Roundtable Session 1 – Table 3 – Validation of Biophysical Methods Used in QC: How to apply and implement ICH

Facilitator: Ivan Budyak, *Eli Lilly and Company*

Scribe: Anastasiia Vasiukhina-Martin, *Eli Lilly and Company*

Abstract:

Method validation is a critical aspect of quality control (QC) in the pharmaceutical and biotechnology industries. At this roundtable, the application and implementation of the International Council for Harmonization (ICH) guidelines in the validation of biophysical methods used in QC will be discussed. Specifically, the discussion will focus on the key steps of the validation process (method development, optimization, and validation) and method performance parameters, such as accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range. Importantly, examples of the challenges and benefits in applying ICH guidelines to biophysical methods will be reviewed.

Discussion Questions:

- What are the key method validation challenges for biophysical methods? Examples of problems and solutions.
- What ‘phase appropriate’ means when applied to biophysical methods?
- How does one define and then determine method performance parameters? Examples of accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range.
- Beyond ICH Q2(R1) – interpretation and implementation of ICH Q2(R2) and Q14.

Notes:

<u>What are the key method validation challenges for biophysical methods? Examples of problems and solutions.</u>

- Biophysical techniques are moving from characterization space to QC, in particular for novel modalities. Recently, many new modalities (and methods) have emerged. How do you apply ICH and show you are in control of the method for these newer methods?
- Validation is only required for specification methods. Techniques like CD and FTIR are used as characterization tests and typically don’t have specifications associated with them. This because HOS is not considered a critical quality attribute (CQA) for mAbs. Structural integrity is related to potency, so one can monitor potency changes instead.

While biosimilars might require structure quantification (i.e., secondary structure percentage) – yet they likely don't have associated specifications. As a part of method lifecycle planning and management, it is important to understand whether characterization methods used at earlier stage are 'validate-able' in the future if need to be a part of QC.

- Will AUC become a specification test? Some participants said that AUC is unlikely to be a specification / QC test because the instruments are expensive and not available for the majority of the labs in the field. For most sponsors, characterization data go into elucidation of structure section of regulatory application; these data are used to inform regulators that the structural attributes of the molecule are well-understood; there is no specification associated with these tests / data.
- Charge detection MS (CD-MS) is a very promising technology but no commercial instruments exist yet, so currently it cannot be used in the GMP space.
- Mass photometry is not fully ready for GMP applications, despite being a huge breakthrough. Variability is relatively high and random errors occur; this technology is great for characterization but not GMP-ready yet.
- Instead of validation, for platform methods, it may be appropriate to perform qualification, essentially a validation with a limited scope. Robustness looks at parameters that could be "accidentally" varied during the experiment (like fluctuations in room temperature). Part of robustness is to test that method is not operating on the edge of its design space; one is supposed to demonstrate that the method is stable over a certain range of parameter values. Buffer/water is often used as a control when testing for specificity; but it may be appropriate to test a substance similar to the analyte to show they can be differentiated.

What 'phase appropriate' means when applied to biophysical methods?

- Determining method robustness is an expectation for the late phase of development. In early phase, method qualification (limited-scope validation) is often sufficient. Quality by design approach is always the goal, but doing full validation early in development is typically not feasible; in addition, fully representative material is often unavailable at early stages.
- How often does one need to update your biophysical methods? In characterization, platform methods generally stay the same over time. For release tests, one may need to make method revisions along with product changes, for example, there is a change in formulation, etc. Robustness specification is method-dependent; reasonable limit should be well outside of what one would expect the variability to be.

How does one define and then determine method performance parameters? Examples of accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range.

- This question was not discussed in detail.

Beyond ICH Q2(R1) – interpretation and implementation of ICH Q2(R2) and Q14

- ICH Q2(R2) expands on Q2(R1). ICH Q14 is the latest update; the latter talks about lifecycle management of analytical procedures to ensure that the analytical methods remain up to date. For instance, Q2(R2) talks specifically about approaches to the

validation of a dynamic light scattering (DLS) method. This said, Q2(R1) is not obsolete; R2 and Q14 are just providing additional clarifications.

- Potency is an important CQA for AAVs; reporting % species is not sufficient if not related to potency. Empty capsids are considered an impurity; hence there is a specification associated with them; this is why AUC is often a specification test for AAVs (see above). AAV capsid degradation: in case of capsid rupture and DNA leaking out, AUC would detect it; DLS is unlikely to detect. Electrophoretic mobility of empty and full AAVs is approximately the same, so non-denatured CE would not work very well – this is likely why it is not commonly used currently for AAV analysis.