EMA /US FDA Workshop on

support to quality development in early access approaches

Risk-based assessment of comparability for a mAb undergoing accelerated development

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London, Nov 26 2018

Problem statement

- **For an accelerated program, the comparability exercise may be on the critical path due to changes late in development, therefore what is an appropriate amount of comparability given limited time and (potentially) limited pre-change data?**

  - A comparability exercise for biotechnological/biological products follows the principles set out in ICH Q5E

  - Applicants tend to be conservative when performing comparability, performing a full comparability assessment, including extensive characterisation of the molecule

  - There should be a distinction between characterisation and comparability. The molecule will be fully characterised, but the comparability exercise should focus on the most relevant assays

  - Depending on the nature of the change(s) and the stage of development, a full comparability assessment may not be relevant, however the applicant must still ensure the quality, safety and efficacy of the post-change material

Case study

- This is an example of a mAb under the investigation for the treatment of a rare disease, for which a platform non-optimized drug substance (DS) manufacturing process was used to progress to the first in man (FIM) study quickly

- The programme was further accelerated with ~9 months between FIM and confirmatory study manufacturing campaigns
  - Due to the molecular properties of the mAb, further development work was required to optimize the process for commercial use
  - It is not possible to use the clinical development facility for commercial manufacture due to scheduling limitations, therefore the commercial process needs to be transferred to a CMO
  - Due to the accelerated timelines, an optimized commercial process will not be ready and available for transfer to the CMO in time for the start of the confirmatory study
  - It is still intended to launch with the commercial material, therefore demonstration of comparability between the clinical and commercial material is critical

- A risk-based approach has been developed to assess the extent of comparability exercise for a particular change, with appropriate justification

Risk-based assessment of comparability

Questionnaire used to assess:

- The potential of each individual change to impact quality attributes, for example:
  - Molecule
    - Primary structure
    - Glycosylation
    - Other post-translational modifications
    - Higher order structure
    - Biological activity
  - Impurity profile (process- and product-related)
  - Stability
- Have product contacting materials changed?
- Are there any device considerations?
- The capability of the analytical methods to detect changes in the quality attributes based on prior knowledge and forced degradation studies
- Are there any small scale data / platform data / prior knowledge that could support the comparability exercise?
- Can the proposed comparability exercise confirm that the change does not impact safety or efficacy?

Risk-based assessment of comparability continued...

