ESCMID Online Lecture Library
© by author

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Recent advances in regulation to meet the challenge of AMR

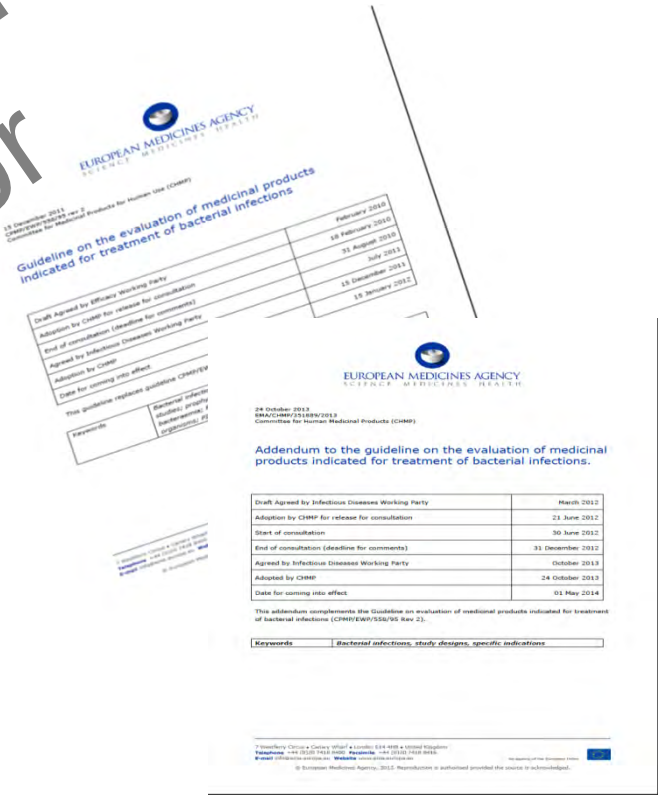
Drug development to meet the challenges of antimicrobial resistance, Vienna, Austria
22nd September 2016

Presented by Marco Cavaleri Head of Anti-infectives and Vaccines – European Medicines Agency

An agency of the European Union

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

- 2011: **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 (general issues for endpoints, NI margins and analysis populations);



ESCMID Online Lecture Library © by author

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 to support major standard infection-type indications (no details in core guidance)
  - to provide options for clinical development of antibacterial agents to address unmet need;

ESCMID Online Lecture Library © by author

Addendum: major indications - general features

- 24 hours of prior antibacterial therapy allowed;
- Clinical and/or microbiological primary endpoints at post-treatment TOC visit;
- Specific guidance covering five major indications for which non-inferiority studies are acceptable (ABBSI, CAP, HAP/VAP, IAI and cUTI)
- Indications for which a superiority study is needed (e.g. acute exacerbation of chronic bronchitis, acute sinusitis)
- Other indications that require specific considerations (e.g. bacteraemia, development of agents intended to target organisms within the gut)

ESCMID Online Lecture Library © by author

Addendum: major indications - general features (II)

- Major patient selection criteria proposed for the 5 major infection types
- Criteria kept to minimum considered essential to enhance development of single protocols that can be accepted across regulatory agencies
- NI margin set at 10% for CAP, cUTI, ABSSSI, and at 12.5% for HAP/VAP, IAI
- Although there are some differences with US FDA in primary endpoints and some other features the Addendum was designed to allow a single clinical development programme to satisfy multiple regulatory authorities

ESCMID Online Lecture Library © by author

development specific for MDR pathogens in areas of unmet needs

- Eligibility criteria for accepting limited clinical development:
  - Potential of treating infections for which there are few remaining therapeutic options
  - Good understanding of the impact of all possible resistance mechanisms on activity
  - If active against a single genus/species, justification that clinically problematic

- Possible scenarios
  - New drug in new class (new target);
  - New drug of existing class not affected by some or all existing resistance mechanisms;
  - New or known drug of existing class coupled with new protective agent (beta-lactam/beta-lactamase inhibitor).

ESCMID Online Lecture Library © by author

development specific for MDR pathogens in areas of unmet needs

- 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).

