Method Qualification vs. Validation – What Does That Mean Now?

At all stages of product development, a sponsor must assure that analytical test methods are ‘scientifically sound and suitable for their intended use’. Using applicable ICH, FDA and EMA regulatory guidance documents, there are relatively clear technical expectations for the test method validation elements necessary to support full cGMP compliance by the time of product approval (“Big-V” validations). Legal statutes, quality system guidances and GMP inspectional guides provide insight on the compliance requirements for ‘Big-V’ validated methods in QC labs for use with approved products. But exactly what does this process entail from an operational perspective for methods that are not yet, or may never be, used in cGMP labs for release and stability testing of commercially-approved products? What are the risks associated with using unproven, non-optimized, uncontrolled test methods to generate data for any CMC decisions?

Statutes and regulatory guidances provide for increasing levels cGMP compliance of CMC during clinical trial phases, except for elements that directly impact product safety (eg microbial and adventitious agents). ICHQ7, as well as US and EU guidances, define a sliding scale of cGMP which includes a phase-appropriate continuum of method validation studies. But other US and EU guidance documents for INDs and IMPDs indicate ‘method validation data should be available upon request’. The 2016 draft revision of the IMPD guidance even adds a new point for Ph 3: “Validation of the analytical methods used for release and stability testing is expected.” Some feel this means a completed validation is necessary before entering Ph 3, while others interpret is as having completed method validations by the end of Ph 3. For project teams, this difference of interpretation is not trivial, and can have a significant impact on CMC timelines and resources.

Method validation activities conducted prior to BLA/MAA are further challenged with abbreviated or accelerated clinical trial phases (e.g. for biosimilars or breakthrough products), which may not follow the typical CMC stage gates of Ph 1-2-3. Also, there may be different types of qualification studies for methods that are used only in R&D for process and product development, vs qualification of QC release/stability methods that will eventually undergo Big V validation. Regardless of when or where an analytical method is used, it should be scientifically suitable for making the intended measurements, the results obtained should be reliable and repeatable, and the data integrity should be sufficient to support critical CMC decisions. But how to do this?

To address these expectations, a 2003 CMC Strategy Forum launched industry-regulatory discussions of phase-appropriate, intended-use-appropriate method validation (“qualification”) vs “Big-V” validation studies for biotech products1. More than a decade later, confusion over timing and content of method qualification/validation studies still persists across the biotech industry. And since 2003, evolving concepts such as analytical method QbD and continuous analytical method verification (CMV) have emerged. These are valuable analytical quality activities which lead into (QbD) or come out of (CMV) the clinical-phase use of QC methods; some key concepts might be adaptable for phase-appropriate method development and monitoring.

The January 2018 CMC Strategy Forum will target the policies and practices specifically related to phase-appropriate method validation for QC testing of clinical trial materials, and method qualifications for

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R&D methods used only for characterization, comparability and biosimilarity studies. The Forum will encompass technical strategies to support a method’s ‘intended use’, quality practices to document ‘assurance’ that methods are scientifically sound, and regulatory expectations for what should be provided ‘upon request’ by a regulatory agency for these types of methods. Forum discussions will focus on identifying and mitigating elements of greatest risk to the reliability of testing results in any CMC analytical lab at any phase of development.