The Evolution of the Biopharmaceutical Control Strategy through Continued Process Verification

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The conference was built off a case study for continuous process verification (CPV) from BPOG that is available at http://www.biophorum.com/article/103/cpv-continued-process-verification-case-study. The 2-day meeting included numerous presentation related to the case study as well as related examples and ideas. Slides from conference presentations as well as an overall summary slide presentation will be available at http://www.casss.org within a few weeks of the conference close on 21 Jul 2015.

From the BPOG case example:
"CPV is fundamentally a formal means by which commercial manufacturing process is monitored to ensure product quality. It encompasses a written plan for monitoring a licensed biopharmaceutical manufacturing process, as well as regular reporting and actions based on the results of monitoring the process". This approach arises from the concept that "validation is not an event, it's a state" and is consistent with ICH Q10 and the FDA's 2011 Guidance for Process Validation. ICH Q10 states that "Knowledge should be managed from development through the commercial life of the product up to and including product discontinuation".

CPV takes a life-cycle approach to process verification building on development (QbD) as well as what is learned as part of pivotal clinical trials as well as during commercialization. CPV requires a plan and ongoing gathering of process data with the ultimate goal of feedback to either provide assurance of a high level of operation or an indication for a need of action. System flags generated from monitoring can lead to more defined processes of deviations, investigations and CAPA management. Review of this information spans the realm of daily team meetings without a formal report-out, to defined intervals for reviewing data, to the annual product review.

Key components of CPV include specifications, data, monitoring, process understanding and statistical analysis. Monitoring is essential to CPV, usually in the form of some application of SPC (statistical process monitoring). Components of CPV include elements that can be applied to more than just manufacturing processes and during the course of the meeting it was mentioned by presenters and attendees that the principles can be applied to methods, stability studies, environmental monitoring, etc.

Specifications:

Multiple presenters as well as audience members mentioned the need for appropriate specifications (acceptance criteria) that weren't based on process capability. The desire is to build off of QbD and/or customer requirements to establish acceptance criteria with capable processes utilized to produce material in a narrower range than the acceptance criteria range. During the meeting several attendees

emphasized the need for the spec range to be larger than normal process variation. Long-term implementation of this approach also necessarily requires that companies and regulators can't narrow acceptance criteria to observed process capability over time. While the FDA and Health Canada was represented at the meeting the need to implement CPV as part of a world-wide regulatory strategy was comprehended.

The idea of CPV and/or SPC, leading to either wider initial specifications or wider long-term specifications because acceptance criteria wouldn't be narrowed over time led to the question of how CPV would by comprehended in regulatory submissions and quality systems. For example, are target values, alert limits, and action levels included in BLA submissions, potentially becoming requirements? Is a better alternative to include a general approach of CPV and/or SPC Quality System (QS) included in a submission for reviewers with a review of the QS during inspections? The only example provided was by Laura Durno (Health Canada) who indicated that Health Canada found it acceptable for a submission to describe the approach used for CPV/SPC. Left unanswered at the meeting was a consensus on what should be in submissions and how changes to alert target values, alert limits and/or action levels might be communicated to regulators. Avoiding pre-approval of most changes within defined acceptance criteria seemed to be the desire of the majority of attendees.

The data used to support CPV generated much discussion. One case study discussed during the conference indicated the need for 30 plus independent measurements with a normal distribution to establish means and variances for input into SPC – an idea echoed in other presentations and comments. Michael Krause (Baxalta) commented in his presentation that the data is not usually normally distributed unless method variability is larger than process variability and the focus should be on obtaining relevant signal ("events") not statistical ones. Others in the conference mentioned that requiring the large data base to initiate SPC would minimize or prevent application by small biotechs, for certain orphan drugs, and for certain drugs where production was across multiple sites. The difficulty in currently applying the process to CMOs was also mentioned. Some ideas on how to incorporate the advantages of SPC included pooling data across sites or pooling data across products. Examples were provided but these concepts weren't universally accepted by attendees.

Discussion of monitoring data at the conference ranged from system type (manual or automatic), what part of the system needs to be validated or verified (all), what data to collect, and how to set flags for alert limits and action limits. Ideas arranged from collecting all data and conservatively evaluating a large number of flags including when the process was in statistical control to the idea that knowledge of the process should allow a focus on certain parameters with flags being established to balance false alarms with missing the need for action. Speaking to several members of the audience who started implementing SPC there was the acknowledgement that the amount of data can be overwhelming, even with sophisticated software for monitoring, and the generation of a large number of flags requiring evaluation minimized the ability to identify the flag that reflected a process change needing to be addressed. My experience from outside the biopharmaceutical industry was where SPC was rolled out tracking "everything" but the inability to address the information led to knowledge and risk-based application refinement in information tracked as well as targets, alert limits, and action limits.

In summary, the concept of utilizing CPV based on QbD with extensive use of SPC was discussed during this 2-day meeting. Key concepts such as SPC have valuable applications beyond CPV and implementation should not be limited to just high-volume products. It will be interesting to see how CPV application evolves at large companies with high-volume products as well as application of elements of CPV in various industry niches.

This conference summary is not intended to reflect the opinion of the presenters or of the consensus of attendees at the conference.