EMA Guidance Documents with statistical content: Overview of recent developments

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EMA Biostatistics Working Party

Organisation

- Oct 2009 Biostatistics Drafting Group
- Oct 2010 Biostatistics Working Party
- 10 Members / 7 Observers
- Monthly teleconference
- 2 meetings in London / year

EMA Biostatistics Working Party

Tasks

- Preparing, reviewing and updating of guidelines (GL) and concept papers
- Contributing to Scientific Advice Working Party activities upon request
- Contributing to product-related assessment following specific CHMP requests
- Preparing specific position papers and question-and-answer documents following specific CHMP requests
- Interacting with stakeholders under the supervision of the CHMP
- European and international co-operation under the supervision of the CHMP
- Contributing to other EMA committees' needs
- Training assessors

EMA Guidelines covering statistical aspects

2001	• Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study • Points to Consider on Switching between Superiority and Non-inferiority
2003	• Points to Consider on Adjustment for Baseline Covariates • Points to Consider on Multiplicity Issues in Clinical Trials
2006	• Choice of a Non-Inferiority Margin
2007	• Clinical Trials in Small Populations • Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design
2011	• Missing data in confirmatory clinical trials (update)
2012	• Concept paper on the need for a guideline on multiplicity issues in clinical trials
2013	• Guideline on adjustment for baseline covariates • Guideline on the investigation of subgroups in confirmatory clinical trials • Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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Multiplicity GL, to be revisited

- Adopted 2002
- Pragmatic style: when to correct, when not
- Meanwhile methodological advances: e.g. gatekeeping, graphical approaches
- increasing complexity of the primary and secondary hypothesis framework in confirmatory clinical trials
- (combination of) numerous sources of multiplicity: different dose groups, treatment regimens, interim analyses, multiple endpoints, subgroups
- estimation problems: e.g. simultaneous CIs

Multiplicity GL – new & open issues

- Multiplicity issues arising from interim decisions
- reflect higher degree of complexity due to combinations of different sources of multiplicity
- multiplicity in context of trial objectives: primary objective for trial success and secondary for labelling claims →
- adequate adjustment when testing secondary endpoints

Multiplicity GL – new & open issues

- type of error control: introduce other concepts than FWER?
- link to benefit/risk assessment: reasonable concepts for confidence intervals
- usefulness and limitations of new strategies/concepts
- update/harmonise terminology

Baseline covariates GL

- Minor changes:
  - Former ‚Points to consider' document **discouraged dynamic allocation (minimisation)**: ‚it remains controversial whether the analysis adequately reflects the randomisation scheme'
  - New Guidance document:

    possible **implications of dynamic allocation** methods on the analysis e.g. with regard **to bias and type I error** control should be carefully considered, taking into account that for some situations (e.g. planned unbalanced treatment allocation) it is has been shown that these methods might **impact the validity of conventional statistical methods**. To properly account for such problems, the use of re-randomization methods in the analysis should be considered.

Subgroups GL

- Subgroup analyses important for regulatory decision-making
- Conflicting goals:
  - keeping a phase III trial population broad enough → external validity
  - Understanding/ checking consistency of a treatment effect in specific patient subgroups
- The more heterogeneous the trial population, the more important subgroups investigations
- Multiplicity as methodological problem

Subgroups GL – scope and goals

- Scope: late phase randomised clinical trials
- Goal:
  - Clarify definitions
  - Describe common scenarios where subgroup analyses are planned/seen and important for decision making
  - Give general recommendations for planning/analysis/assessment

Subgroups – typical scenarios

- **Scenario 1: 'internal consistency'** clinical data are overall statistically persuasive with therapeutic efficacy demonstrated globally; of interest to verify that the conclusions of therapeutic efficacy and safety apply consistently across subgroups of the clinical trial population
- **Scenario 2: 'evaluating neg. outcome in subgroups, label restriction'** clinical data are overall statistically persuasive, but with therapeutic efficacy or benefit/risk which is borderline or unconvincing; it is of interest to identify post-hoc a subgroup where efficacy and risk-benefit would be convincing
- **Scenario 3: 'searching for pos. outcome in subgroup, enabling label'** clinical data fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed

Subgroups GL - definitions

- Subgroup: any subset of the recruited patient population that fall into the same category with regard to one or more descriptive factors
- Prognostic factor: differentiating groups with different clinical progression
- Predictive factor: differentiating groups with different response to treatment
- Pre-defined vs. post-hoc vs. post-baseline
- Heterogeneity - homogeneity - consistency

Subgroups GL – credibility concept

- biological plausibility
- replication (consistency of subgroup findings across trials)
- consistency across endpoints

Comparison of quality attributes

Triggers of initiative:
submitted requests for EMA scientific advice regarding biological compounds

Source Data / Variables:
(Critical) Quality Attributes (CQAs) which characterise a drug substance:
e.g.
pH
Purity
Protein concentration
…

Comparison of quality attributes

Companies were asking CHMP's opinion whether:

- a proposed statistical approach was adequate to **compare the quality attributes** of a (candidate) **biosimilar** product to that of a **reference medicinal product.**
- a proposed statistical approach was adequate to **compare the quality attributes** of batches of a biologic **pre/post manufacturing change**

Problem statement

- Comparison of quality data ('critical quality attributes' CQAs) of two (or even more) drug compounds
- **Batch** of production is frequently proposed as **unit of observation for statistical comparison**, usually **low number** of batches available per compound is identified as a **limiting factor**
- 'similarity' has to be demonstrated for a certain number of CQAs defined, nature/rigour of similarity criteria might be different

Methods proposed/applied in the past

Several different methodological approaches had been proposed to define **comparability ('acceptance') ranges** as well as **'similarity' criteria**, mostly based on information on batch-to-batch variability, sometimes also based on variability within batch

Statistical Methods proposed:

Confidence Intervals (difference in / ratio of means),

Tolerance Intervals

Six sigma

…

Consequences and plans for Reflection Paper

The use of statistical routines usually performed on basis of clinical patient-data practically impossible to apply

→ important to identify and discuss methods which may be adequate to serve for comparative purposes

→ Reflection paper (RP) to be prepared will try to

- reflect on (the limitations of) methods proposed in the past
- come up with alternative approaches for the evaluation of 'similarity/equivalence' in quality attributes.

Outlook

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

  Start of consultation Q1 2014, Adoption Q4/2014

- Guideline on adjustment for baseline covariates

  End of consultation Dec 2013, Adoption Q1/Q2 2014

- Guideline on the investigation of subgroups in confirmatory clinical trials

  Start of consultation Q4 2013, Adoption Q4 2014

- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

  Start of consultation: Q2/Q3 2014, Adoption Q1 2015