Quality by Design in Biomanufacturing

Implementing real-time data consolidation, visualization and modeling for improved quality and lower compliance costs.
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Introduction

Recent FDA and ICH guidance has focused on the need to implement quality systems based on real-time data and a deeper understanding of manufacturing process. Quality by Design (QbD) is a manufacturing design philosophy that increases upfront experimentation, and continuous monitoring, to establish a ‘design space’ where the process is in control and good quality product will be produced.

Biopharmaceutical manufacturers have struggled to understand how to value such an investment, and how to use the wealth of data coming from the manufacturing floor to reduce risks and increase product quality.

In this whitepaper we outline an implementation approach for QbD based on reducing compliance burden while iteratively increasing process understanding. Whatever level of design-of-experiment work done as part of late stage process development, continuous quality verification has immediate value to the organization. It links automation systems to the process design and manufacturing process more closely with quality attributes, allowing root cause analysis. The approach allows biomanufacturers to understand the relationships between process parameters and quality attributes, driving a better understanding of the biologic process. And this approach allows shorter (and ultimately real-time) release of product at some stages of the biomanufacturing process; lower reject rates; lower compliance costs; and better process understanding.

Managing Risk in Biomanufacturing

The quality systems in biopharmaceutical manufacturing today are a product of a historical approach to product development where cell growth mechanisms and purification processes were relatively poorly understood. Apparently small changes to the manufacturing process – a 5% adjustment to the speed of the impeller in a bioreactor, for example – had significant impact on final product quality. In such an environment, the focus for engineers and scientists was to create a repeatable process that manufactured consistent product that could then be validated using clinical trials.

Such an approach has been very successful in licensing the first generation of biotherapeutics, but in the last decade there has been a realization that the processes borne from this philosophy are quite rigid and inflexible. Cash-to-cash cycle times (a measure of how long it takes product to move through the supply chain) are 3 times any other industry and dominated by quality release times, which one author notes comprise over 90% of the overall time to produce a batch of material1. This ties up hundreds of millions of dollars in inventory, and more importantly discourages innovation. The approach also discourages a fundamental understanding of the link between quality attributes and process parameters, which can reduce the ability for a biomanufacturer to quickly respond when faced with inevitable adverse events like contamination.

ICH Q8, Q9, and Q10

Quality by Design and ICH Q8, 9 and 10 are guidelines that are designed to better manage risk in the manufacturing process. The objectives of these guidelines are to achieve high quality product on a consistent basis, establish and maintain a state of control, develop effective monitoring of product performance, do statistical process control and capability analyses, and meet the important goal of facilitating continuous improvement.

At the core of these guidelines is the need for increased data to support the biomanufacturing process. In the Figure below we outline the elements of ICH Q8, 9 and 10 overlaid onto the process development and manufacturing process. The top left of the diagram shows the process development process, where a set of unit operations are strung together and evaluated to determine optimal operating ranges. This includes a risk assessment process, a set of initial process parameters and quality
attributes, and a design and operating space for the facility. The bottom right of the diagram shows the manufacturing process, where continuous improvement is used to iteratively focus attention on key risks to the organization and correct them.

This design also includes ‘feedback loops’ (production economics and design lessons boxes) which improve both process design and manufacturing processes in the facility. The Production Economics feedback loop suggests a set of changes to the manufacturing process that can be used to lower failure rates, improve productivity, or focus monitoring efforts based on their economic value to the organization. The Design Lessons loop provides data that allows future processes to properly focus around risk to the organization.

Together, the manufacturing and process improvement cycles provide concrete ways of designing and operating better biopharmaceutical production processes, that deliver on the promise of better quality and lower compliance costs to manufacturers. Central to this effort is the middle box: Collecting and Understanding Process Data in the Facility.

Figure 1: Cycles of process development and manufacturing improvement.
Moving to a Proactive Quality System

Collecting process data seems like a relatively easy thing to do, and something that most biopharmaceutical manufacturers are doing today. However, exploding volumes of data have overwhelmed our ability to visualize and analyze quickly. What is needed is a “Google” for quality data: a means by which experts can focus on the small number of critical process and quality parameters that really matter on the manufacturing floor. Toolsets like Minitab, PI Processbook and others are tools for specialists. They do not provide solutions for biomanufacturing on their own, since they cannot provide the specific data analytics, or massive correlation analysis that is needed. This means that – despite the flood of data available – it is often difficult for biopharmaceutical groups to understand the root cause of deviations or issues, let alone pro-actively build a model of their manufacturing process.

In the Figure above we outline a number of common toolsets and analysis methodologies, plotted against process complexity and variability. Emerson’s experience is that biopharmaceutical organizations are generally in the lower-left quadrant, performing offline analyses in Excel, JMP and other general-purpose toolsets with a limited ability to analyze highly complex processes with variability. Such analysis is generally performed on a case-by-case basis and by highly experienced troubleshooters with specialized statistical training.

Three Steps to QbD

In the following sections we outline three critical elements we believe are important in implementing QbD. These three elements are based on a foundation of risk assessments by SMEs, as well as real-time data capture systems in the organization. These three steps allow organizations to see, and respond to variability in real-time, and to model that variability in complex biomanufacturing systems.
1. Statistical Process Control and Statistical Quality Control

Current FDA guidance suggests that statistical process control / quality control (SPC and SQC) systems are a critical first step to understanding the variability that exists in biotech manufacturing systems. These toolsets provide insights since it is the variation of data from the ideal, or the variability, that we are primarily interested in when looking at understanding and controlling quality.

