigations for the development of antibacterials

EMA Workshop planned 12-13 November 2015



1 20 February 2014
2 EMA/CHMP/792679/2013
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept Paper on revision of the points to consider on
5 pharmacokinetics and pharmacodynamics in the
6 development of antibacterial medicinal products
7 (CHMP/EWP/2655/99) and conversion to a CHMP
8 guideline
9

Agreed by Infectious Diseases Working Party	November 2013
Adopted by CHMP for release for consultation	20 February 2014
Start of public consultation	28 February 2014
End of consultation (deadline for comments)	31 May 2014

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11 The proposed guideline will replace CPMP/EWP/2655/99

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13 Comments should be provided using this [template](#). The completed comments form should be sent to
IDWPsecretariat@ema.europa.eu

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Keywords	Pharmacokinetics; pharmacodynamics; exposure-response; target attainment
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WHAT NEXT?....

Alternative therapies

Bacteriophages:

- Call from interested parties (public, policy makers, microbiologists, treating physicians) to further explore bacteriophages as an alternative approach to antibiotics
- Regulatory issues related to manufacturing and clinical studies for these products
- Regulatory issues related to the need of changing the composition of the medicinal product over time

EMA Workshop held on 8 June 2015



Modernisation of product information for „old antibiotics“

- ensures that updated information, e.g. indications of use, posology, clinical breakpoints, is provided in a harmonised way for all EU healthcare professionals
- should not replace treatment guidelines/antibiotic stewardship but contribute to achieve more rational use
- efforts/initiatives to generate new supportive data are welcomed
- prioritisation of the exercise is key, in view of the limited resources.



Conclusions

- AMR-a major public health problem
- EU regulatory standards with respect to development of new antibiotics have recently evolved
- EMA involved in many activities aiming at improving the harmonisation of the regulatory requirements
- Ongoing update of the EU regulatory guidance on PK/PD
- Discussion on alternative therapeutic approaches that could help tackle AMR
- Modernisation of SmPCs of “old antibiotics”
- Importance of continued discussion on policies and incentives



Thank you for your attention

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