Table 1: Mass Spec in QC

SESSION 1:
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SESSION 2:
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SCOPE:
Mass spectrometry has become a key analytical technology in support of product development of biologics (degradation pathway identification, critical quality attribute, process understanding, comparability assessment). As mass spec technologies become more mature, mass spec tests are being introduced into QC testing for biologics.

QUESTIONS FOR DISCUSSION:
1. What are and how significant are the benefits of using mass spectrometry in QC?
2. What tests will be become QC-able and what tests will be replaced ? Any experiences to date?
3. What are the challenges / main hurdles associated to MassSpec application in QC (e.g. instrument qualification, method robustness and transfers, software requirements/data integrity, data processing, …)?
4. What are the costs and /or savings (investments and resources, cycle time)?
5. What is the expectation related towards broad implementation of MS in QC and what are the future trends?

DISCUSSION NOTES:
Session 1:
- The advantages of using Mass Spec (MS) in the lab with qualified equipment and validated methods were discussed.
    - MS can be beneficial for rapid identity testing
    - MS can be useful specifically in Peptide Mapping with UV detection, where peak retention time is changing with different instruments. Having additional MS information would help to remove the ambiguity. A QDa mass detector was suggested as a solution to be used in combination with LC-UV method
    - MS methods were found useful in QC/Lot Release (LR) especially for small molecules and could be helpful in biologics to understand sample heterogeneity (e.g. if there are other species detected under the main peak)
    - Characterisation and control of specific Critical Quality Attributes (CQAs) could be more straight forward with MS comparing to chromatographic or electrophoretic methods only
- Multi-attribute monitoring (MAM) methods are more frequently seen in QC labs nowadays
- What is driving the use of MS in QC?
    - Molecules are characterised thoroughly

    - With higher level of characterisation, it is more challenging to create a similar molecule (in the context of biosimilars it may be more challenging to demonstrate that a molecule is similar to an inventor molecule)
    - It would be desirable to use MS in QC to monitor CQAs more specifically (i.e. oxidation, deamidation, pyroQ, etc…)
    - MS could be efficiently used to monitor identity of host cell proteins (HCPs)
    - New attributes that cannot be easily controlled by other methods
    - MS in QC could replace for example ion exchange chromatography and give more specific information rather than just a fingerprint profile
    - It can be accepted to have more complex method, such as MS method as long as the bias is removed and more advantage over the traditional method is seen in terms of method specificity/accuracy

- There are some trends in the industry observed with increasing use of MS to report critical quality attributes
- There were some concerns raised regarding the size of the data but this could be addressed by optimisation of ways to handle and store the data. It was advised to work with the vendors to optimise this process.
- Considerations around instrument comparability were discussed and challenges related to instrument tuning. It was concluded that it is important to establish robust SOPs and to provide sufficient training to ensure that MS instruments are tuned the same way in different labs.
- For chromatographic methods that are not MS compatible, the 2D-LC could be an option
- Discussion around Mass Spec costs concluded that cost should not be an issue taking into consideration the cost of failure (e.g. batch failure) vs the cost of instrument
- Some key points were highlighted which would enhance using MS in QC
    - Ease of use (e.g. QDa)
    - Robustness
    - Reproducibility
    - QC friendly software
- MS can be beneficial in the in-process control (IPC) testing and inform on the product quality. MAM methods were discussed in this context and could give more granularity with advantage of a high throughput.
- When are we going to see MS in QC? 5-10 years. Both scientist and vendors would like to see MS in QC. Business drive to introduce MS in QC could be more emphasised in development of biosimilars
- For now MS is viewed to have a potential to support IPC methods

Session 2:

1. What are and how significant are the benefits of using mass spectrometry in QC?
    - Lifecycle vs action approach → Retroperspective analysis of the collected MS data (e.g. MAM data) from production batches would enable the identification of trends

- Implementation of MS in QC could improve the rate of false positive/negative results from traditional methods.

2. What tests will be become QC-able and what tests will be replaced?
   - MALDI-based methods: MALDI analysis and instrument control is straight forward.
   - MS-analysis which are based on a yes/no decision, i.e. identity testing, component present or absent

3. Any experiences to date?
   - Lots of discussion on-going everywhere – but hardly anyone has MS implemented in QC to date and nobody wants to be first
   - One participant has a MALDI in QC, which is used for raw material testing. The MALDI was introduced as this is the only way to analyse the compound of interest.
   - Another participant uses MS for Phase III testing, not for release testing.
   - Vendor perspective: QDa detector was specifically designed for use in QC, however, it has only been used in development so far.

4. What are the challenges / main hurdles associated to MassSpec application in QC (e.g. instrument qualification, method robustness and transfers, software requirements/data integrity, data processing, …)?
   - Lack of MS experts in QC environment
   - Companies are worried to detect additional peaks/species which would require additional investigation and justification
   - It is very difficult to change methods in a QC environment
   - Results can be instrument-dependent (e.g. different oxidation levels on different TOF instruments)
   - Frequent instrument qualification required (time consuming & down-time), e.g. once per month vs once per year
   - Amount of data is NOT considered problematic (number of production batches is limited)
   - MS instrument reliability is NOT considered problematic if the instrument is looked after.

5. What are the costs and /or savings (investments and resources, cycle time)?
   - At least two instruments are needed (in case something goes wrong; reference instrument) → significant investment
   - QC would have to invest in resources for exhaustive analysis of MS data (MAM)

6. What is the expectation related towards broad implementation of MS in QC and what are the future trends?
   - To date we are not at the stage of replacing QC methods by MS methods, we are rather at the stage of adding orthogonal methods (MAM).
   - At present, QC manages to fulfil agency requirements with the methods available. Therefore, there is little demand from the QC-side.

- QC labs do not have the capacity to do peak investigations (due to lack of expertise and resources) – additional characterization activities are usually escalated to experts in analytical technology/development departments.
- Is the additional information/higher sensitivity gained by MS relevant for release purposes or is it rather relevant for process monitoring/control?
- The consortium of pharma companies and vendors led by Richard Rogers is putting considerable effort into promoting the use of MS (MAM) in process quality control and in QC to simplify and minimize the number of release assays.