EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Human Medicinal Products (CHMP)

Concept paper on preparation of a revised guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

Agreed by IDWP	December 2017
Adopted by CHMP	31 May 2018
Start of public consultation	13 June 2018
End of consultation (deadline for comments)	13 September 2018

This guideline will replace and merge the following:

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2)
and
Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013

Comments should be provided using this template. The completed comments form should be sent to IDWPSecretariat@ema.europa.eu

Keywords	*Bacterial infections; antibacterials; treatment.*[1]

[1] To be identified here during preparation of the concept paper - keywords represent an internet search tool - Rapporteurs to propose and Working Party/Committee to adopt.

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1. Introduction

This Concept Paper proposes the development of a single guideline on the clinical evaluation of medicinal products indicated for treatment of bacterial infections. The development of this single guideline is intended to merge, revise and add to the guidance that is currently included in two separate documents as follows:

- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2), adopted 2011 and in force since 2012

and

- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), adopted 2013 and in force since 2014

CPMP/EWP/558/95 Rev 2 was the second revision of a text first adopted in 1997 and revised in 2007 that covered general principles for antibacterial drug development. Due to the perceived need to issue the revision as soon as possible, it was decided to finalise the text and subsequently to develop an Addendum (EMA/CHMP/351889/2013) to provide guidance on data requirements to support certain infection site-specific indications for use and on clinical development programmes for antibacterial agents expected to address an unmet need. Inevitably, there is some overlap and repetition between the two documents.

This Concept Paper proposes that both texts require revision and that they should be merged to provide a single core guidance document for antibacterial agents.

2. Problem statement

Since the adoption of the two guidelines mentioned in section 1, several new antibacterial agents have been approved in the EU, including one that has been granted a pathogen-specific indication for use in patients with limited therapeutic options. Many other antibacterial agents have been the subject of CHMP Scientific Advice. During these interactions, agreement was reached with sponsors on some aspects of clinical development programmes that are important for programme feasibility and conduct but which differ from, or are not included in, current guidance. It also became apparent that there is a need to include a detailed explanation of the indications that may be supported by various clinical development programmes for antibacterial agents expected to address an unmet need.

Two new guidelines have been finalised since 2012 and there is a need to adequately cross-refer to these texts without repeating their content. These are the:

- Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products [EMA/CHMP/594085/2015]

and the

- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to *Mycobacterium tuberculosis* [EMA/CHMP/EWP/14377/2008 Rev 1].

Furthermore, a draft Addendum to the guideline on the evaluation of medicinal products indicated for bacterial infections to address paediatric-specific clinical data requirements (EMA/187859/2017) is expected to be finalised during 2018. Thus, several sections that appear in CPMP/EWP/558/95 Rev 2 and in EMA/CHMP/351889/2013 are either out of date and/or can be replaced by cross-reference to the new guidance specific to paediatric programmes.

Finally, in 2016-2017 three meetings were held between the EMA, US FDA and Japanese PMDA to identify areas within each Agency's guidance documents where some harmonisation of the requirements could be possible. As a result, some of the issues that have been the subject of alignment up to October 2017 now conflict with the existing text and there is a need to reflect what has been agreed in the revised guidance.

3. Discussion (on the problem statement)

Several problems arise at an operational level when designing clinical studies intended to support the approval of medicinal products for treatment of antibacterial agents. Due to a resurgence of activity in the development of products intended to treat bacterial infections it is important that CHMP guidance is clear, integrated and up to date. For all the reasons described above, there is a need to revise the CHMP guidance. Merging of the text of the abovementioned Guideline and Addendum at the same time as making all necessary revisions would remove repetition as well as provide a single core document of reference.

4. Recommendation

The Infectious Disease Working Party recommends drafting a revision of the 'Guideline on the evaluation of medicinal products indicated for the treatment of antibacterial agents' that also incorporates and adds to the content of the Addendum (EMA/CHMP/351889/2013). It is proposed that the exercise to revise and merge the documents should include the following revisions:

- Update of the text to clarify the preferred and less favoured options for clinical programmes with antibacterial agents expected to address an unmet need and an explanation of the indications that could result from different programmes;
- Clarification on clinical data requirements to support new combinations of known beta-lactam agents with new beta-lactamase inhibitors expected to address an unmet need, including data with the combination to support claims for indications already granted to the beta-lactam agent alone;
- Update of the text to reflect the points of alignment that have been agreed in recent meetings with US FDA and Japanese PMDA, affecting matters such as primary analysis populations, non-inferiority margins and some other aspects of trial designs to support some of the major infection site-specific indications;
- Clarification of the considerations for acceptance of single pivotal studies to support infection-site-specific indications and pathogen-specific indications;
- Addition of guidance on clinical trials to support indications of uncomplicated urinary tract infections and uncomplicated gonorrhoea;
- Removal of text that addresses PK-PD, tuberculosis and paediatric development and replacement with appropriate cross-references;
- Clarification of the content of section 4.4 of the SmPC in circumstances in which there are important limitations to the clinical data that would constitute warnings;
- Clarification of the content of section 5.1 of the SmPCs for antibacterial agents: i) possible removal of susceptibility testing interpretive criteria from section 5.1 of SmPCs to the EMA website (which then provides for an easily updated and consolidated list of criteria) and ii) guidance on the inclusion of clinical trial data in section 5.1 of the SmPC, including the level of detail that might be

acceptable depending on the indication(s) that have been studied and whether the agent addresses an unmet need.

5. Proposed timetable

Concept Paper to be released for consultation Q2 2018.

First draft of the Guideline to be released for consultation by Q4 2018.

6. Resource requirements for preparation

The resources needed for this addendum relate to the Infectious Disease Working Party (IDWP). The Biostatistics Working Party will be consulted for comments during development of the draft guidance.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- The content of CHMP scientific advice.
- The content of regulatory submissions, including those to support antibacterial agents expected to address an unmet need.

8. Interested parties

Healthcare professionals, pharmaceutical industry, patient organisations, European learned societies involved in research into antibacterial agents and antimicrobial resistance.

9. References to literature, guidelines, etc.