European Medicines Agency

London, 19 February 2009
Doc. Ref. EMEA/CHMP/EWP/435635/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

CONCEPT PAPER ON THE NEED FOR REVISION OF THE NOTE FOR GUIDANCE ON EVALUATION OF MEDICINAL PRODUCTS INDICATED FOR TREATMENT OF BACTERIAL INFECTIONS (CPMP/EWP/558/95 REV 1)

AGREED BY EWP	January 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 February 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2009

The proposed guideline will replace guideline CPMP/EWP/558/95 Rev. 1

Comments should be provided using this template to EWPSecretariat@emea.europa.eu

KEYWORDS	*Bacterial infections, antibiotics, antibacterials, microbiological.*

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1. INTRODUCTION

This Concept Paper proposes a revision of the Note for Guidance on Evaluation of New Anti-bacterial Medicinal Products (CPMP/EWP/558/95 Rev 1) that was developed during the period 2002-2003 and was adopted in April 2004 (in operation since October 2004).

Since the adoption of CPMP/EWP/558/95 Rev 1 the CHMP and its Working Parties have accumulated considerable experience in the provision of scientific advice on, and the assessment and approval of, new antibacterial agents. Important issues have also come to light during revision and/or harmonisation of the product information for existing antibacterial agents. Experience gained has demonstrated that some areas of the guideline would benefit from further explanation of the position and requirements of CHMP.

Some of the issues that have emerged are not covered in the current version of the guideline. In some instances the revision will reflect the position already reached by CHMP on a specific matter during the handling of actual applications for advice or approval. However, the CHMP does not have an established position on all issues that need to be addressed and it is intended that these will receive detailed consideration during the revision period.

The issues that have been identified for inclusion or further consideration in the revision are detailed below. In making these changes it is possible that other sections of the guideline will need to be updated or expanded accordingly. Some general revisions may also be needed to reflect recently approved guidance documents that are of particular relevance to antibacterial agents.

2. PROBLEM STATEMENT

The experience gained since the adoption of CPMP/EWP/558/95 Rev 1 has raised several issues that are not considered to be adequately covered or are not mentioned in the current guideline. It has become clear that additions to the existing text and modifications of some sections are now needed to update the guideline in accordance with CHMP's current position (established or to be developed) on various matters.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Most of the changes that are proposed for the guideline are intended to reflect the position that CHMP has already established on specific matters since 2004. In many cases the position of the CHMP can be discerned from the outcomes of recent procedures but the issues are not adequately reflected in the current guideline. These changes to the guideline are therefore relatively straightforward since they have already been thought through by CHMP, its relevant Working Parties and, in some instances, by the Scientific Advisory Group.

However, a few of the changes that are proposed will represent recent or not yet established positions of the CHMP on specific matters. These changes are likely to attract considerable attention and discussion during the consultation period.

4. RECOMMENDATION

The Working Party/Committee recommends a revision of the Note for Guidance on Evaluation of New Anti-bacterial Medicinal Products (CPMP/EWP/558/95 Rev 1) that incorporates the following additions or modifications:

Study design issues

- Further clarification on requirements for superiority studies to support indications for use in infection types known to have high spontaneous cure rates (such as otitis media, acute bacterial sinusitis and exacerbations of obstructive airway disease).

- Discussion of expectations regarding the types of infections to be treated in a study according to the indication sought (including consideration of the terms complicated and uncomplicated).

- Expansion of advice regarding categorisation of patients according to severity of infection at baseline and provision of pre-planned analyses of outcomes according to baseline characteristics related to severity.

- Consideration of the enrolment into clinical studies of certain age groups (e.g. elderly patients in adult studies or premature infants in studies in infants and young children) or patients with specific conditions that would be expected to affect outcomes (e.g. immunosuppression).

- Further clarification on the choice of delta and the need to avoid “biocreep”.

- Consideration of the use of co-primary clinical and microbiological outcomes, the primary patient populations for analyses and circumstances under which adaptive designs might be appropriate for studies with antibacterial agents.

- Expansion of the section on rarely encountered infections. In this context to discuss on how early regulatory approval may be obtained against pathogens of major public health interest.

- Addition of sections to cover co-development of a beta-lactam agent with a beta-lactamase inhibitor and the development of hybrid antibacterial agents.

Issues related to indications

- Provision of detailed examples of acceptable wordings and layouts of section 4.1 to improve consistency.

- Explanation of circumstances under which it may be considered appropriate to restrict an indication to reflect issues regarding the safety and/or efficacy of the agent.

- Clarification of circumstances under which some extrapolation of efficacy between indications against specific organisms might or might not be acceptable.

- Discussion of some very specific types of indications considered to be potentially problematic. In particular, discussion regarding:
    - Wording of indications that might be acceptable and which closely reflects the clinical data;
    - Studies that might be considered to support certain wordings of indications.
- Some of indications to be discussed include (but may not be limited to) treatment of bacteraemia, treatment of patients suspected to have bacterial infections on the basis of persistent fever during a period of neutropenia, catheter-related infections and eradication of carriage.

Microbiological issues

- Expansion of the section on rare, difficult to treat pathogens.

- Further discussion regarding the numbers of organisms of a species (with or without a specific resistance mechanisms) to be treated to gain an endorsement that clinical efficacy has been demonstrated (which may or may not be indication-specific).

- Expansion of the section on PK/PD investigations in line with current developments in the field.

- Further clarification of the content of Section 5.1, including (but not confined to) the calculation of prevalence of resistance according to S/I/R breakpoints, circumstances under which breakpoints other than those of EUCAST might be included and mention of mechanisms for revision of breakpoints (reflecting the updated SOP covering the working relationship between CHMP and EUCAST).

Miscellaneous issues

- Discussion of circumstances under which certain perceived deficiencies of the clinical data might need to be included in the SPC (usually 4.4 and/or 5.1).

- Expanded discussion of the need for and design of appropriate post-approval studies of the prevalence of resistance to the new agent.

- Updating of several sections in light of other CHMP guidelines adopted or revised since 2004.

5. PROPOSED TIMETABLE

- Adoption of Concept Paper by EWP/CHMP Feb 2009.
- First draft revision by end April 2009.
- Antibacterials drafting group meeting June 2009.
- Discussion EWP/CHMP and release for consultation July 2009.
- If a 6-months consultation period is adopted, then comments to be requested by end January 2010 and then revision and finalisation during first half 2010.

6. RESOURCE REQUIREMENTS FOR PREPARATION

Limited resources are needed for this revision, especially with regard to those issues already agreed but not fully reflected in the SPC, but at least one drafting group meeting will be necessary and possibly also a SAG meeting as seems necessary.

7. IMPACT ASSESSMENT (ANTICIPATED)

The most important impact is expected to be on:

- Sponsors currently developing antibacterial agents for treatment of infections expected to have high spontaneous cure rates since the revision is expected to further clarify circumstances under which superiority studies will be expected.

- Sponsors with ongoing studies or plans for studies intended to support applications for indications that are perceived to be problematic or potentially problematic. Sponsors will need to be aware that the final indication that might be granted would very closely reflect exactly what has been demonstrated in the study.

8. INTERESTED PARTIES

European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
European Society for Paediatric Infectious Diseases (ESPID)
Federation of European Microbiological Societies (FEMS)