Roundtable Session 1 – Table 7 – Strategies and Qualification of Critical Reagents

Facilitator: Mark Lies, *Advanced Electrophoresis Solutions (AES)*

Scribe: Niomi Peckham, *US Pharmacopeia (USP)*

Abstract:

Evidence of proper control for any analytical method is critical to successful approval and subsequent commercialization of biotherapeutics. Even routine, well-established tests and processes are subject to error and therefore require close monitoring. To help minimize potential errors, detailed knowledge of analytical tests, their makeup, and performance is imperative. In this roundtable, we will dive into a better understanding of and best practices for the identification and qualification of critical reagents incorporated into analytical testing.

Discussion Questions:

1. How do you define a 'critical reagent'? How variable is qualification of these kinds of reagents?
2. What factors should be considered when incorporating reagents into release assays?
3. Are there any factors that should be considered in method development to be considered when setting a product specification? (e.g. shifts in experimental pI due to variation in ampholyte lot)
4. How can system suitability (assay acceptance criteria) best be set up to facilitate investigations when something does go OOT or OOS? Are there criteria that allow for assays to be easily invalidated? (e.g. stray peaks due to air bubbles or crystals – undissolved urea or debris). Can control charting (trending) be routinely applied and if so, what factors should be charted?
5. What are some real-life examples – both positive and negative experiences - of critical reagent qualification?

Notes:

Defining a 'critical reagent' –

A reagent that if you don't have it you can't run your method and can't release. Or if something changes about it, there will be an impact on your assay.
Participants try to keep one lot and a backup or an alternate supplier.
Single source can make a reagent critical.

Examples of 'critical reagents' –

For an HPLC method, column X drifts, fails system suitability, and prevents lot release.

Ampholytes for cIEF showed different performance. Had to qualify different lots from different suppliers to replace and as contingencies.

Discussion of how you qualify if you only have one vendor –

Leaning system suitability criteria. It was suggested that vendors could provide data that the end users could replicate. But what if they need a wider specification?

Participants mentioned some cases where mulitple lot examples are used for validation. It was noted that Beckman used to have muliple lots as a development kit.

Factors to consider for reagent selection and inclusion in SOPs –

For selection of reagents shipping conditions to mulitple climates, customs, receiving, storage conditions, etc. should be taken into account.

Participants agreed that most SOPs should state muliple vendors because of possible cyclic problems w/ lots.

It was suggested that some kind of standards should be used to look at lots, columns, etc.

The example of columns and how do you write that into your SOP was discussed. It was suggested to write in a discription and a suggested brand.

It was mentioned that RS data is trended and monitored and the data reviewed. This trending data is very significant.

Participants recommend against 'just in time' for reagent ordering!

It was also noted that for some reagents, they are being used for applications they were not originally developed for. As an example, Pharmalyte from Pharmacia was developed for IEF stack gels, not high resolution.

Don't underestimate what the vendor can do to help you! Develop a relationship with critical reagent vendors. As an example, a random resolution problem was seen with the Biolyzer. The vendor responded and improved a specification in response, resolving the issue.

Recommendations to Vendors –

Participants indicated that they are looking for data on Certificates!

Participants mentioned the need for vendors to use a sample that challenges the vendor's product better, and better simulates the end user's method.

Real-life examples –

As an example, when the vendor for Pharmalytes had issues, there was a lack of data on the certificates. Other participants mentioned HPLC columns, where the data provided are not relevant assays.

One participant talked about an intercompany study on CZE – everyone got the kit, only variable was the analyst but the consumables were different. No issues were seen at the time.

An example of neutral capillaries for a CZE release assay was discussed. Some lots would give different resolution. The root cause was traced back to a target vial, which was glass, and it was determined to be a lot specific problem. The coating on the glass that was leaching off. Took effort to trace the source.

In another example, one company had problems with plastic vials. They would see issues with things leaching off vials. The recommendation was don't tie yourself to a single part number!