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Implementation of comments received on "Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development" (EMA/CHMP/138502/2017)

CHMP adoption of the Reflection Paper (RP) on 23 March 2017 was followed by a 1-year Public Consultation (PC) phase ending 31 March 2018. In May 2018 an EMA Workshop took place with stakeholders involvement [link] to reflect and discuss RP content as well as comments received during the PC. After this event it was decided to revise the first published draft of the RP. Whilst some comments received during the PC suggested the development of an EMA-guideline document on the basis of the RP content, the decision was made to stick to the format of a RP, as many fundamental methodological aspects in relation to the comparative assessment of quality attributes (QA) continue to require in-depth considerations in an open manner. Further exchange with stakeholders and within regulatory expert groups revealed that it would be premature to provide explicit guidance for the diverse settings of QA comparison tasks. In consequence, a targeted revision of the RP was preferred over the development of a guideline. In the framework of the revision, an attempt was made to reflect as many PC comments as possible. In the paragraphs below a high-level overview is given on how those comments (which were found most helpful and relevant) were accounted for during revision work.

During the PC, comments were received from 15 consortia/organisations/individuals. As triggered by the format of the EMA template, comments were categorised into 'specific' and 'general'. About 300 general comments were made, accompanied by about 1000 specific comments. In the following, focus is put on the reflection of general comments.

One of the most relevant comment received was the criticism that the draft RP gives no answer to the question: "What is similarity?" Based on this observation, the RP drafting group identified the need to differentiate between 'similarity condition' and 'similarity criterion'. After an extended explanation on how a manufacturing process can be understood as a data distribution when looking at a certain QA, the new section 4.2 of the revised RP-version introduces the concept of the 'similarity condition'. Thereby, it is pointed out that – in the first place – indeed a description is required when the two data distributions to be compared would allow the conclusion of 'similarity', given their assumed shape and location on the QA's measurement scale. The draft version of the RP was not sufficiently clear concerning the importance of having the best possible (common) understanding of the similarity condition. During the revision, a description of a 2-step-approach (agreement/definition of similarity condition needs to precede the selection of a suitable similarity criterion) seemed essential to enable a more profound way of thinking in the RP's problem description.

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During the PC many stakeholders expressed concerns that statistical methodology might eventually get a too prominent role in the QA data comparison in the future, potentially overriding or ignoring the expertise of pharmaceutical development and manufacturing. These concerns were acknowledged. The revised RP now offers – aside a thorough problem description – a rather open framework to approach the task of comparative assessment of QAs. However, it is also clearly emphasised that – in the context of regulatory decision making – the best possible estimation of the risk to draw a 'false similarity decision' shall be targeted. Such an estimation is suggested with the idea to involve the exploration of operating characteristics of potential similarity criteria which could be applied based on sample data in a certain QA data comparison context. The revised RP still contains an overview of frequently seen/applied similarity criteria. It is however (now more clearly) pointed out that their adequacy (operating characteristics) in a certain comparison context will always depend on the underlying (agreed) similarity condition. In that sense, the RP does not clearly promote or depreciate any specific criterion, it just mentions obvious potentials and limitations in various contexts.

As regards the scope of the RP, a rather heterogeneous set of comments was received during the PC. Some called for a more focused approach (e.g. exclusive focus on biosimilars), others rather supported the more general context of the problem description. In the revision process, it was once more realised that the principal methodological issues discussed in the RP are sufficiently similar between the contexts described: comparison of biologicals, comparison of small molecules and pre/post manufacturing changes, so that the decision was made to maintain the inclusion of all those contexts. However, an attempt was made to better streamline the information provided, also avoiding repetitions as suggested.

The revised RP now contains a more concrete recommendation in Section 6 to prospectively plan any QA data comparison which is supposed to relevantly influence regulatory decision making. The preparation of a 'Quality Attributes data comparison protocol' is suggested. This suggestion also summarises the main methodological issues brought up and replaces the former "check list" in the RP's Appendix.