EMA Draft Reflection Paper on Statistical Methodology for the Comparative Assessment of Quality Attributes in Drug Development

Richard Keane (Biogen) on behalf of the EBE Biomanufacturing Working Group Topic Group
CASSS Meeting May 2018
Outline

- Reflection Paper Proposal and Background
- EBE Biomanufacturing Working Group (BWG) Topic Group (TG)
- EMA Workshop Update
- Next Steps
- Acknowledgements
Reflection Paper Proposal and Background

- 30 May 2013 Concept Paper issued for public consultation by EMA Biostatistics Working Party
  - EMA/CHMP/297149/2013 Rev. 1 - Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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.
Reflection Paper Proposal and Background

  - EMA/CHMP/138502/2017- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

Disclaimer: This reflection paper has been written to provide current regulatory considerations regarding statistical aspects for the comparative assessment of quality attributes where these are used, or are proposed for use, in drug development and Marketing Authorisation Applications. It was also prepared to invite comments in relation to the opportunities and limitations related to inferential statistical methodology applied on quality attributes' data in the exploration of similarity of two drug products. Whilst in some parts the paper describes Frequentists statistical methods, the field is also open to explore alternative approaches, e.g. following Bayesian methodology.

The current document does not contain explicit guidance on which statistical approaches are most suitable. It rather tries to establish a framework and a common language to facilitate future discussions among stakeholders.

The content of this reflection paper and its implications shall be further discussed at a European Medicines Agency’s public work shop at the end of the 12-month public consultation phase. A longer than usual consultation period will allow companies to come forward to EMA via interaction with the Scientific Advice Working Party with proposals that may include the principles and methods discussed in this document or alternative approaches that are not discussed in this document.
EBE Biomanufacturing Working Group (BWG) Topic Group (TG)

- EBE BWG issued a call for interested parties to form a Topic Group to co-ordinate industry response to the draft reflection paper
- Group kicked off June 2017 led by two co-chairs:
  - Richard Keane (Biogen) & Christoph Agut (Sanofi) with close support from Véronique Debaut (EBE)
- Representatives from a broad range of interested companies on the TG including Sanofi, Biogen, AbbVie, Amgen, Bayer, Merck, Roche, UCB, Eli Lilly, Johnson & Johnson, Novartis, GSK & Synthon
- Feedback was very much that industry welcomed this draft reflection paper and the opportunity to work further with the EMA to develop this area
- Primary aim of the group was initially to co-ordinate industry comments on the draft reflection paper from EBE (co-ordinating at various stages with other organisations such as EFSPI, Vaccines Europe and EFPIA)
- In addition the group discussed the EMA Workshop which was anticipated on this topic in the draft reflection paper
• TG were initially planning to send comments by the EMA deadline of 31 March 2018
• In Sep 2017 the EMA in their communication on the set up of the workshop stated “Stakeholders are therefore encouraged to provide comments well in advance (ideally by the end of November 2017).”
• Also in Sep 2017 the FDA issued a draft guidance on “Statistical Approaches to Evaluate Analytical Similarity - Guidance for Industry”
• By that stage the TG had received a significant number of comments and so proposed to EMA to provide high level comments by the end of November with full comments by 31 March 2018
• In addition the TG agreed to work to develop some case study proposals in around the same timeframe
EBE Biomanufacturing Working Group (BWG) Topic Group (TG)

- 29 Nov 2017 – Consolidated High Level comments provided to the EMA
- Feb 2018 – Started to see some early draft agendas for the workshop from the EMA
- 6 case study proposals (5 EBE & 1 VE) were submitted to the EMA in mid March 2018 and all accepted for inclusion in the workshop
- Case Study leads have been working closely with the individual session chairs to work on the presentations up to the workshop
- 22 Mar 2018 – Consolidated comments provided to the EMA (62 pages)
- Late April the TG met (including VE & EFPIA workshop representatives) to discuss the case studies

Workshop on the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

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<tr>
<th>Details</th>
<th>Documents</th>
<th>Multimedia</th>
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<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Workshop on the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development</td>
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<tr>
<td><strong>Date</strong></td>
<td>03/05/2018 - 04/05/2018</td>
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<td><strong>Location</strong></td>
<td>European Medicines Agency, London, UK</td>
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<td><strong>Summary</strong></td>
<td>The European Medicines Agency has published a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017), for a 1-year public consultation until 31 March 2018. In order to facilitate multidisciplinary interaction between regulators and stakeholders on statistical methodology applied to the quality of medicines, a 1.5-day workshop is held. The main focus of the workshop is the discussion of comments received during the public consultation. Stakeholders are therefore encouraged to provide comments well in advance (ideally by the end of November 2017). Stakeholders can express their interest to participate in this workshop by writing to <a href="mailto:RP-stats-QA@ema.europa.eu">RP-stats-QA@ema.europa.eu</a>. Due to limited spaces, priority will be given to those who provided relevant comments. The output of the workshop will have a direct impact on the finalisation of the reflection paper.</td>
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Registration
- Registration by invitation only.
- Registration open until 31/03/2018.
- Places limited.
- Express Interest to participate by writing to RP-stats-QA@ema.europa.eu

Contact point:
Ina-
Christine.Rondak@ema.europa.eu
Next Steps

- EBE TG will meet again to discuss workshop output and agree on any follow up or next steps
Acknowledgements

**EBE Topic Group**
- Christophe Agut (Sanofi) – topic co-leader
- Véronique Debaut & Livia Le Metayer (EBE)
- Keith Watson (Abbvie)
- Brenda Ramirez & Jose G Ramirez (Amgen)
- Barbara Miller & Chris Fisher (Bayer)
- Vivien Le Bras (Merck)
- Frank Zettl & Felix Kepert (Roche)
- Cyrille Chery & Bianca Teodorescu (UCB)
- Kristi Griffiths (Eli Lilly)
- Bill Pikounis (Johnson & Johnson)
- Valerie Tsang & Veronique Bailly (Biogen)
- Franz Innerbichler & Florian Wolschin (Novartis)
- Alan Gardner (GSK)
- Nienke Vriezen (Synthon)

**Additional Industry Trade Association Workshop Participants**
- Robert Shaw (AstraZeneca) & Mourad Mellal (GSK vaccines) – VE
- Bev Ingram (Pfizer) & Trine Kvist (Novo Nordisk) - EFPIA