EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory pathways and approaches to unmet needs

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An agency of the European Union

Approval pathways

- **Full approval**
- **Conditional marketing approval**
- **Approval under exceptional circumstances**
- **Art. 58 Scientific Opinion** for use only outside of EU

FDA- July 2016

Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

Scope (at least one):

- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- **orphan** medicinal products.

Criteria (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

'**unmet medical needs**' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

Regulation (EC) No 507/2006

Marketing authorisation under exceptional circumstances

- *Article 14 (8) of Regulation (EC) No 726/2004:* In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted **subject to certain conditions**, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can **show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use**, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the **annual reassessment** of these conditions.

  http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

- *CHMP Guideline EMEA/357981/2005*
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf

Criteria of MA under exceptional circumstances

Criteria as per Annex I to Directive 2001/83/EC :

- the indications for which the product in question is intended are encountered so **rarely** that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the **present state of scientific knowledge**, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical **ethics** to collect such information

Conditional MA

- Comprehensive data expected after authorisation
- To later switch to ‘full’ MA
- Valid for 1 year only
- Annual renewals
- Only in centralised procedure

MA under exceptional circumstances

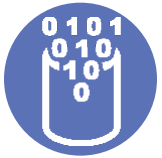
- Comprehensive data not possible
- To remain such indefinitely
- Normal validity of MA
- Annual re-assessments
- Possible in all registration procedures

PRIME scheme - Goal & Scope

To foster the development of ***medicines with major public health interest.***

Reinforce scientific and regulatory advice

- Foster and facilitate early interaction
- Raise awareness of requirements earlier in development



Optimise development for robust data generation

- Focus efficient development
- Promote generation of robust and high quality data

Enable accelerated assessment

- Facilitated by knowledge gained throughout development
- Feedback of relevant SA aspects to CHMP

Building on existing framework;

Eligibility according to existing ‘Accelerated Assessment criteria’

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.

development specific for MDR pathogens

(CPMP/EWP/558/95 Rev 2)

- 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 only on single genus/species, justification that organism is problematic

- Possible scenarios
  - 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).

development specific for MDR pathogens

- 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

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

- The current EMA guidelines do not demand for a single specific approach to be followed, but highlight potential options for clinical development
- The goal is to enlarge the portfolio of acceptable clinical development options besides the standard approaches in light of unmet medical needs
- It illustrates circumstances which would allow either an indication for unmet needs or both an indication for unmet needs and a standard type of indication
- Efforts to collect data with target pathogens are expected, but prevalence will drive the ability to collect such data
- Importance of discussing with Eu regulators the specificities of the proposed program

Addendum: development specific for MDR pathogens Examples: scenario i

- Single randomized NI study in one indication (e.g. HAP/VAP, cIAI for Gram negative targets)
- standard alpha and NI margin expected
- Alternatively a study in UTI provided PK extrapolation to other body sites possible
- Data with MDR pathogens may derive from a limited controlled or uncontrolled study

Indications for both unmet need and selected type of infection could be granted

Addendum: development specific for MDR pathogens Examples: scenario ii

- randomized study in mixed infection types with target organisms;
- exclude infections likely to need different regimens and/or where PK is lacking (e.g. osteomyelitis, meningitis);
- Superiority or NI likely not possible: not powered for formal inferential testing
- Superiority on secondary clinical endpoints to be explored
- control therapy may need to be flexible (e.g. “BAT”);
- use (experimental) RDTs to enrich enrolment.

Indications for unmet need could be granted

Addendum: development specific for MDR pathogens Examples: scenario iii

- Uncontrolled study confined to target organisms
- Historical /external control
- Justification based on rarity of the target pathogens
- use (experimental) RDTs to enrich enrolment.
- Least preferred option – data need to be convincing

Indications for unmet need could be granted

Addendum: labels 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.

Thank you for your attention

Further information

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