Table 1: How Can We Ensure Our CE Methods Are QC Ready?

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Scope:

The goal of biopharmaceutical analytical method development is to deliver robust methods for validation and transfer to a Quality Control (QC) group for routine control testing of licensed products. In the context of capillary electrophoresis, an analytical method development team needs to consider which method parameters to optimize and assess for Robustness. Parameters to be assessed could include sample preparation conditions, sample injection, electrophoresis conditions as well as peak integration and data analysis. Additional considerations to be considered are the availability of instrumentation in QC, the setup of system suitability criteria, the software used, the consistent supply of critical reagents, monitoring of method performance and training of QC analysts. In this workshop, we will discuss what should go into the preparation to ensure a successful hand-off of CE methods from an analytical development team to a QC group.

Questions for Discussion:

1. What does a QC-ready/friendly method require?
2. What are the key method parameters to assess for robustness?
3. What are the current challenges of implementing CE methods in QC environment?
4. What role does analyst training play in successful method transfer?
5. What are the strategies to manage vendor-driven changes and discontinuations of instruments/critical reagents?

Discussion Notes:

1. What does a QC-ready/friendly method require?
    - QC is the customer. When developing a method, keep in mind what QC needs for a successful transfer.
    - Robustness
    - Flexible and alternative suppliers for critical reagents, materials, some instruments/equipments
    - Clearly written method—don't leave things open to interpretation. QC team may be able to help with the language
    - QC prefers methods to have automated integration
        - Try to standardize the integration

    - Always include figures for integration. Example—Figure 1: Show a large unzoomed version that includes all peaks. Additional figures to show a zoomed in version of each peak and integration of each peak.
    - Add a figure of a heat stressed sample to show worst case scenario.
    - Clearly specify which peaks are system peaks and which ones to not integrate
- Setting up good system suitability criteria
    - There is a minimum number of runs that need to be used to setup a criteria
    - Control charting—we know how its supposed to behave. Run at beginning and end and perhaps inbetween to confirm you can trust the entire run (bracketing).
    - Think about if the system suitability sample should be the same as the sample being tested or something more general.
    - Reference standard will be put on stability. Prepare a bulk stock of it.
    - Press vendors to have a standard type system suitability.
    - What does the QC need for system suitability? Should it be a product specific system suitability or more generic molecule?

2. What are the key method parameters to assess for Robustness?
    - Lot to lot variability of reagents and other supplies. Labs should test a minimum of 3 different lots of critical reagents/supplies to ensure method is robust.
        - Validation kits—e.g. For LC methods, Waters sells validation kits with multiple column lots/packing lots. CE vendors should have these types of kits for evaluating method robustness.
        - Align vendor release criteria to the QC acceptance criteria
        - Sometimes there are only a few vendors that make a CE reagent compared to more common supplies
    - How do you know which parameters to test in robustness?
        - For iCIEF you know certain parameters which will affect result—e.g. urea concentration, ampholyte concentration, so these things should definitely be evaluated in robustness.
    - Perform DOE and use aQbD approach for method robustness assessment
        - Multifactorial design, it is the most efficient way
    - Early phase may not need as robust a method as later phase. Methods are still in development as they go through the clinical phase.

3. What are the current challenges of implementing CE methods in QC environment?
    - Need to have good communication between the development lab and the QC lab.
    - The sending and receiving labs should be involved in a study prior to actual transfer to ensure everything runs smoothly and are able to meet precision requirements.

- Software—auditing changes such as reintegrating. GMP separate Empower server from research.

4. What role does analyst training play in successful method transfer?
    - Having good trainers is very important
        - The trainers have secret knowledge. Sometimes there are things that can't be written into QC methods.
        - Real time video training—hollow lens camera
        - Important to have in person training. Watching someone actually doing a procedure to learn small details that might not be captured in the written procedure.
    - Multiple steps of training
        - Videos, vendor comes in to give training, make sure analysts are well known with the instrument, technology, method, everything
        - Need to be specific with exactly how to prepare urea solutions. Important to make fresh urea daily. This is a key roustness factor—is 1 day old urea usable? Is 24 hours acceptable since its within 1 day?
    - For reverse pipetting, it is important to clearly document in the procedure when you need to do it.
    - Clearly need to know when to use plastic vs glass—adsorption reasons. For pI marker sticking to marker, will cause pI shifting. Will affect the ampholytes pH.

5. What are the strategies to manage vendor-driven changes and discontinuations of instruments/critical reagents?
    - If there is a change in a product from a vendor, they need to communicate the change—part of the quality agreement.
    - Perform comparability experiments to show equivalency
        - in order to do comparability, may need to purchase several of the newer instrument for comparability testing which is a huge capital investment—make sure capital spending team is involved
    - There needs to be diversity of vendors for a particular application.
    - Also discussed discontinuation of software