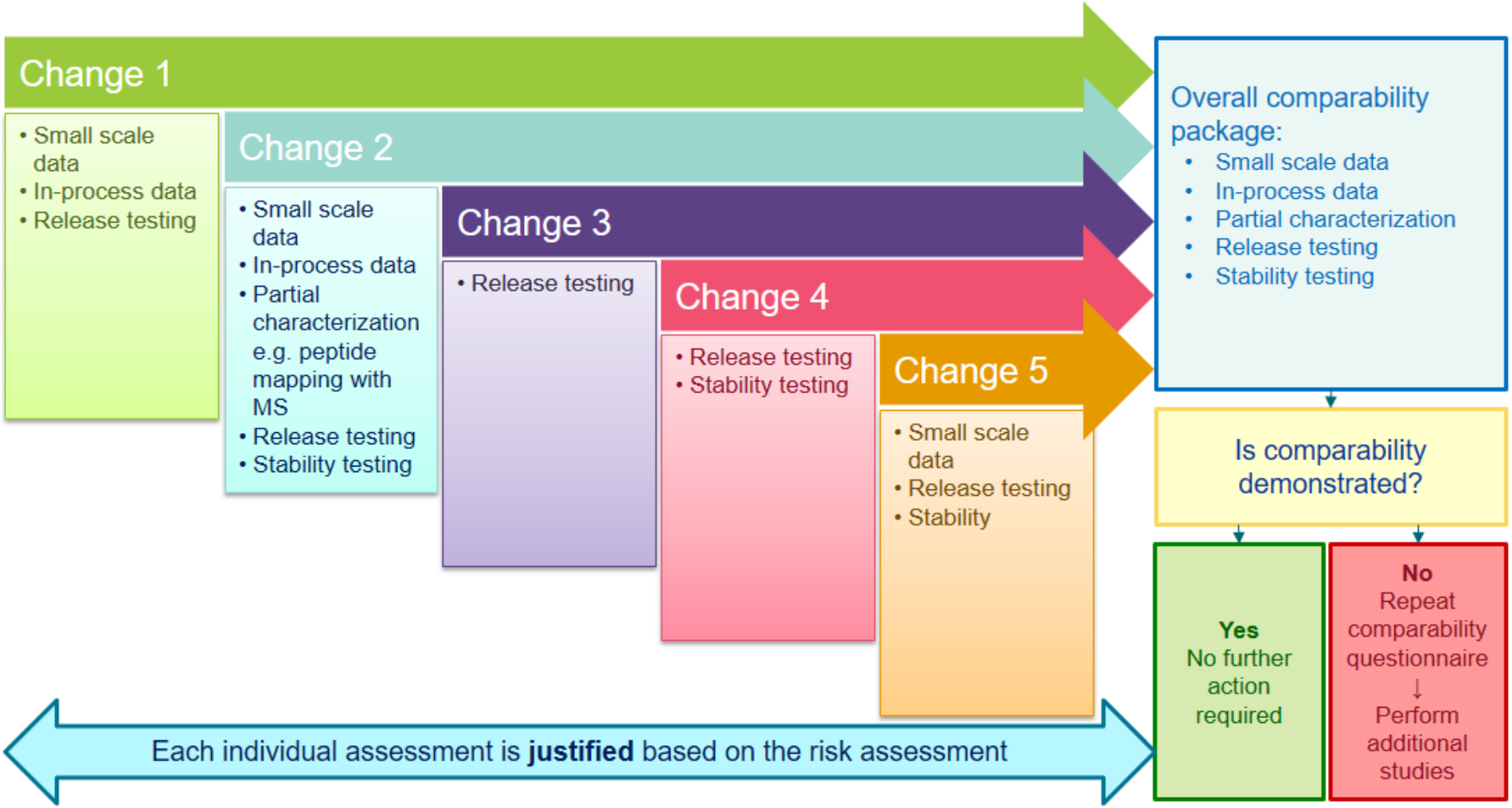
- From this assessment, the overall analytical comparability package is determined, with appropriate justification
  - Relevant methods are selected for inclusion in the comparability exercise
    - e.g. peptide mapping with MS to confirm no impact to primary structure following change to media/feeds
  - Some analytical methods normally included in a full characterisation study may not be considered necessary, depending on the particular change(s)
    - e.g. for a scale change UCB would not perform the full range of higher order analyses. We would use Circular Dichroism but not FTIR and fluorescence
  - The stability package may be adjusted depending on the change
    - e.g. for a change from MCB to WCB, since there is no change to the cell line, the introduction of the WCB is not expected to have an impact on quality attributes, therefore a stability study is not required for comparability exercise

- If necessary, clinical comparability will likely be assessed on a case-by-case basis
  - For accelerated programs, a clinical bridging bioequivalence (BE) study in healthy volunteers is considered appropriate

- Typically, comparison of 3 pre-change and 3 post-change batches is expected.
  - For an accelerated product, the proposal is to perform comparability with fewer pre- and post-change batches, potentially supported by small-scale data / platform data / prior knowledge

- This forms the pre-assessment of comparability. Following the exercise, if results are inconclusive, further studies (analytical, nonclinical or clinical) may be required

Example of compound change – 5 changes made at the same time



Risk-based assessment of various changes

Example	Changes between processes	CMC comparability package	Studies excluded from CMC comparability based on risk assessment
1	DS: • Transfer to CMO • Scale-up • Replacement of non-optimal chromatography resin • Change in formulation due to non-optimal stability • Other minor changes to optimize commercial process DP: • Transfer to CMO only	**Full** analytical comparability • DS release testing • DS stability • DS in-process data • Full characterisation of molecule using orthogonal methods • Forced degradation studies • DP release testing • DP stability • DP in-process data • Small scale studies where relevant	None
2	DS: • Transfer to CMO • Scale-up DP: • Transfer to CMO only	**Reduced** analytical comparability • DS release testing • DS stability • DS in-process data • **Reduced** characterisation of molecule focusing on predicted CQAs using relevant methods • DP release testing • DP stability • DP in-process data • Small scale studies where relevant	• Full characterisation of molecule • Forced degradation studies
3	DS: • No changes DP: • Increase in DP vial size	**Reduced** analytical comparability • DP release testing • DP stability	• DS release testing • DS stability • DS in-process data • Characterisation of molecule • Forced degradation studies • DP in-process data • Small scale studies

Acknowledgements

- UCB
  - Alexandra Clinch
  - Annick Gervais
  - Carl Jone
  - David Kirke
  - John O’Hara
  - Agata Slopianka

- Biogen
  - Richard Keane

- Amgen
  - Andrew Lennard