Table 7: Role CE in Real Time Release and Sample Prep Automation

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Scope:

Real Time Release Testing (RTRT) is defined as the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data. This is a concept for designing, analyzing and controlling pharmaceutical manufacturing processes through measurements of critical quality and performance attributes. CE (capillary electrophoresis) in particular has a role to play in these efforts given a long and successful track record in analyzing the size and charge variants of a wide variety of novel pharmaceuticals. In the case of real time release testing, it remains an open question how much of a role CE will play in future manufacturing processes, given there are already a number of routinely used techniques in play. Sample preparation automation may perhaps demonstrate the most gains given the complex sample preparation for some assays, such as CE-SDS. This roundtable aims to discuss the strategic questions surrounding real time release testing and sample preparation automation, and what role CE may play in the RTRT environment.

Questions for Discussion:

1. How can CE be used for RTRT?
2. What are the pros and cons of CE with respect to RTRT?
3. How can RTRT with CE be integrated within the production or formulation process?
4. What is needed in order to integrate CE into the RTRT process?
5. What is the impact of sampling on RTRT? Is it required?

Discussion Notes:

- Automated sample preparation for CE has an added benefit of correcting for incorrect pipetting, and having automated records for such pipetting. This necessarily makes it more GMP-compliant potentially
- Real time release testing (RTR) is a harder problem than automated preparation, however; automated preps are quickly becoming the norm across the industry since it benefits from processing large sample sets
- Inline vs offline real time release testing: inline meaning integrated into the manufacturing process. Inline is the harder problem but very much the goal. May have to begin with offline testing first since this topic is so new
- Some examples of inline testing: cell culture monitoring probes for temperature, spectroscopy; there are, however, no analytical chemists on the production floor (at least for now)
- CE inline testing for RTR is still a hard problem and will require collaboration with academia, mostly because there's the added worry of electrophoretic conditions (which is not an inherent problem with LC)

- LC is an easier problem to solve and has had some in-roads; i.e. Amgen created a "Frankenstein" system of different parts from different vendors for a reverse phase analysis that does sample cleanup and LC-MS (https://onlinelibrary.wiley.com/doi/10.1002/bit.21759)
- Another concern with RTR and automation is data analysis, which can be a huge bottleneck
- RTR testing will require looking at what CQAs need to actually be monitored during process development. Another consideration is what is actually critical for your process? For example, cell culture may only care about charge variants but not necessarily size variants. So you will need a charge assay potentially
- MAM approach: LC-MS has the promise of answering a list of questions for what you are asking of your process within a single assay.
- Coming back to CE: why CE then? CE-SDS is great for LMW characterization for example, so the question is, is that needed for RTR? Another consideration is speed of separation. Perhaps a PA800+ isn't the best choice if a microchip system can do a separation in under a minute
- General RTR question: is real time release necessary for every stage of your process? If the industry is moving towards smaller batches and a more continuous process, perhaps we need more fast and dirty analysis for RTR, followed up by side-by-side QC
- Crucial question regarding RTR: what do you do with the information you get?
- Metric: manufacture-to-release should go down to a week's time for smaller batches (vs 1 month or several weeks per industry norms).
- The real bottleneck with RTR though would be microbial methods, since you have to wait for growth. Safety assays and bioassays are also quite time consuming.
- Step-by-step quality seems to be the goal so production floor can make real-time decisions
- Metric: monitor your process for continuous improvement for higher yield and quality
- Future state: AI that monitors feedstock automatically and makes decisions based on feedback loop
- COVID a good test scenario for less people available for a process (hands-off approach)