Change Management Protocols: Overview and Comparison of Regulatory Procedures in US and EU

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Agenda

• US and EU Overview of Change Management Protocols
• When might a CP be useful for a CMC change
• When might a CP be inappropriate
• Similarities between the new EU PACMP and US CP Approach
• US and EU Post-Approval Regulatory Procedures and Timelines
• Concluding remarks
US Overview

• Section 601.12(e) allows for the use of protocols “…describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes…”

• In US, Comparability Protocols (CPs) have a long history and have been applied for many years to facility changes, process changes and method changes.

• Draft Guidance for CPs introduced in 2003 specifically for protein drug products and biologics\(^{(2)}\)

• A CP can be used for single time or multiple time changes that impact one or more changes to the process e.g.
  • when the sponsor would like to provide the development data, gain agreement on the future data package and request a downgrade on the reporting category = single time change
  • for new sources of critical excipients when acceptance criteria are well known and will not change = multiple time change

• A CP is required to provide the development data / historical knowledge about the potential impact to product quality of the proposed change.
US Overview cont..

- Other uses of US CPs may include:
  - **Trans-BLA\(^{(1)}\):** a CP containing identical changes that affect multiple Biologics License Applications (BLAs)
  - **Expanded CPs (eCPs):** may also be discussed:
    - Less commonly used as project specific/single change Comparability Protocols
    - Generally used in complex changes or Quality by Design (QbD) setting
    - Same guidance, submission and review pathways as for CP, but data package for eCP is much larger and generally has much higher level of scrutiny, as it allows for a larger group of changes.
US Overview cont..

• Comparability Protocols in the US must prospectively specify the planned CMC change, the tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be met to assess the effect of CMC changes.\(^{(2)}\)

• CPs are submitted as Prior Approval Supplement – review will determine if a specified change can be reported in a reporting category lower than the category for the same change implemented without an approved comparability protocol.

• Changes are assessed in a step-wise approach, i.e.
  • Early evaluation of strategy
  • Later, separate evaluation of data,

  **BUT**, if part of the study is complete, a sponsor may include this data to supplement the review and provide the reviewer a greater sense of comfort with the potential change.

• Typically, categories designated for reporting changes under an approved comparability protocol are one category lower than normally would be the case (e.g., from PAS to CBE-30, CBE to AR).
EU Overview

EU Post Approval Change Management Protocols (PACMP)

- Relatively new concept - introduced in January 2010 when the latest revisions to the EU Variations legislation became effective

- Opportunity to submit a PACMP via a Type II variation for the DS or DP, with a follow-up submission of the resulting data package via Type IA or Type IB (always for biotech) variation i.e. typically one category lower than would normally be the case (e.g., from Type II to Type 1B, Type 1B to Type 1A).

- This mechanism can in theory significantly reduce the EU approval lead time for changes such as manufacturing site transfers, compared to the traditional Type II variation route (1-2 m review time versus 2-7 m)

- In addition, the Emerging Market submissions and approvals, contingent on EU approval as a pre-requisite to filing, can also be accelerated.
EU Overview cont…

• PACMP describes specific changes that a Company would like to implement during the lifecycle of the product and how these would be prepared and verified (3)

• Changes are assessed in step-wise approach, similar to US CP approach, i.e.:
  • Early evaluation of strategy
  • Later, separate evaluation of data produced on agreed strategy

• PACMP must only contain changes which are interrelated i.e. consequential or meaningful to be assessed together

• The concept of future-proofing the PACMP has been addressed in the EMA Q&A on PACMPs
When might a CP be Useful for a CMC Change

Some examples of when a CP might be a recommended approach are:

• When sufficient manufacturing and analytical experience exists to specify in advance the tests, studies, analytical procedures, and acceptance criteria appropriate to assess the impact of the change on the product.

• When you expect the product resulting from the changes to meet the approved drug substance and/or drug product specifications and predetermined acceptance criteria for non-routine characterization studies.

• When appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for non-routine tests such as characterization studies) to assess the effect of the change on the approved product.

• When the approved manufacturing process and equipment have been fully qualified and validated, when appropriate.

