Roundtable Session 1 – Table 7 – ICHQ6 - Challenges and Opportunities for Using an Enhanced Approach to Lifecycle Management of Specifications

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Abstract:
The data to support the specification setting for drug substances (DS) and drug product (DP) at the marketing application stage can vary significantly in the number of batches available, as can the approaches used to set the specifications. Frequently the approach is on patient centric specifications, especially when there are very limited batches, and the use of clinical exposure at higher doses is frequently utilized. This can result in post approval commitments to re-evaluate the specifications when more data are available.
After approval to meet the commercial demands and to optimize the manufacturing processes, changes can be made which may include the addition of new manufacturing sites or changes to the manufacturing process. These changes typically do not result in changes to the specification, but there are many more batches available which could trigger a re-evaluation of the specifications.
This discussion plans to focus on what triggers specification changes during the lifecycle and the challenges and opportunities.

Discussion Questions:

1. Do you have experience taking post approval commitments to re-evaluate DS or DP specifications?
    a. What approaches did you use to re-evaluate the specifications
        e.g. solely process capability or a combination of approaches, and if so, what approaches were used?
    b. What challenges and opportunities did you encounter?
    c. How successful was this?
    d. Which countries?

2. Do you have experience of re-evaluating and/or updating the DS and/or the DP specifications for post approval changes?
    a. Was this triggered internally due to the change being submitted or requested by the agency?
    b. What type of changes are triggering a re-evaluation of the specifications?
    c. What approaches did you use to re-evaluate the specifications?
    d. What challenges and opportunities did you encounter?
    e. How successful was this?
    f. Which countries?

Notes:

Approaches for setting specifications:

- Few batches with limited variability.
    - Traditional approach based on SD. 4-5SD instead of 3SD if data is limited to a few batches
    - Clinical Data exposure is used in justification
    - Post-approval commitments received for many countries including US and EU.
    - Sometimes the precision of the method is also included in the justification of specifications.
- Common pain of having different specs for different countries.
    - Even though clinical range supported the range, they still asked to tighten based on what they had seen in other similar products or process capability.
    - Some countries jumped on the bandwagon when they found out one HA had asked for tightened specs.
- Not focused on a specific attribute because one HA phrased the ask generally for all release and stability specs, the commitment applied to all.
- ICHQ6(B) Concept Paper: Current ICHQ6 includes ‘process consistency’ as a factor of setting specifications. The concept paper positions a predictable, consistent process as accomplished by robust process controls.

Life cycle changes triggering the agency to request specifications changes include site additions or process changes. With these changes the agency requested specifications to be tightened based on process capability only even if accepted a mixed approach during initial marketing application. Challenging countries included Switzerland, South Korea, Brazil and New Zealand.