Building Blocks of Quality by Design

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This is the first of a monthly series of short commentaries on the use of Quality by Design (QbD) in the pharma and biotech industries. The use of QbD has steadily grown since its introduction around 2005. The growth has not been fast enough for some and perhaps too fast for others. Some of the resistance is due to lack of understanding what QbD is. This is not uncommon for a new idea. QbD is new to pharma and biotech but not new to other industries. This is good news as pharma and biotech can learn from the experience of others. The breadth of application and understanding of QbD has grown since it was first introduced mainly in the chemical industry in the 1950s and 1960s. I learned about QbD in my graduate work at Rutgers University and practiced and enhanced the art and science, first during by 24 year tenure at DuPont and today as a keen focus of my consulting practice and research programs.

It is important to begin these commentaries by answering the question 'What is QbD'; and then discuss the building blocks of QbD. The ICH Q8 (R2) definition is that QbD is a "Systematic approach to product and process development that begins with predefined objectives, emphasizes product and process understanding and process control and is based on sound science and quality risk management (1)." In other words, Quality by Design is about building quality into products and processes, not attempting to inspect quality in at the end on the line.

This definition leads us to the "building blocks" of QbD needed to provide the process and product understanding that is fundamental to the ICH definition of QbD stated above and its effective use (2).

The principle building blocks of QbD are:

- Critical Quality Attributes (CQAs) that are the most important process output measurements linked to patient needs.
- Product specifications that define what a quality product is; a product that meets the stated needs of the patient.
- Critical Process Parameters (CPPs) that encompass the process input (API and excipient), control, and environmental factors that have major effects on the CQAs.
- Raw Materials Factors that include the stability and capability of raw material manufacturing
A Process Model, represented schematically as \( Y = f(X) \), where \( Y \) is the CQA and \( X \) represents the CPPs, provides a quantitative picture of the process based on fundamental and statistical relationships that predict the CQA results.

- **Design Space** that is the combinations of input variables and process parameters that provide assurance of quality product that meets specifications.
- **Process and Measurement Capability** that tracks process performance relative to CQA specifications and provides measurement repeatability and reproducibility regarding CQAs.
- **Process and Measurement Robustness** is the ability of the process and measurement system to perform when faced with uncontrolled variation in process, input, and environmental variables.
- **Process and Measurement Control** includes the use of control procedures, including statistical process control, to hold the process and the measurement system on target and within the desired variation.
- **Failure Modes and Effects Analysis (FMEA)** of the CPPs, including raw material variables, identifies how the process can fail and, after appropriate controls and fixes are in place, the areas of the process that remain at greatest risk of failing.
- **Risk Level** that is a function of the design space, FMEA results, and process and measurement capability, control, and robustness.

Life Cycle management: Continuous improvement and continued process verification as specified in the FDA Process Validation Guidance (3).

These building blocks should not be viewed a list of "to dos" but each as a block of work that is linked together and sequenced over time as shown in the following figure in which the word "process" is used to represent both the manufacturing process and the measurement process. This figure points out an important characteristic of QbD, the sequential nature of the approach. QbD is implemented over time not as a single event. The building blocks are linked together to produce the process understanding needed to get the product approved and launched successfully with the desired performance sustained throughout the product lifecycle.

It is in reduced risk that all of these critical elements converge. As football Hall of Fame quarterback Johnny Unitas said, "There is no risk of an intercepted pass, if you know what you are doing." QbD provides the process understanding that enables you to know what you are doing, resulting in greatly reduced risk. With the ability to determine precisely where the greatest risks and opportunities lie and address, life sciences organizations can realize the many operational, business, and financial benefits that QbD generates, including:

- The ability to design new products and processes and bring them to fruition faster, with fewer setbacks
at critical stages such as scale-up, validation, and transfer
- Processes performing on target and within specs at minimum cost with fewer defective batches and fewer deviations over the product lifecycle
- Greater flexibility in process operation
- Greater regulatory flexibility based on a science-based approach to risk management
- Working within the design space provides the ability to continue to optimize and improve the manufacturing operation without facing additional regulatory filings or scrutiny
- Faster time to market and reduced rework, resulting in reduced costs and increased revenues.

QbD is generally viewed as an activity of product and process development. Next month I will discuss how QbD is also useful in improving existing processes and products. Instead of incrementally improving unit operations that, in isolation, may have little effect on overall process performance or quality, manufacturers can adopt a holistic approach to QbD that is applicable at every stage of the product lifecycle (4). When combined with sound deployment methodologies, improvement management systems, and appropriated infrastructure, QbD dispels misconceptions with the most convincing corrective of all – a sustainable, significant increase in value (5).

I'm very much interested in receiving your comments and questions regarding QbD. Your input will be very useful in identifying future commentaries.

REFERENCES


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