<table>
<thead>
<tr>
<th>FDA Guidance for Industry, January 2011</th>
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<tbody>
<tr>
<td>1 “Managers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process”</td>
</tr>
<tr>
<td>2 “We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan…”</td>
</tr>
<tr>
<td>3 “We recommend continued monitoring and sampling of process parameters and quality attributes … process variability should be periodically assessed”</td>
</tr>
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SPC and SQC also provide the ability to move the biomanufacturing organization away from using highly trained ‘black belts’ in statistical analysis to troubleshoot problems, to operators closer to the shop floor. SPC has been credited with creating Toyota’s brand as one of the world’s most successful car manufacturers and is used in some form today by nearly every advanced manufacturing organization in the world.

The Figure above shows an X-Bar chart from Emerson’s Crosswalk software with individual points representing measurements for 5 batches, and the colored areas indicating 1, 2 and 3 standard deviations from the sample mean. This highly visual representation allows an operator to see in real time, any ruleset violations. (The colored areas are automatically calculated and are different in meaning from control limits.)
Such SPC and SQC charts provide highly visual feedback mechanisms to detect process drift, process shifts and other variation in data beyond what is considered ‘normal’. It is important that such charts be carefully set up to avoid false positives, i.e. identifying issues where in fact no issue exists.

**SPC for non-stationary processes**

Figure 3 shows statistical process control for a stationary process, such as temperature in a bioreactor, where we aim to meet a particular target and hold at that target. SPC for non-stationary processes must take a different approach. In the Figure below we show an output from Emerson’s Crosswalk software showing a chromatogram, with 6 batches overlaid. The reference, or ‘Golden’ batch is also shown (in this case the median batch). The areas of green yellow and red show deviations from the golden batch, and whether those deviations are significant. Such a graph can be used to indicate how closely the ‘shape’ of a continuous time process matches some reference shape, for example an ideal batch. This is an example of non-classical statistical process control technologies developed by Emerson specifically for the biopharmaceutical community.

![Figure 4: ‘Golden Batch’ measurements for a chromatogram, showing deviation from a reference batch.](image)

**2. Correlate Process Parameters and Quality Outcomes**

Statistical process control is a good means of tracking critical process parameters and quality attributes, but does not on its own allow the identification of critical manufacturing process parameters. What is needed is a means of correlating the hundreds of potential process parameters, with any number of possible quality attributes (or even early indicators of quality).

In the Figure below we show one such simple implementation of this task, again in Emerson’s Crosswalk software. The matrix shows, on the X-axis, the set of process parameters which may affect quality. Down the Y-axis we show the set of quality attributes that may be affected by the process parameters. Each cell in the heat map is the correlation of that process parameter, with the associated quality attributes. Hot-colored cells are areas of high positive or negative correlation; cool colors indicate little or no correlation.
This graph allows engineers to visually see which process parameters are important for which quality attributes. The highlighted process parameters shown in columns 9 and 10 show a high degree of correlation with the quality attributes shown in rows 2 and 3. The highlighted column third from the right indicates that variations in this process parameter have little or no impact on quality – and therefore not a place to invest in process analytic technologies, additional sensors, etc. Such data-informed decision making is an important supplement to risk-based assessments that are done as part of ICH Q9 activities and can help the biomanufacturing organization.

3. A Stochastic Modeling Framework

Finally, we turn to one of the most critical elements of biomanufacturing quality systems: assessing the impact of process variability across different unit operations. Changes in temperature in the bioreactor, for example, may affect titer and therefore downstream purification efficiency. SPC / SQC toolsets, however, do not understand the relationship between unit operations: that fermentation can affect purification, but purification cannot affect fermentation (since it happens at a later time). Such models require both more data, and a more complex modeling framework, than even multi-variate SPC tools at our disposal today.

Emerson’s experience in this area is that a modeling framework is the only way to accurately capture the relationships within detailed processes and between sequential unit operations in a biomanufacturing facility, while allowing quality impacts to be accurately quantified. Multi-variate stochastic process control toolsets like the Real-time Modeling System (pictured on next page) allow users to specify the causal associations between activities in the facility.
Such toolsets have the ability to integrate with data in real time, to incorporate variability (monte-carlo or discrete event simulation analysis) in their formulation and have sophisticated design-of-experiment and optimization functions. Such toolsets are the next generation of biomanufacturing, and are already being used by first-in-class biomanufacturers to improve their manufacturing and quality systems.

Conclusions and Return on Investment

Quality by Design (QbD) is rapidly gaining traction in the biopharmaceutical industry, but implementations of QbD have been hindered by difficulties associated with understanding exactly what is required to implement QbD systems. It is not sufficient to purchase a historian and start tracking data; rather, the task is to gather relevant data and use it to make better decisions. This whitepaper proposes an approach based on SPC, correlation of process parameters and quality attributes, and the implementation of a stochastic modeling environment for more advanced analysis.

The inherent biological variability in current manufacturing systems confounds biomanufacturers’ efforts to apply classical statistical process control (SPC) techniques ad-hoc from other industries. The approach we suggest in this paper – blending classical SPC with more advanced approaches, such as the ‘golden batch’ example for non-stationary processes – is required to avoid false positives and deliver on the promise of increased quality to the consumer, at a lower compliance cost to the manufacturer.

Once such systems are in place they have significant benefits across manufacturing, quality, and process development groups. Biomanufacturers implementing such systems can expect improved productivity, since resources are focused on a small number of key variables. Closer monitoring of this reduced set can justify reduced time batch release, and dramatic decreases (50-80% reduction) in the time to perform root cause investigations.

Finally, a closer understanding of key process parameters and quality outcomes can result in better platform processes in the future, helping the development of robust processes with lower rates of production failures and scrap. Ultimately real-time data consolidation, visualization and modeling can improve quality and lower compliance costs.