Table 12: Replacing Non-MS Legacy Assays with MS: Determining Assay Comparability and Strategies for Assay Bridging

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Scope:

The sensitivity, specificity and multi-attribute nature of mass spec methods make it highly attractive in replacing legacy assays for process development and quality control. This table will discuss the strategy and requirements for assay comparability and assay bridging studies needed for GMP implementation.

Questions for Discussion:

1. What are the high priority areas for replacing non-MS legacy assays? Do you aim for process development or QC Release/Stability?
2. What challenges have you experienced during the implementation of MS assays in GMP environment? How do you ensure instrument-to-instrument reproducibility? Can similar results be obtained using different MS platforms?
3. How to set the system suitability criteria for LC/MS analysis? To what extent MS assays are qualified or validated? Do you validate the MS software?
4. Do you perform co-testing? If so, for how long and at what stage of product development? What to include in the assay bridging protocol?
5. Do you need to identify all peaks in the legacy assays in order to correlate with the LC/MS analysis?
6. How do you define the acceptance criteria for individual attributes? How does MS assay fit into the overall control strategy?

Discussion Notes:

1. What are the high priority areas for replacing non-MS legacy assays? Do you aim for process development or QC Release/Stability?

    a) Replacements/addition of MS methods happens first during the development stage, starting from clone selection, characterization, process support and stability testing.
        i. Non-MS legacy assays and MS methods should be performed in parallel to collect bridging data and provide extra testing flexibility during process validation and commercial production.
    b) Replacement of non-MS legacy assays should be fit-for-purpose and based on control strategy needs.

2. What challenges have you experienced during the implementation of MS assays in GMP environment? How do you ensure instrument-to-instrument reproducibility? Can similar results be obtained using different MS platforms?

    a) Need lifecycle management of the MS methods over decades. Frequent instrument and software upgrades require change controls and make the method maintenance challenging.
        i. One participant expressed desire for MS vendors to provide line of products that would maintain similar performance and support over years to ensure testing continuity.

b) In addition to vendor qualification, internal qualification for MS system and software may be needed to ensure GMP compliance.
c) Some participants from CRO companies indicated that once project moves into late development/commercial phase, their clients want them to replace MS analysis with UV detection.
d) Challenge remains for QC analysts to correctly interpret MS data.
e) Achieving reproducibility between different instrument platforms is still challenging:
    i. One participant observed large differences in the dynamic range between different MS platforms.
    ii. Variation was also observed from the same instrument before and after vendor preventive maintenance.

3. How to set the system suitability criteria for LC/MS analysis? To what extent MS assays are qualified or validated? Do you validate the MS software?

    a) Setting appropriate system suitability criteria for LC/MS analysis is challenging due to performance difference among different MS instruments.
        i. Historical data from multiple instruments and sites can be leveraged to select appropriate system suitability criteria.
        ii. System suitability criteria should not be stage dependent.
    b) Software validation is still challenging.
    c) MS assays are qualified if used during late stage development and validated for GMP implementation.

4. Do you perform co-testing? If so, for how long and at what stage of product development? What to include in the assay bridging protocol?
    a) Need for parallel co-testing was discussed during Question #1. During the follow up discussions, some participants suggested to test new molecules with the LC/MS methods from Day 1 and not to use the profile methods, as long as LC/MS is fit-for-purpose for CQA monitoring.
    b) Assay bridging/comparability when replacing legacy method with MS method is necessary.
        i. Approach is similar to the traditional method bridging, with assessment of precision, linearity, LOQ, LOD, etc.
        ii. Typically, forced degradation samples are needed for method bridging, but one company indicated that they use historical data from reference standard only for the method bridging.

5. Do you need to identify all peaks in the legacy assays in order to correlate with the LC/MS analysis?
    a) 1:1 correlation is not needed, as long as the general trending between non-MS methods and LC/MS assays is similar.
        i. Hard to establish exact correlations between peptide map data and charge variants profiles, since the peaks in IEX and cIEF methods are mixture of product variants.
    b) Large body of historical data from both methods are needed to establish correlations.

6. How do you define the acceptance criteria for individual attributes? How does MS assay fit into the overall control strategy?
    a) Selection of MS method and acceptance criteria should be fit-for-purpose and support the overall control strategy design.