Table 1: Qualifications and Validations of MS Methods From Discovery to QC

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Scope and Discussion Topics:

Mass spectrometry is one of the most used techniques in the pharmaceutical industry and there is a continuing need to develop MS based methods that are robust and transferrable between labs and throughout the molecule's lifecycle. There are many challenges in developing methods and in the end, such methods need to be qualified and/or validated. Challenges may arise from sample preparation, instrumentation, method development, compliance and data analysis. What are some of the challenges that this group is experiencing? In this roundtable we will discuss what method qualification and validation means to different mass spectrometry labs across discovery, development and QC laboratories. It would be quite beneficial to share our knowledge, experience and best practices we have developed to solve these problems.

Discussion Notes:

- Consult the ICH and compendia for validation guidance
    - ICH Q2R1 will outline the 3 types of testing and minimum validation requirements for each
        - Revision was published within the last 12 months, so ensure that the most accurate version is being used
        - Note that precision is defined differently by QA vs MS community
    - Individual compendia may also have instructions for MS-based methods (e.g. Japan)
    - FDA does not tell us what to measure, just that you need to develop and execute a validation protocol
- Characterization work requires high resolution tools but QC applications may not. Use the most appropriate tools for the intent of the method.
- Once methods get to QC, there is often little interest in learning "new" information
- Consider platform MS tools for QC methods to allow for easier transfers across labs. Consider not only MS, but also LC and software comparability
- Initial MS qualification: Understand variability from different instrument models, different physical instruments, etc.
    - Generally leverage a Design of Experiments (DOE) approach to do this
    - Also need to establish the variability/error in sample preparation, reagents, data processing
- Precision is done in technical triplicates

    - Same lot 3 times—3 lots of product
- Validations:
    - Reference standards are good surrogates for sample batches for validations
    - Establish acceptable range/variability and use this as criteria for methods
- How to choose a Reference Standard
    - Generally your product in QC space
    - May also want to consider running a product-independent standard to allow for evaluation of instrument performance over time
        - NIST mAb intact or myoglobin are potential options
        - Also consider a peptide retention mix (Pierce) as is to evaluate column, mobile phases, pump leaks, injectors, etc.
    - In clinicals- choose one compound and use this repeatedly
        - Used for system check
        - Can use NIST mAb, digest in the lab, and then run to ensure instrument and digest are working as expected if there is no product-specific reference standard
- Good practices
    - Control samples are run before every sample set
    - Run at start and end to ensure consistent performance
        - Consider how criteria are set to ensure proper system performance is monitored
            - Evaluate software option to make it easier to track over time
            - Set threshold to determine action
- Note: It is possible to execute a workflow in Chromeleon to run peptide map and reduced peptide map as system suit
- New peak considerations:
    - How to properly quantitate without standard of that component?
        - Execute study showing comparable response of related products by MS to allow for relative quantitation? This assumption is often made by UV analysis
    - Do new peaks need to be identified?
        - Depends on level of impurity, large vs small molecule, tox opinion, daily dosage, half life, etc.
        - Recommendation is to track retention time of new peaks (and mass if allowable by method)
- Data integrity is critical in QC
    - Audit trails, history of data file, software, etc. must all be considered
    - Must have documentation to support this
- SIM/MRM is often path forward in many QC labs so methods must be designed accordingly
- Instrument maintenance: when is the vendor needed
    - Defined by each unique instrument maintenance strategy

        - This defines preventative maintenance timing, return to service testing, and what work can be completed by lab vs vendor
    - In some labs, parts treated as consumables are okay to be changed by lab (i.e., Ion transfer tubes)
- Qualification vs validation
    - Qualification: determines the capability of method, sets spec of tests to generic value based on history – is the method scientifically sound and fit for purpose
    - Validation: uses qualification data and expands on it. Determines the method variability and follows specific protocol. Will use real samples, if possible.
- Determining peptide map limit of quantitation
    - Dilution curve- serial dilution and factors of 3
    - Use modified and unmodified peptide- use only modified peptide for LOQ