Roundtable Session II – Table 2 – Communicating Issues with Capillary Electrophoresis Methods to Management, QA, and Regulatory

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Abstract:

Capillary electrophoresis (CE) methods are critical for characterizing biopharmaceuticals. However, analytical scientists often face challenges in method performance, data interpretation, and variability. In the race to bring medicines to patients faster, communicating these issues to management, quality assurance (QA), and regulatory stakeholders requires not only technical expertise but also the ability to translate complex technical issues into clear, actionable information. This roundtable will provide an open forum to discuss best practices for bridging the gap between CE technical details and organizational decision-making, with the goal of improving alignment, efficiency, and compliance.

Discussion Questions:

What kinds of issues with CE methods have you found hardest to explain to leadership, QA, or regulatory?

How do you decide how much technical detail to include, and when to simplify?

What tools—graphs, risk summaries, analogies—have worked well in your communications?

How can we make sure different audiences walk away with the right level of understanding and confidence?

What examples (good or not so good) from your own work could help us learn together?

Notes:

1. What kinds of issues with CE methods have you found hardest to explain to leadership, QA, or regulatory?

    - These issues are the most challenging to explain: artifact peaks, signal fluctuations, non-reproducible peaks, and peaks that we suspect are artifacts but have no proof. For example, a tiny air bubble in the sample could lead to an abnormal peak in the electropherogram. However, it is hard to reproduce it for QA to see.
    - The main challenge of explaining issues to QA is that they want to know the root cause of everything. Since QA personnel are usually not CE experts, it can sometimes be challenging to explain to them the sensitivity of the method, artifact peaks that cannot be reproduced, and dilution errors. Typically, the artifact peak will

be gone when we repeat the run. However, obtaining approval from QA for a repeat run in a GMP testing setting is a challenge. Some QA won't allow repeats.

- Tiny air bubbles can impact a CE run, and this issue may be a general one for CE assays. But it is hard to explain it to QA. On the other hand, common issues for HPLC-based assays are more easily accepted by QA.
- LC methods also have their own issues. A common problem is the column-to-column variation. In one case, during the transfer of a new LC method to GMP, only 3 out of 10 columns worked. In another case, only pre-qualified columns from the vendor could be used for an LC method to analyze small molecules. Analysts are restricted to ordering only those column batches that work. The reasons why some of the columns did not work were still unknown.
- If the potential issues can not be explained effectively with words, the SOP needs to be rewritten or updated with electropherogram examples of both good and bad runs. A quality system with good SOPs is the way to control outlier issues.
- Need to show QA with several more reproducible injections. Anything out of the norm, they will question it.
- CE is not like HPLC. Many people are familiar with HPLC but not CE. We need a lot of CE experts in certain organizations.
- Some QA expect science to follow the rules. This is challenging.
- Quality is paramount for patient safety; science ensures the quality.
- Some issues were caused by changes in raw materials or consumables provided by vendors. For example, a coated capillary worked when the CE method was qualified/validated. However, after the method transfer, the vendor made a change in capillary coating, causing numerous issues with extra peaks being observed. In another example, a tiny cutting difference of the capillary end can make a significant difference for certain molecules.
- Vendors should start communicating the changes to customers as early as possible.

2. How do you decide how much technical detail to include, and when to simplify?

- Some common scientific justifications, previous cases, system suitability, and sample acceptance are all helpful.
- A common practice is to describe different scenarios in which abnormal injections can be rejected if current traces are abnormal.
- Out-of-spec and out-of-trend results need a thorough protocol plan or protocol to cover if the data are acceptable.
- A protocol or SOP should define how to handle these abnormal results.
- In the method, you can establish system suitability criteria to cover some situations that you have discovered during method development.
- Define "Must be" and "should be" in the acceptance criteria to make them more objective, so there is no room for misinterpretation.
- When inside experts can not convince QA, outside experts can be brought in to help explain some challenging topics.
- Acceptance criteria should not be too tight at the beginning of method development. Otherwise, it is tough to widen them later, especially with internal QA and regulatory.

A lot of historical suitability data that correlates with what happened and shows the trend can be used to set or reset the acceptance criteria. It is always better to start with wider acceptance criteria and tighten them later based on data collected over time. In contrast, it is challenging to broaden the acceptance criteria because revalidation is often required and difficult to accomplish.

- Make sure that even after changing the criteria and the method is still validated.

3. What tools—graphs, risk summaries, analogies—have worked well in your communications?

    - The infographic is helpful.
    - Risk assessment is part of the investigation for QC failures and deviations.
    - Risk assessment should start before doing the method development in the lab, not in the late stages. Every risk needs to be addressed through mitigation actions, parameter optimization, and the use of QbD tools. Continuous updates to the original risk assessment, including more parameter evaluations during method development, are essential.
    - Some risks need to be addressed early on. For example, if tubes may cause a problem, we need to capture that knowledge and document it.
    - Approximately 80-90% of the risk can be covered at the beginning; the rest will be covered through updates later, when dealing with unexpected issues.
    - Avoid running unnecessary tests. If you covered some situations in the risk assessment, you already have the justification.
    - Give a little background to QA: CE is not the same as HPLC. Even with HPLC, there is column-to-column variation.
    - In the method SOP, specify that the current profile be included in the report and provide injection acceptance criteria. Then, if the current trace is abnormal, you can show this section to QA and point out that the data from this injection should be discarded based on the SOP.
    - QA personnel are often unfamiliar with CE. So, it's essential to establish acceptance criteria based on objective, measurable parameters to ensure transparency and prevent misunderstandings or unfounded accusations.
    - Establish trust between scientists and QA. For example, instrument logbooks need to be reviewed every three years. Every time, the logbooks need to be annotated to show they have been reviewed and signed. When you have a large number of instruments, it can take considerable time to show QA that you have reviewed every logbook on time. However, when you have established trust with QA, they would say, 'I don't need to see them; I trust you.'

4. How can we make sure different audiences walk away with the right level of understanding and confidence?

    - Different audiences may have different levels of understanding of CE. So when communicating CE issues, it's a good idea to verify that different audiences understand the issues.
    - It is hard to know if they accept or understand during a single presentation. Follow-up meetings are usually needed.
    - Example of a pipetting error. QA required repeating the error. It took 1-2 weeks of work.

- How much do they trust us? Quality does not come from rules; however, we should adopt a better quality mindset.

5. What examples (good or not so good) from your own work could help us learn together
   No time left for discussion of this question.

Helpful comments from the discussions:

- Rules don't make quality, science does!
- QC test is performed as an extra safety measure because not everything is under 100% control. Therefore, QA should expect to see some abnormal results from time to time.
- Good practice in writing SOPs: provide examples of electropherograms and current traces to illustrate what good data look like, what a blank looks like, and what bad data look like. Describe situations like stressed samples, which would have peaks outside the acceptance criteria.
- "Must be" means it has to pass. "Should be" means it depends.
- We can't prevent everything bad from happening. However, when it does happen, we can capture as much information as possible to update our test documents. If it happens multiple times, and we capture all of them in the documents, it would help with risk assessment if it happens again.
- Scientists should push back on unreasonable requests from QA, such as saving all the pipettes used until the QC test passes, to ensure the QC personnel do not use the wrong pipettes.
- Risk assessment is useful. However, its usefulness will depend on specific situations.
- Very often, we don't know why we are seeing extra peaks. They could be caused by dust, a contaminated sample tube, or a new impurity in the sample.