Table 4: CE's Role in Real Time Release Testing/PAT

Session 1:
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Session 2:
Facilitator: Nathan Lacher, *Pfizer, Inc.*
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Scope:
Process Analytical Technology (PAT) is a system for designing, analyzing and controlling pharmaceutical manufacturing processes through measurements of critical quality and performance attributes. Raw and processed materials are tested to ensure final product quality. For that reason, PAT can be used to release the product at the time of production, hence real time release. The idea behind PAT is to become more efficient by reduction of over-processing, sample motion, sample and product storage. In this roundtable, we would like to discuss the way PAT could be preferred over quality by testing and the role of CE in this.

Questions for Discussion:
1. How can CE be used for PAT?
2. What are the pros and cons of CE with respect to PAT?
3. How can PAT with CE be integrated within the production or formulation process?
4. What is needed to integrate CE in the process as PAT?
5. What is the impact of sampling on PAT, can we do without?
6. CE explorative or release testing to set up PAT and real time release.

Discussion Notes:

Session 1:

- Clarification of meaning and scope of the session:
  - PAT as tool to get better control over the process.
    Real-time release testing aims to replace the release tests for the final product with tests within the process.
  - Focus on large molecules, biologics only.
- Requirement for CE technologies in PAT:
  - Quick testing, quick separation e.g. with chip-based instruments
  - high tolerance for salt required or very good sample preparation (Downstream).
  - In-line CE is challenging, but is possible: issues are removal of cells, debris, buffer, thus sample preparation is seen as the key limitation
  - Direct sampling from the fermentation is challenging, e.g. sensitivity of material to fouling;
  - Online sampling for MS and HPLC is already available on the market.

- Criteria for CE in PAT assays:
  - Dependent on purpose: if intended for better process control or as replacement of release testing. These are two different intentions.
  - In-process testing does not simply replace drug substance release testing. Downstream process needs to be understood very good to shift testing of specific parameters from release to process.
  - Set dependent on CQAs of the molecule
  - Testing at multiple points in the process.
- CE techniques required for PAT:
  - purity with respect to size

    - charge variants
    - capillary zone electrophoresis in specific cases for affinity/ activity
    - monitoring of additional parameters by CE would be helpful like HCPs, HCP DNA.
- Attendees experience with PAT/RTR:
    - No attendee currently uses CE for PAT/RTR.
    - Chromatography is used, but resistance from manufacturing with regard to complexity of handling.
    - RA accept, if sufficient data and if proven that tests are in correct position and give the right information.
      Replacement of normal release test by RTR: a certain amount of batches is required with parallel strategy.

Conclusion:
PAT/RTR technology needs to be quick and easy: Sample in – data out.
Sample preparation is the main challenge for CE.
Establishment of RTR means a shift in responsibility from QC to manufacturing.

<u>Session 2:</u>

- Many of the same points in session 1 were discussed.
- Who is doing Real Time release today? Amgen (maturing), Biogen mentioned
    - MAM and Raman used in this space. RPLC could be used for peptide map.
- Speed is key for Real Time Release
    - Current at-line techniques are baseline. Analysis can be immediate but data still needs to be analyzed and reviewed.
- Current solutions cited as Waters Patrol and Agilent systems.
- Real Time Release generally used in commercial and subsequent transfer steps
- MAM is potentially powerful technique but won't be able to pick up cell culture issues, degradation via peptide mapping
- CE-SDS still a necessary tool

- Dream scenario is to put sample in, have automated feedback loops for course correction of process, to qualify finished product. Control room to be used in monitoring overall progress, results, and keeping things on track in regards to maintenance etc.

- Question posed: Is goal speed-to-release or course correction of process at the bioreactor? Course correction could only be done up to first purification since the product can't be modified retroactively.
    - Likened to 'racing to a red light'
    - Course correction would need to be defined as corrective actions for the next manufacturing batch.
- Instrument maintenance during operation is important aspect of RTR. Inoperable instrument in-process could bring process to a stop.
- Fabricated, disposable devices/supplies would help simplify process and circumvent potential issues.