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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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Start of public consultation	28 June 2013
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Comments should be provided using this template. The completed comments form should be sent to Biostatistics@ema.europa.eu.

Keywords	*statistical methodology, quality attributes, equivalence testing, biosimilar, biological product*

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1. Introduction

In the recent past, several requests submitted for EMA scientific advice contained questions concerning the adequacy of planned inferential statistical approaches to compare quality attributes:

- of a (candidate) biosimilar product to that of a reference medicinal product;
- of a particular biological drug compound in versions pre- and post-manufacturing changes.

For comparative purposes, 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.

In the process of assessing and answering these requests, members of different CHMP working parties had been involved. In the discussions of Companies' proposals, the required degree of rigor on the one hand, and the limitations of inferential statistical methodology usually applied in the context of equivalence testing on the other hand have been scrutinized. The diversity of candidates of critical quality attributes within specific developments, as well as the usually low or unbalanced number of drug batches available for the drug compounds to be compared, had been identified as the most limiting factors, rendering the use of statistical routines usually performed on basis of clinical patient-data inappropriate most of the time. Despite these limitations, it seems important to identify and discuss methods which may be adequate to serve for comparative purposes. The Reflection Paper (RP) to be prepared will try to reflect on (the limitations of) comparison techniques proposed in the past, but will also try to come up with alternative approaches for the evaluation of 'similarity/equivalence' in quality attributes. In this context, the importance and feasibility to pre-define similarity criteria will be addressed.

Although this initiative for a dedicated guidance document was primarily triggered by questions related to biological compounds' developments, similar issues have also been seen and reported in the context of assessment of quality data in dossiers for chemical compounds.

The RP will not provide guidance from a methodological perspective regarding criticality assessment of quality attributes. However, the discussion on criticality for a specific quality attribute could have an impact on the methodology finally chosen for comparative purposes.

2. Problem statement

Description of the 'standard' setting of the problem:

- Comparison of quality data ('critical quality attributes', CQAs) of
  - two (or even more) drug compounds in the biosimilar setting; or
  - two versions of the same drug compound pre/post manufacturing change; or
  - a combination of the two tasks mentioned above; or
  - two (or even more) drug compounds – including small molecules – where the comparison on the quality level is of importance for regulatory assessment and decision making;
- Batch of production is frequently proposed as unit of observation for statistical comparison, usually the low number of batches available per compound is identified as a limiting factor;
- Several candidates of CQAs could be subject to statistical comparison; no standard 'list' of CQAs exist, even not for a particular product class; from the statistical perspective, the potential for a 'multiplicity problem' might need to be addressed in some testing situations;

- The following methodological areas are considered out of scope of the RP:
  - statistical methods used to identify and select CQAs from a larger set of QAs;
  - statistical methods for classical (in process) quality assurance/quality control.

3. Discussion (on the problem statement)

The RP should provide an overview of statistical principles with a potential of useful application in the context of the comparison of quality attributes as mentioned above. For situations where a meaningful set of CQAs can be identified, the RP should give an overview of what statistical methods for the comparison are available, and which of those might be preferred under which circumstances (e.g. number of batches available). The document should also discuss options and limitations of alternative approaches for comparability evaluation were repeated (correlated) samples within batches are considered as unit of observation.

The RP will also try to comment on deficiencies/limitations of particular methods which have been discussed in regulatory dossiers in the past (e.g. tolerance interval, confidence interval for difference in / ratio of means, six sigma, etc.).

The RP might primarily be applicable for comparison tasks for quality aspects within biosimilar developments and/or the situation to compare versions of drug compounds pre/post manufacturing change in the development of biologics. However, the RP might also be applicable for other situations of comparative evaluation, e.g. the analysis of in-vitro assays or the comparative analysis of quality attributes for small molecules (chemicals).

4. Recommendation

It is proposed to prepare a Reflection Paper according to the background presented above. All considerations should be based on discussion of methods in literature as well as regulatory experience to date and further expert opinion.

5. Proposed timetable

The Concept Paper was adopted by CHMP on 30 May 2013. It is anticipated that the CHMP Reflection Paper will be available 12 months after adoption of the Concept Paper. A 6-month release for external consultation would then follow.

6. Resource requirements for preparation

The preparation of the RP will directly involve members of the Biostatistics Working Party (BSWP) and the Biologics Working Party (BWP). The Biosimilar Medicinal Products Working Party (BMWP), the Scientific Advice Working Party (SAWP), and the Quality Working Party (QWP) will be invited to contribute and review during the development phase on an on-going basis.

7. Impact assessment (anticipated)

The RP should have an impact on industry's development plans, clarifying requirements and possibilities of comparative statistical (inferential) assessments of quality data under different circumstances (e.g. biosimilar, or pre/post manufacturing changes within the development of drug compounds). It is anticipated that this document will lead to a harmonised understanding on the

regulators side, of what could be expected from making use of selected statistical methodology under various circumstances.

8. Interested parties

- The pharmaceutical industry (incorporating Contract Research Organisations)
- Several EMA Working Parties and Scientific Committees
- (Quality) Assessors at national agencies
- Other regulatory agencies outside the EU (e.g. FDA)

9. References to literature, guidelines, etc.

None.