Table 33: Post-approval Analytical Comparability: Global Convergence

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SCOPE:

This table will discuss post-approval analytical comparability requirements and strategies used for post-approval process changes and technology transfers. The discussion will focus on challenges and successful examples used throughout post-licensure changes with a global perspective in mind.

QUESTIONS FOR DISCUSSION:

1. Can the same CMC content / level of detail be used in all geographies? Do you tailor registration-enabling analytical comparability packages for each region/country?
   a. If your company tailors for countries/regions, for what reasons (e.g. different information / level of detail in each country/region registered dossier, differing guidance / quality requirements between countries, different supply chains [e.g. sites of manufacture], intellectual property issues)?
   b. Where differences exist between comparability packages submitted to a country/region, what differs?
      i. Are the same tests and acceptance criteria included?
      ii. If results indicate that substances / products are not comparable can similar rationales be used?
      iii. Is the same data included (e.g. Release, Extended Characterization, Stability)?
      iv. Number of batches needed / data on all SKU (bracketing / matrix acceptability)?
      v. Amount of stability data required?

2. How have analytical comparability plans been communicated to Health Authorities?
   a. Included as part of a formal Health Authority meeting?
   b. Submitted prior to initiating or after completing studies (e.g comparability protocol or change management plan)?
   c. Do you communicate plans with multiple authorities or one/two core authorities prior to execution?

3. Does a comparability strategy differ for a manufacturing process change versus the transfer of an existing process to different manufacturing site (e.g. are risk-based approaches to selecting a sub-set of attributes for inclusion in comparability plans accepted equally in all regions/countries)?

4. How is comparability handled when you have limited data sets and/or limited number of batches?
NOTES:

1. Can the same CMC content / level of detail be used in all geographies?

Round table perspective is that there is divergence between US and EU expectations regarding comparability, thus the CMC content has to address country specific expectations. A common base cause can be prepared and provide much of the details, with specific changes incorporated (or removed) depending on territory being filed. Example: DS process change requiring additional DP comparability elements for EU; US only focused on DS change, minimal DP data requested.

2. Do you tailor registration-enabling analytical comparability packages for each region/country?

Yes, as noted above. There was additional discussion on the different criteria one could use to define or assess comparability. Most participants do not use a statistical approach, as the comparability data is generally not powered to allow for a meaningful statistical discussion; although use of historical ranges allow one to establish basic parameters or limits when assessing comparability for quantifiable assay results.

General consensus is that there is not global alignment on use of statistics and/or the specific statistical approach that can be used.

a. If your company tailors for countries/regions, for what reasons (e.g. different information / level of detail in each country/region registered dossier, differing guidance / quality requirements between countries, different supply chains [e.g. sites of manufacture], intellectual property issues)?

b. Where differences exist between comparability packages submitted to a country/region, what differs?

Discussion was mostly around stability and potential use of bracketing approach for DP and the differences between US/EU and other territories regarding how much data is provided or generally perceived as being acceptable. Also including data (supportive or part of historical data) obtained from material from a facility that may not be registered in a particular region in a filing in that region was generally viewed as not likely to be accepted.

And the differences in
i. Are the same tests and acceptance criteria included?

ii. If results indicate that substances / products are not comparable can similar rationales be used?

Situations where differences are observed require consideration of the degree of difference and ideally the ability to take into consideration the clinical relevance of the change. This was viewed as the most meaningful basis for a justification argument regarding an observed difference (clinical experience as well as known or potential impact to clinical efficacy/safety). Use of risk
assessment tools and inclusion into filing was viewed as another component of a comparability strategy that has the potential to add significant value to the overall package.

iii. Is the same data included (e.g. Release, Extended Characterization, Stability)?

iv. Number of batches needed / data on all SKU (bracketing / matrix acceptability)?

v. Amount of stability data required?

Appeared to be consensus that US and EU are more aligned, with other countries being a case-by-case basis for extent of data submitted, some countries may require more than others, example of South Korea as a country that requires more data. The potential impact these higher bar countries have on global implementation of the desired process change was discussed and was highlighted as something companies need to take note of and build into overall timelines.

3. How have analytical comparability plans been communicated to Health Authorities?
   a. Included as part of a formal Health Authority meeting?

Most participants have experience using pre-submission meeting to outline comparability strategy, with limited experience with use of a pre-approved comparability protocol. Part of this discussion centered on the use of stressed stability samples for forced degradation aspects of comparability, comment was that this may not be a globally accepted approach. Additional discussion was on alignment of agencies (ie TGA and EU) versus individual requests (ie Mexico requiring 6 mo DP data for a DS process change).