Table 5: Continued Process Verification: Making Data Driven Decisions

Session 1:

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Session 2:

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SCOPE:

The commercial manufacturing process is defined based on knowledge gained through development and scale-up activities, followed by an evaluation whether the process design is capable of reproducible commercial manufacturing. Subsequently, there should be continual assurance that the process remains in a state of control during commercial manufacture. A process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. A system for detecting unplanned departures from the process as designed is essential. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. The information collected should verify that the quality attributes are being appropriately controlled throughout the process. With the trend towards accelerated development timelines and introduction of continuous manufacturing, continued process verification (CPV) will play an important role. Improved process knowledge gathered during CPV might also suggest ways to improve and/or optimize the process.

QUESTIONS FOR DISCUSSION:

1. How to identify parameters to monitor? Which tools facilitate? What frequency do you evaluate data and update control limits? How do you manage CPV for low volume manufacturing versus high volume manufacturing?
2. Discuss cases when CPV was especially important: Accelerated programs with limited process experience; Traditional PPQ looks good but manufacturing issues post approval; Data trending resulted in understanding of sources of process variability; Regulatory acceptance of reduced PPQ runs coupled with plan for CPV.
3. What is the role of the Pharmaceutical Quality System in managing CPV? At what point should unexpected trends observed in CPV be addressed in the Quality System? When should trends affect disposition of individual batches? What mechanisms can be used to avoid overreacting to such trends before they are fully understood?
4. How can recent advances in information technology (e.g. machine learning be used in conjunction with more traditional data trending rules to improve our understanding?

DISCUSSION NOTES:

Sessions 1 & 2:

Participants' Background: Manufacturing, Technical services, Analytical Development, Regulatory, Process Development, former FDA

Overall: CPV has been implemented by most companies over the last 5 years.

High level notes:

- Companies are setting strategies to deal with both Internal and Contract manufacturing CPV. For contract manufacturing, it be complicated if the quality agreement with the CMO does not adequately address communication on any potential issues identified through CPV.
- Many companies base their CPV program on the PPQ protocols but with a reduced number of parameters.
- Analysis of 20 batches seems to be a reasonable expectation to generate a data set to support statistical analysis and outline risk assessments for reduced testing panels.
- It is critical to ensure that processes are put in place to make sure that the batch data generated is reviewed for scientific integrity. For example, are there any early trends that can be identified even though the process is operating within parameters?
- Real world impacts to CPV: depends on life cycle stage of the product as it can help with life cycle management for small changes of legacy product and it is essential for new products to gain knowledge. And can aid in investigations in reviewing process changes and trends in the bioreactor.
- Raw material variability presents a challenge to the number of lots required for statistically meaningful analysis. Especially with limited numbers of raw material lots. Potentially trends due to raw material variability might be detected before a more severe impact of a material change.
- Raw material impacts on upstream (bioreactor) is an area which is particularly hard to assess as source of variability. CPV may be the best approach to assess these impacts. This is more of a concern with commercial media depending on a proprietary media supplier vs. CMO's own.
- CPV programs including parameter selection do not receive much focus during inspections unless there are problems observed at the facility.

Case study #1: CPV based on full set of PPQ criteria, data assessed, and a subset of that data is chosen for CPV based on a justification

- Strategy: keep narrowing to a smaller and smaller subset of data/criteria to review over time
- Pre-set batch number is not needed to determine what demonstrates CPV
- Continue to track and trend data
- OOT treated in quality system as a deviation

Case Study #2: 3 batch PPQ, 20 batch CPV, the 20 batches are chosen for statistical analysis and to set specifications for 1 lot a year to undergo CPV review with all PPQ criteria. Set action limits for routine monitoring and trend batches.

- Testing panel reduced except for 1 batch per year
- Risk assessment is critical after the CPV batches to defend the reduced testing
- What is the reasonable expectation of batch number? 20, and then statistical process trending controls can be implemented
- Yearly post PPQ study still needs to meet the PPQ acceptance criteria
- Action limits vs PPQ validation criteria: how do you deal with tighter criteria? Control limits are based on CPV which are routinely monitored
- Any CPV/PPQ results outside of the study range need to be investigated as a deviation
- If an investigation yields an intrinsic issue, then PPQ needs to be re-performed.

Learning opportunities and future discussion topics

- When implementing CPV, does the input/output of the study go into 1 report or do we need both reports? Overall, consensus is that both input and output of process characterization need to be documented clearly.
- Legacy products need to start thinking about how to implement CPV.

- Is machine learning starting to be implemented by companies? Yes, starting to be included in some principal component analysis to look at data logistically. Using AI to mine data is being assessed by some companies. Requires maturity of manufacturing with many lots.
- How do you bridge between validation and routine manufacturing? What does the hand-off look like and how is historical knowledge shared?
- Can you use CPV to have reduced PPQ? Likely no, ROW agencies unlikely to accept this as they interpret the guidances directly. For FDA in particular, there may be reluctance to reduce PPQ requirements because of concerns about verifying a company's ability to supply the market especially in oncology. Depends to some degree on a company's track record/experience. Considerations would also include breakthrough status, very compelling clinical data, expected demand for product. (Low demand products present less of a market supply risk than high demand products.) Full package for PPQ continues to be the typical expectation. Continuous manufacturing may be an opportunity for increased leverage of CPV. Hard to do 3 PPQ runs with a 30-day process, could leverage development data and use CPV as part of a process validation strategy. Especially if the scale-up factor from clinical to commercial is low (bigger scale-up factor is more risky). However, implementation of continuous processing is not sufficiently advanced to have a clear idea of what will be feasible.