- Further evidence of safety and efficacy post-approval:
  - Pivotal studies planned for additional site-specific indications
  - Prospective uncontrolled studies
  - Observational data from registries

ESCMID Online Lecture Library © by author

development specific for MDR pathogens in areas of unmet needs

- Critical to conduct an extensive microbiology and PK/PD programme to fully document expectations for the product
- CHMP guidance does not demand a single specific approach to be followed, but outlines some of the options for clinical development
- Illustrates programmes that could support either an indication for patients with limited treatment options or this indication plus standard type(s) of indication
- Prevalence will drive the ability to collect clinical efficacy data in patients infected with the target resistant pathogens
- Stresses importance of discussing the proposed programme with EU regulators

ESCMID Online Lecture Library © by author

Addendum: development specific for MDR pathogens

Examples: *preferred scenario if spectrum allows*

- Single randomised NI study in one indication (e.g. HAP/VAP, cIAI)
- Standard alpha and NI margin if a standard type of infection indication is pursued
- Larger NI margin can be accepted if the goal is unmet need indication only
- Supplementary data on treatment of target resistant pathogens can be obtained from a separate small controlled or uncontrolled study

A pathogen-specific indication for use in patients with limited treatment options ± any indications that are supported by trials with standard alpha and NI margin could be granted

ESCMID Online Lecture Library © by author

Addendum: development specific for MDR pathogens

Examples: *other scenarios outlined*

- Randomised study in selected infection types caused by or enriched for target resistant organisms; not powered for formal inferential testing but explore results for any evidence of superiority based on clinically important endpoints vs. comparator/BAT

OR (least preferred option)

- Uncontrolled study in selected infection types caused by or enriched for target resistant organisms; consider an external control; justify design based on rarity

BOTH

- Use RDTs to enhance patient selection

A pathogen-specific indication for use in patients with limited treatment options could be granted

ESCMID Online Lecture Library © by author

Addendum: SmPC issues 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.

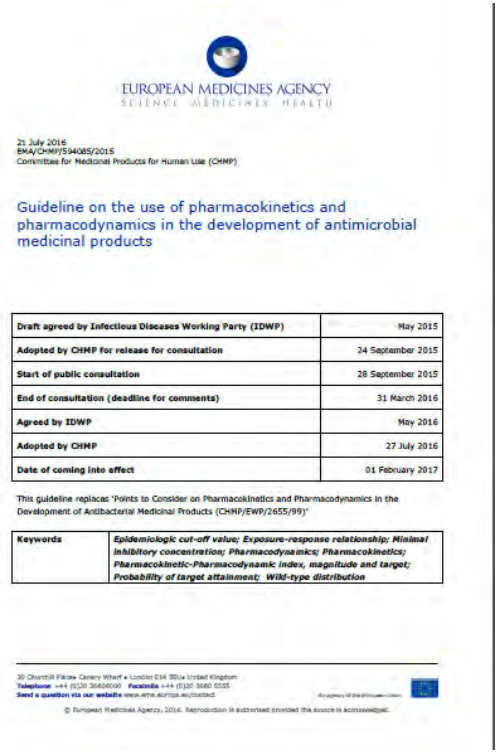
Section 4.2:

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.

ESCMID Online Lecture Library © by author

New Guideline on PK/PD of antibacterial agents EMA/CHMP/594085/2015

- 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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/594085/2015
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products

Draft agreed by Infectious Diseases Working Party (IDWP)	May 2015
Adopted by CHMP for release for consultation	24 September 2015
Start of public consultation	28 September 2015
End of consultation (deadline for comments)	31 March 2016
Agreed by IDWP	May 2016
Adopted by CHMP	27 July 2016
Date of coming into effect	01 February 2017

This guideline replaces 'Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products (CHMP/EWP/2655/99)'

Keywords	*Epidemiologic cut-off value; Exposure-response relationship; Minimal inhibitory concentration; Pharmacodynamics; Pharmacokinetics; Pharmacokinetic-Pharmacodynamic index, magnitude and target; Probability of target attainment; Wild-type distribution*

© European Medicines Agency, 2016. Reproduction is authorised provided the source is acknowledged.

ESCMID Online Lecture Library
© by author

New Guideline on PK/PD of antibacterial agents

- Determining PK-PD indices and PK-PD targets (PDTs)
- Clinical PK data to support PK-PD analyses
- PK data from uninfected subjects and infected patients
- Determination of the probability of target attainment (PTA)
- Clinical exposure-response (E-R) relationships
- Identification of beta-lactamase inhibitor dose regimens
- Regulatory implications

ESCMID Online Lecture Library © by author

New Guideline on PK/PD of antibacterial agents
Selecting the PDTs

- For potentially life-threatening infections that usually involve high organism burdens (e.g. HAP/VAP) and low spontaneous resolution rates, report PTA for the PDT associated with ≥ 1 log10 reduction in CFU
- For infections usually with lower organism burdens and/or for which important adjunctive treatment is used (e.g. surgery) reporting PTA for the PDT associated with net stasis may be considered sufficient
- Sponsors may consider other aims when selecting PDTs to be used in analyses of PTA, e.g. a PDT associated with minimization of the risk of selecting for resistance

