EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2012
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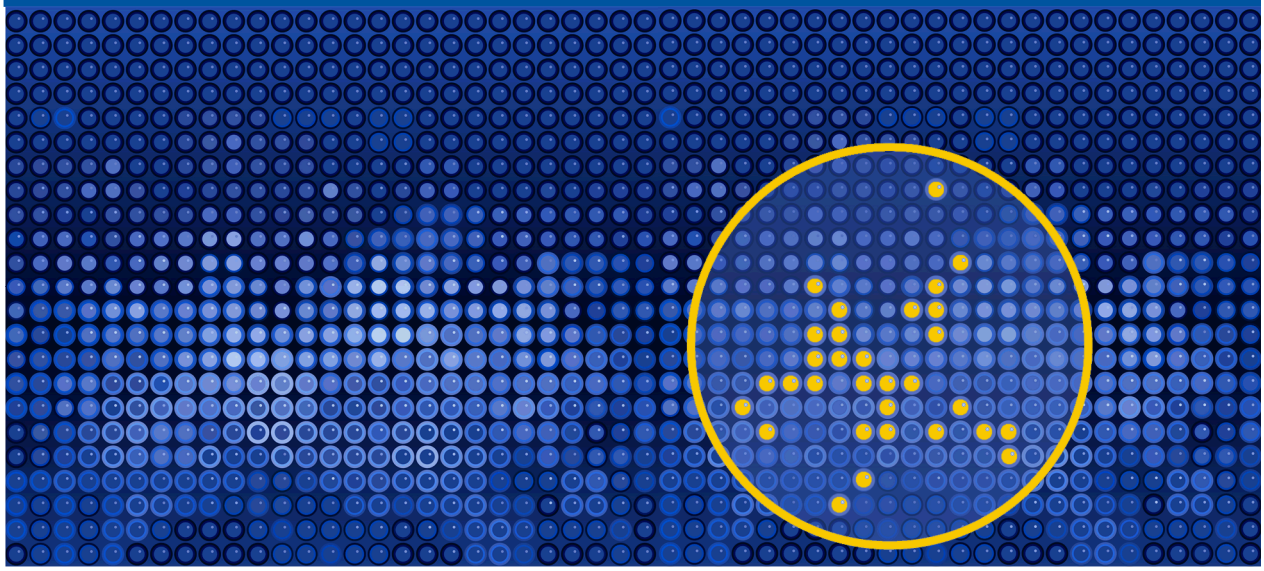
Human Medicines Development and Evaluation

EMA workshop on multiplicity issues in clinical trials

Programme

16 November 2012
European Medicines Agency, London, United Kingdom



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Background

Multiplicity issues in clinical trials

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.

CHMP has recently published a concept paper on the update of the current guidance document. Since the guidance document 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.

Objectives of the workshop

- Discuss current standards and strategies to address multiplicity in clinical trials.
- Identify issues where the current PtC document on multiplicity issues in clinical trials needs to be updated and issues where guidance is missing so far.

Scientific Organizing Committee

David Wright (Chair), Medicines and Healthcare Products Regulatory Agency, UK; **Martin Posch (Co-Chair)**, Medical University of Vienna, Austria; **Norbert Benda**, Federal Institute for Drugs and Medical Devices, Germany; **Armin Koch**, Hannover Medical School, Germany; **Patrik Öhagen**, Medical Products Agency, Sweden; **Steven Teerenstra,** Radboud University, Netherlands; **Amelie Elsäßer**, University Medical Center Mainz, Germany; **Marisa Papaluca-Amati**, **Falk Ehmann**, European Medicines Agency, UK.

Programme details

Friday, 16 November 2012

8:00 **Registration**

8:30 **Opening statement**

Marisa Papaluca – Amati, European Medicines Agency, UK

8:40 **Session 1: Experiences with the current guidance document – how are multiplicity issues addressed in MAAs and their assessment?**

Chair: Tomas Salmonson

CHMP's view on multiplicity; through assessment, advice and guidelines
Rob Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

The FDA perspective (tbc)
Kathleen Fritsch, Food and Drug Administration, USA

Current experience with multiplicity issues in PMDA
Eisuke Hida, Pharmaceuticals and Medical Devices Agency, Japan

The update of the multiplicity guideline
Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany

Discussion

10:15 **Coffee break**

10:45 **Session 2: Usefulness and limitations of newly developed strategies to deal with multiplicity Part 1**

Chair: Patrik Öhagen, Medical Products Agency, Sweden

Multivariate Analysis of treatment in Multiple Sclerosis using the Wei-Lachin procedure
Thomas Zwingers, CROS DE GmbH, a CROS NT Group company

Discussant: Peter Volkers, Paul-Ehrlich-Institut, Germany

Dunnett and Bonferroni Corrections in Bioequivalence Testing
Jiri Hofmann, ZENTIVA, k.s.

Discussant: Thomas Lang, AGES, Austria

Optimal multiplicity adjustment and the necessity to use separable multiple test procedures as gate keeper for secondary endpoint testing: case study
Vincent Haddad, Amgen Limited

Discussant: Franz Koenig, Medical University of Vienna, Austria

Multiplicity Issues in Defining the Testing Strategy for Two Large Outcome Studies
Jennifer Shannon, Rebekkah Brown, Greg Cicconetti, and Rich Davies, Cardiovascular Metabolic MDC, Statistics, GlaxoSmithKline

Discussant: Patrik Öhagen, Medical Products Agency, Sweden

12:20 Lunch break

13:20 Session 3: Implications of multiplicity for estimation

Chair: Rob Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

Multiplicity and Estimation (tbc)
Peter Bauer, Medical University of Vienna, Austria

Discussant: **Brian Austin Millen**, Elli Lilly and Company, USA

Panel Discussion
Kathleen Fritsch, Peter Bauer, **Norbert Benda**, **Amelie Elsäßer**, **Brian Austin Millen**

14:10 Coffee Break

14:20 Session 4: Usefulness and limitations of newly developed strategies to deal with multiplicity Part 2

Chair: Armin Koch, Hannover Medical School, Germany

Gatekeeping strategies in Phase III clinical trials with multiple endpoints and doses
Olga Marchenko and Alex Dmitrienko, Center for Statistics in Drug Development, Quintiles, USA

Novel multiple testing procedures for structured study objectives and families of hypotheses
Frank Bretz, Bjoern Holzhauer, Willi Mauer, Guenther Mueller-Velten, Novartis Pharma AG, Switzerland

Multiplicity: Is it of value to make it so complicated?
Andy Stone, AstraZeneca

Panel Discussion
Frank Bretz, **Alex Dmitrienko, Andy Stone, Rob Hemmings, Kathleen Fritsch**, **Martin Posch**

16:20 Session 5: Closing remarks

David Wright, Medicines and Healthcare Products Regulatory Agency, UK

16:30 End of meeting

Conference venue and secretariat

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