• According to EU and US guidance, they should be submitted only for changes intended to be implemented, BUT in US, protocols for general, common changes (e.g. new excipient vendors) that will always be the same and use the same acceptance criteria can be approved and held open indefinitely.
When might a CP be Inappropriate

Some examples of when a CP might not be a recommended approach are:-

• A CP can be included in an original submission (MAA/NDA/BLA), BUT if manufacturing experience is limited, it may be difficult to identify the elements of an appropriate comparability protocol in a MAA / NDA / BLA.

• If suitable scientific knowledge and understanding of the process, coupled with an appropriate QRM and QMS cannot be demonstrated.

• When the feasibility of a change has not already been investigated and supported by relevant data.
  • NB: Surrogate data can be used to support development / feasibility of change

• When comparability cannot be demonstrated with CMC data alone i.e. if assessment of clinical or non-clinical data are also required e.g. any changes which might require a CTA / IND, a new original application (MAA/NDA/BLA) or a Line Extension.
When might a CP be Inappropriate cont’d

- When the adverse effect of the change on the product cannot be definitively evaluated by pre-specified tests, studies, analytical procedures, and acceptance criteria.

- When the plan for evaluating the effect of the CMC changes on the product, and the supporting data requirements, cannot be fully described or locked down in advance.
Similarities between new EU PACMP approach and US CP Approach

- Both can describe a single change or multiple changes, BUT in PACMP, multiple changes must be consequential or meaningful to be assessed together. FDA also recommend that multiple changes are interrelated.

- Content of PACMP and Trans-BLA CP highly similar but format is different as the US CP is trans-product (with product-specific annexes) whereas in the EU, the PACMP is placed in 3.2.R for each product.

- Follow-up implementation submission must be carried out exactly in accordance with the agreed CP. If comparability criteria are not met, either withdraw the CP, or, implementation submission is escalated to a Type II in EU and a PAS in US thus losing advantage of CP.
### US and EU Regulatory Post-Approval Procedures and Timelines

<table>
<thead>
<tr>
<th>Submission Type</th>
<th>Product may be Distributed</th>
<th>Approval</th>
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<tbody>
<tr>
<td>US Prior Approval Supplement (PAS)</td>
<td>After approval</td>
<td>Within 4 months</td>
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<tr>
<td>US Changes Being Effected, 30 days (CBE-30)</td>
<td>30 days after FDA receipt, if no objections.</td>
<td>Within 6 months</td>
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<td><strong>US PAS (CP) + CBE-30 (Data) supplements</strong></td>
<td>Once PAS/CP has been approved, products can be distributed after FDA receipt of each CBE-30 (i.e. 3 months earlier than with traditional approach of 1 PAS per product). Assumes site approved (for cGMP) for site transfers.</td>
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<tr>
<td>EU Traditional Type II variation</td>
<td>After approval</td>
<td>Within 2-7 months</td>
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<tr>
<td>EU Type IB variation</td>
<td>After approval</td>
<td>Within 1-2 months</td>
</tr>
<tr>
<td><strong>EU Type II (PACMP) + Type IB (Data) variations</strong></td>
<td>Once PACMP has been approved, product can be distributed after approval of each Type IB i.e. up to 5 months earlier than with traditional approach of 1 Type II per product. Assumes site approved (for cGMP) for site transfers.</td>
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Concluding Remarks

• CP pathway in EU and US is a significant positive development, helping Industry manage change more efficiently while maintaining necessary regulatory agency oversight

• CPs are valid for more significant manufacturing changes such as site transfers or risk mitigation

• CP requirements are very similar in EU and US - main difference is that PACMPs must be product specific whereas US CPs can be trans-product - will the EU adopt this trans-product protocol approach for identical changes to multiple products?

• Submission documentation also very similar for PACMPs and US CPs

• Therefore, CPs can be standardized across US and EU for common changes such as introduction of new WCB/WVSS, new reference standards or shelf-life changes in the initial BLA/MAA

• We are confident that this procedural mechanism offers the possibility of reducing time to market in both US and EU (& therefore other country) approvals e.g. reducing approval of site transfers by at least 3-6 months

• We recommend that other global regulators adopt the protocol approach!
References

1. SOPP 8422: Processing of Trans-BLA Submissions (version 1, effective April 2011)


3. EMA Q&A on Post approval change management protocols (effective October 2012)
Acknowledgements

- Roger Greene
- Jason Hampson
- Nidia Gomez
- Anneli Gilbert
- Toshi Mori Bajwa