Table 7: Process Analytical Technologies

Facilitator: Marta Germano, *Janssen, Infectious Diseases and Vaccines*
Scribe: Tom Branson, *Janssen, Infectious Diseases and Vaccines*

Scope:
The concept of process analytical technologies (PAT) in the pharmaceutical industry was introduced in 2004 in an FDA Guidance for Industry *"PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance"*. This concept was subsequently adopted by the EMA, who has provided guidance in a number of documents, for example, EMEA/INS/277260/2005 *"Reflection Paper: Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed"*. RTRT is also described in the ICH guideline on Pharmaceutical Development, Q8(R2), as *"the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls"*.
Whereas regulatory frameworks and guidance for PAT and real-time release testing (RTRT) of pharmaceuticals is available for quite some time, remarkably, there is only limited application of such concepts in the biopharmaceutical industry. However, the need for PAT is dramatically changing with recent developments in biomanufacturing technologies. If biomanufacturing of the future will include continuous manufacturing, then it will be essential to implement PAT, in order to allow successful development and commercialization of such processes.
This roundtable intends to capture the current experience in the industry with development and application of PAT for process understanding as well as for RTRT.

Questions for Discussion:
1. Is PAT applied at your company and, if yes, which analytical technologies are being used?
2. For what purposes is PAT being used in your company?
3. What are the obstacles to introducing PAT and RTRT in biopharmaceutical manufacturing?
4. How could we overcome such obstacles?
5. What are new developments in analytical technologies that could be applicable or useful for in-line, on-line or at-line testing in biopharmaceutical manufacturing?

Discussion Notes:
1. PAT at your company.

QDa identity/quantity to check predominant charge states. – currently one of the only options.
CZE possible (also on chip).
LS a possibility.
SEC a possibility, but not currently in place.

2. For what purpose is PAT used?

None yet. Currently evaluating possibilities.
Is used for aggregation measurements and titre measurements.

Needed when speed is an issue.
CZE for titre measurements.
HCPs can be a good target – need more communication with vendors and bioassay scientists.
QDa/MS for checking modifications (for example, oxidation, deamidation).
Continuous manufacturing would massively need PAT implementation.

3. What obstacles are there for implementing PAT?

Rely on vendors for techniques.
Sample sterility can be difficult to control.
Miniaturisation of technology.
Robustness of the technology.
Simplicity of the tech – do not want to need a fully trained MS expert. Big challenge.
With automated results, how do we deal with retention time shifts or automatic integration variation?
Want a feedback loop for automatic adjustment of systems – e.g. CEX clean-up not sufficient so feedback loop says adjust settings and/or retry. – very challenging to set up.
FDA/regulatory authorities not yet accepting real time release testing as sufficient – still demand QC release tests.
Interpretation of results is difficult – e.g. HCP analysis may have too many targets.
There is no consensus between companies yet.

4. How do we overcome those obstacles?

Implement directly from literature (if available) – LC-MS methods / glycan analysis.
Work with instrument vendors to realise these developments.
Work with regulatory authorities working groups on new technologies.
Alignment between analytical and process development scientists.