Table 15: Emerging Strategies on PAT, Modular Manufacturing, and Real Time Release Testing (RTRT)

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Scope:

This roundtable will discuss process analytical technology (PAT), modular manufacturing, and control strategies that enable real-time release testing (RTRT) for critical quality attributes (CQAs) in biopharmaceutical manufacturing. PAT, modular manufacturing, and RTRT can enable increased productivity including faster release and potentially decreased costs—all of which improve the value to patients. Modular manufacturing is gaining momentum as it provides flexibility and enables cost effective use of GMP space. Advances in PAT/RTRT analytical technologies and digital solutions are being implemented for biopharmaceutical manufacturing to achieve the potential of PAT/RTRT.

Discussion Questions:

1. In-line / on-line / at-line analytics are available; which of these is most commonly used in the process development and manufacturing, and where in the process are they used? What are the biggest needs/challenges/opportunities? Is there a lack of regulatory guidance around validation of PAT in GMP manufacturing?
Are PAT technologies being used for complex raw material testing?
Are upstream PAT technologies like RAMAN probes, capacitance probes, and low field NMR being used in manufacturing?
Are downstream PAT technologies like Flow VPE/VPX, Patrol UPLC, and MALS being used in manufacturing?
Are drug product PAT/RTRT technologies like RAMAN being used in manufacturing?
2. What are the challenges faced in implementing PAT/RTRT tools in modular manufacturing where single-use technology is increasingly utilized? Are single-use versions of the PAT/RTRT tools used in manufacturing?
3. What are the best practices to implement, transfer and maintain PAT technologies in manufacturing? What has been the regulatory feedback on PAT/RTRT technologies on the manufacturing floor for biopharmaceuticals?
4. Data analytics and data visualization are key to effectively using PAT tools; what are the digital solution needs and opportunities that are being explored to support PAT/RTRT?
5. EMA RTRT guidance states that CofA can say “complies if tested” for tests that do not need to be routinely performed; how is this applied for biopharmaceutical manufacturing for batches released using RTRT (i.e., what should go on the CofA)? How does this affect E2E control strategies (in-process testing, release testing, stability testing), in-country testing, registration testing, etc.?

Participant’s Representation:

Analytical development, QC, Regulatory CMC, process development scientists, Instrument rep, industry publication editor and Data analytics experts joined the round table discussion.

Discussion Notes:

● As part of a survey by Biophorum Operations group's (BPOG) PAT sub team, it was identified that PAT is mostly used in process development and clinical manufacturing space but not in commercial manufacturing space.
● One of the risks for introducing PAT in commercial space is its associated potential for contamination
● Interest to use PAT technology in commercial space would become reality only when they can promise improved yield, quality along with the speed. As there are already existing analytical technologies which meet the current manufacturing needs, there should be a strong driving factor to make investments on PAT.

- o Data from Raman and capacitance probes can help run the process at optimal conditions which helps increase yield and can be beneficial for commercial implementation.
- o Strategically, the best time to think about implementing PAT technologies and automations related to real time monitoring would be when planning to build new facilities.
- o In commercial space PAT for release testing would be very beneficial.

● Companies don't see value in implementing PAT technology for already approved products as it would be considered a post approval change. If PAT is associated with a process during development, then it would be easier for it to make it all the way to the commercial scale
● With PAT there is a lot of data being collected, but how much of it is being used for real time monitoring on the manufacturing floor?

- o Raman probe is being used in commercial process development for real time glucose level monitoring. This needs mathematical models to assess the addition strategy.
- o Generally, you need to validate the new PAT technique using Raman probe against the known established techniques before you can move to exclusively using the data from Raman probes for monitoring glucose real time.
- o Automation of glucose addition based on the data from the Raman probe is possible.
- o When measuring glucose using Raman probe it is mostly a single spectrum not affected mostly by the nature of the antibody or the nature of the media used. Therefore, same mathematical algorithm can be used for different scales.
- o To use Raman for amino acids or other metabolites monitoring, there is a need for complex mathematical modeling to determine feeding strategies. In such cases during tech transfers to other facilities a correction factor to the models should be considered.
- o Vendors can help with such modeling efforts

● Use of PAT like Raman and capacitance probes in process development space is deemed beneficial by the companies, as it helps in reducing the time and effort needed in analyzing several samples during upstream development. It also helps in learning the design space of the process in development stage and helps in gathering more data required for better characterization and understanding of the process.
● Flow VPX is used in downstream process development for measuring concentration inline while loading product onto the chromatography column during continuous processing and in UFDF processes during the product recovery stage.
● Raman is being explored to monitor the polysorbate content in the final drug product.
● Inline Multi Attribute Method (MAM), a LC-MS (Bioaccord) fully automated method is used during upstream process development for understanding PTM's including glycosylation

- o Cell culture is sampled, sample is purified (cells removed) and then analyzed by peptide-mapping LC-MS in a fully automated workflow
- o Autosampler fouling is not an issue observed so far in using this technique
- o It's a high throughput tool to get more data in less time
- o There are no plans for moving this to commercial space as it is only used for initial characterization and understanding.
- o For at-scale implementation, there is a potential need for automated data analysis in conjunction with mathematical models or AI, it is for now considered not a worthy investment with the technology available o Data from the PAT tools are being analyzed by data analysts

● With PAT technology the need for Data analyst scientists is increasing and companies have a global organization for data sciences to bring all the groups under one umbrella to share the knowledge around data modeling and designing dashboards
● PAT is mostly used for in process testing only and not for release testing for large molecules, only small molecules use PAT for RTRT
● PAT and single use technologies: Sartorius is doing a good job collaborating with companies for customizing bags as needed, so not a limiting factor for implementing technology at scale.
● Mostly the speed aspect of RTRT for certain assays is not very advantageous, as the rate limiting step for release would be other sterility, mycoplasma or potency-based assays. In certain cases, closing investigations decide batch release. But in certain modalities like cell therapy where volume of sample and turnaround times become critical to operate the next step like VP titer in gene therapies, PAT and RTRT can be very advantageous

- o There was a suggestion to use a PCR based assay for mycoplasma testing to reduce turnaround time
- o Strategically removing some of the testing from DP by leveraging the same tests at DS (or vice versa) would also save time in releasing DS/DP batches quickly

● RTRT can be used for certain tests like visual inspection of particles in the vials as they avoid the need of additional sampling for such testing
● Automation is another need to progress the available PAT technologies to be used effectively like in other manufacturing industries.
● Continuous manufacturing along with PAT (for faster sample analysis and data analysis) would be the ideal state to achieve but there are still a lot of developments needed in the field to get there.
● For PAT/RTRT technologies to be implemented at commercial sites, they should be operable by manufacturing technicians/GMP-trained personnel, e.g., not practical to need mass spec experts on the manufacturing floor.