

## **Table 1: Process Analytical Technology**

### **Scope**

For the pharmaceutical and biopharmaceutical industry, the process analytical technology (PAT) concept is defined by the US Food and Drug Administration to follow critical parameters of the manufacturing process. PAT distinguishes and defines Critical Process Parameters (CPPs) of the equipment manufacturing the product, which affects the Critical Quality Attributes (CQAs). Monitoring of CPPs and CQAs aims for real-time measurement of various physical, chemical, and biological conditions of the system, often in-line or on-line modes. However, proper analytical technologies are not always available for the determination of certain parameters, to allow e.g., real-time release of the actual batch. PAT requires continuous analysis, in which calibration and validation are usually difficult. While many of the CPPs (temperature, pH, dissolved oxygen, etc.) can be measured in accurate, robust and repeatable manner, unfortunately there are many CQAs, with no available analytical option. One of such CQAs is protein post-translational modification, e.g., protein glycosylation.

At this roundtable, we will discuss the advantages and disadvantages of the available analytical technologies from an applicability point of view. Direct spectroscopic methods vs separation-based characterization? Targeted sensors vs general-purpose instrumentation? Real-time data analysis – the role of artificial intelligence?

### **Discussion Notes**

This round table was based on the topic of Process Analytical Technology (PAT) in biopharma manufacturing. Some of the points that raised are listed below.

PAT has been used in the past especially for small molecule production where it is easier to employ compared to bioreactors. There are two different routes to Biopharma manufacturing the more widely used is a batch process as this allows the companies to pivot easily between different drug manufacturing, but continuous manufacturing is now being developed to scale down the size of equipment needed. PAT is required for both. Initially for both approaches cell line screening is done using Amber reactors where PAT is used to assess cell line viability.

For PAT the type of technique which will be used would be based on the Critical Quality Attribute (CQA) that are to be measured and this will also determine if the analysis would be online or at-line (offline) and the time to result.

Techniques which are non-destructive such as Raman can be used online and will be used to measure titre trending during production and cell viability. Often these online techniques monitor bioprocess parameter trend and tend to be less precise than at-line or offline techniques but are quick and give a fast answer and are baselined against offline techniques such as HPLC.

Parameters measured online include cell concentrations, titre, PH, temperature, oxygen levels etc. A new technique which is being developed online is NMR. A real time method is being developed which uses a flow diverted from the bioreactor and using low field NMR to monitor attributes. Currently the low field technique is under evaluation but can identify 11 attributes compared to over 30 with a high field NMR and currently the level of cell media interference is being investigated.

Interesting measurements inline vs offline can be different one example was that the 280nm UV titre for the same sample was different if measured inline versus offline as the protein extinction coefficient changed when the protein configuration changed with the sample preparation.

If a more precise CQA needs to be measured, then often offline techniques are used e.g., LCMS and CE. MAM LCMS is an example of an offline PAT. With this PAT testing the testing labs are normally separate labs to the process labs so samples are moved from the process development labs to the analytical lab. With large cell line screening trials high throughput is required so some less precise techniques are used due to throughput needs and more precise techniques are required with higher throughputs.