Table 7: How to Set Clinically Relevant Limits for Highly Sensitive Analytical Test Methods Such as Mass Spectrometry

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Scope:

LC-MS can be used in biopharmaceutical processes such as biomarker, target, and drug Discovery, Process Development, and QC lot release testing. It is often used as an independent validation of ELISA data. This discussion is focused on how to set actionable lower limit of quantitation (LLOQ), upper limit of quantification (ULOQ) for LC-MS assays used to assess levels of drug product and host cell protein impurities for clinical samples and how those varied depending on therapeutic type. We will also discuss hardware considerations and how the type of mass pec detector influence the analysis when looking at clinical relevant settings as well as the LC and sample prep conditions. Software capabilities are also important to consider as relevant in clinical settings, participants will be able to share current implementation, availability and needs.

Questions for Discussion:

1. What regulatory literature serve as a guideline/starting point? FDA, ICH Q8-11, USP, CLIA?
2. How does one develop and validate a bioanalytical LC-MS method?
3. How does one select appropriate QC controls?
4. When/where should QC controls be placed in a LC-MS queue?
5. What is the difference between a qualified and validated LC-MS method?
6. How do you take into account the molecule type, or class? E.g. glycosylated blood products and other cases which are unlike monoclonals? Is there a consideration for coping with PTMs as well as signature peptide?
7. Is the variation in detector types in mass spectrometry a significant problem, or a distraction? (e.g.QTof vs Trap vs Quad which all have different signal detection hardware).
8. Clinically relevant limits presumably also depend on therapeutic type (dosing regimen); so is mass spectrometry sophisticated enough to cope with the wide variation in levels of therapeutic dosing? Should mass spectrometers be expected to cope with the sort of range that comes in immuno-oncology as well as diabetes?

Discussion Notes:

- MAM General Discussion

Discussion around how to define CQAs from development to QC .
In development one strategy could be to assess product attributes, using info based on mechanism of action for example: Stress studies with MS inducing deamidation, oxidation …. To determine what can happen to molecules, to then decide on presumed critical quality attributes (PCQA). Then decide from there if became CQA, by answering questions such as does it impact PK, efficacy, safety, clearance…

Also discussed when going into Phase I trial how there is not a lot of time and how it might or might not be possible to do stress study, asses, and summit results.

- What is the difference between a qualified and validated LC-MS method?
  Usually validation is done in the QC lab while qualifying is done more in development.

- When/where should QC controls be placed in a LC-MS queue?

  In development work could be something that has an established record of performance on, a molecule for example. Performance metrics can be related to ion signal. They could be run in an order for example: Sample to condition column follow by water injections assay control runs and test samples and then assay control to assess level of consistency

  For HCP controls could be BSA, control CHO sample from 5 different cell lines and inject in triplicate.