ESCMID Online Lecture Library © by author

New Guideline on PK/PD of antibacterial agents
Expectations for PTA

- It is generally expected that the proposed dose regimen provides a PTA > 90% at the MIC90 or epidemiological cut-off value
- PTA >95% could be expected for regimens to treat life-threatening infections for which treatment is already available
- PTA <90% may sometimes be acceptable:
  - If the dose needed to achieve >90% PTA is poorly tolerated but the test agent addresses an unmet need
  - In low severity infection types
  - When high MIC isolates are sufficiently rare that the PTA is >90% at MICs observed for the vast majority of isolates

ESCMID Online Lecture Library © by author

New Guideline on PK/PD of antibacterial agents
Other issues of importance

- Collecting adequate PK from patients to support exploration of E-R relationships is recommended
- Need for adequate basic enzymology to assess inhibitors of beta-lactamases and full assessment of the impact of co-existent mechanisms (porin deficiency and efflux)
- Dose regimen of the BLI must be assessed for each of the potential partner beta-lactam agents
- Not expected that BL/BLI should be compared to BL alone in clinical trials

ESCMID Online Lecture Library
© by author

New Guideline on PK/PD of antibacterial agents
Regulatory applications of PK-PD analyses

- Can replace need for dose-finding studies
- Cannot replace need for efficacy data
- Prediction of dose adjustments in subsets
- Understanding of the potential importance of intrinsic and extrinsic factors that impact free drug plasma exposures
- Selection of regimens least likely to select for resistance (use of in-vitro models such as HFIM encouraged)
- Investigation of unexpected efficacy results

ESCMID Online Lecture Library © by author

Interaction with sponsors

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

ESCMID Online Lecture Library
© by author

Alternative therapies/ approaches

Bacteriophages:

- Call from interested parties (public, policy makers, microbiologists, treating physicians) to further explore bacteriophages as an alternative approach
- 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 in June 2015.
- Report of the meeting: E. Pelfrene *et al*., *J Antimicrob Chemother* (2016)

ESCMID Online Lecture Library © by author

Alternative therapies/ approaches

Monoclonal antibodies

-Few scientific advices given.

-Variety of targets. Important to have proof of concept for specific activities

Vaccines for healthcare associated infections

- Some scientific advices given. Target of future interactions with FDA
- Scientific difficulties acknowledged. High potential impact in case of success.

Combination therapy/ innovative delivery systems

- Important to explore the regulatory option to make such approaches viable

Too few information at this stage on other approaches such as immunomodulators

ESCMID Online Lecture Library © by author

On-going harmonisation 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.
- interaction on development plans for antibacterial agents
  - new development plans (scientific advice stage) are discussed between FDA and EMA on a monthly basis… and the process will be further strengthened
  - As a new recommendation, alternatives approaches including vaccines are discussed regularly between FDA, EMA and Health Canada
- Information sharing on upcoming policies, guidelines and options to foster antibacterial agent development

ESCMID Online Lecture Library © by author

On-going harmonisation efforts

Differences in evidence requirements between regulators are limited but do exist:

- For example: endpoints, NI margins, superiority vs. NI, analysis populations
- Take advantage of PPPs such as IMI and CTTI to promote advances in regulatory science with the goal of convergence on evidence required
- Initiatives for setting up clinical trials networks that that could run pivotal studies according to standardised protocols agreed by different regulators
- Ongoing dialogue with US FDA and Japan PMDA on regulatory requirements, e.g. September 1&2 tripartite meeting in London

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

ESCMID Online Lecture Library © by author

Key areas for future focus

- Continuous evolution and expansion of regulatory guidance based on experience gained and need to cover alternative approaches
- Development of specific guidance ongoing for paediatrics
- International interactions to explore convergence on evidence required
- Support for initiatives such as those attempting to create clinical trial networks in order to make clinical development easier and faster
- Contribution to discussions on new business models to foster R&D efforts
- Discussion with HTAs about evidence from limited clinical development programmes and the public health value of new antibacterial agents

ESCMID Online Lecture Library © by author

EUROPEAN MEDICINES AGENCY

Thank you for your attention

Further information

Contact me at Marco.Cavaleri@ema.europa.eu

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**

ESCMID Online Lecture Library © by author