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3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on the need for a guideline on multiplicity 5 issues in clinical trials

6 Draft

Agreed by Biostatistics Working Party	March 2012
Adoption by CHMP for release for consultation	24 May 2012
Start of public consultation	30 May 2012
End of consultation (deadline for comments)	30 August 2012

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Keywords	*Multiplicity, clinical trials, hypothesis frameworks*

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1. Introduction

The CHMP points to consider on multiplicity issues in clinical trials came into operation in 2002. Since then, it has been proven to be useful for both, industry and regulators when planning and assessing confirmatory clinical trials. Meanwhile, methodological advances have been made in more complex multiplicity settings. In line with the development of these methods an increasing complexity of the primary and secondary hypothesis framework is seen in confirmatory clinical trials.

This increasing complexity could be related to different dose groups or treatment regimens, interim analyses, multiple endpoints, and different subgroups. Other aspects like multiregional drug development may also add multiple testing problems for which general guidance is needed. Combinations of different sources of multiplicity may increase the complexity of the multiplicity problem dramatically.

The guideline is not to give advice on technical questions related to a new methodology. However, the increasing complexity of hypothesis frameworks and methods used may result in new issues and pose questions on general principles that haven't been considered before. These include consistency problems, the construction of simultaneous confidence intervals and the usefulness of newly developed methods e.g. gatekeeping and fallback procedures as well as graphical solutions in the regulatory context.

2. Problem statement

Within the framework of the CHMP policy, it is proposed to revisit the document. Since it was first drafted, new methods and concepts for addressing multiplicity in clinical trials have emerged not only in the scientific literature, but also in a growing number of marketing authorisation applications. Therefore, several additions and modifications may be needed to express the current state of scientific knowledge in this guideline.

3. Discussion (on the problem statement)

The topics to be discussed when revising the guidance document should cover the recent developments and discussions as mentioned in section 1. In addition to the aspects already covered in the recent document the following topics will be discussed:

- Usefulness and limitations of newly developed strategies to deal with multiplicity
- Multiplicity issues in confirmatory conclusions in subgroups
- Multiplicity issues arising from interim decisions
- Multiplicity in multiregional developments
- Need for simultaneous confidence intervals corresponding to multiple test procedures

4. Recommendation

It is proposed to revise the current CHMP Points to Consider addressing multiplicity issues in clinical trials. The scope of the revision is detailed above.

5. Proposed timetable

It is anticipated that a new draft CHMP guideline will be available 9 months after adoption of this document for 6 months' release for external consultation.

6. Resource requirements for preparation

The preparation of this revision will involve the BSWP. It is anticipated that at least one plenary session discussions at the BSWP will be needed.

7. Impact assessment (anticipated)

Multiplicity issues are an important issue in every marketing authorisation application. It is anticipated that this document will lead to an improved standard of regulatory assessment of confirmatory trials and improve planning of confirmatory trials by sponsors.

8. Interested parties

- The pharmaceutical industry (incorporating Contract Research Organisations), in particular through affiliations of professional medical statisticians
- The community of medical statisticians in academia
- Reimbursement/HTA authorities
- Other regulatory agencies

9. References

CPMP/EWP/908/99: "Points to Consider on Multiplicity Issues in Clinical Trials"

CPMP/ICH/363/96: "ICH E9 Statistical Principles for Clinical Trials"

CHMP/EWP/2459/02: "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design"

EMA/CHMP/EWP/117211/2010 "Concept paper on the need for a Guideline on the use of Subgroup Analyses in Randomised Controlled Trials"