IMPLEMENTING QUALITY BY DESIGN:

ASSESSMENTS, DELIVERABLES, AND CONSIDERATIONS

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The quality by design (QbD) concept is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management [ICH Q8 (R2)].

With QbD, quality is controlled not by simply testing the product but rather by building quality into the manufacturing process by design. Biopharma and life sciences organizations can achieve this by creating a control strategy based on product and process understanding.

QbD is a process that requires a large amount of forethought, planning, and analysis. While that may deter some, the advantages of leveraging such a powerful concept are worth the initial work.

In this white paper, you will learn:

- Which deliverables and assessments you must execute during stage one of the process validation lifecycle to implement QbD
- Considerations to make while implementing QbD
- The many advantages of QbD

Implementing QbD During Stage One of the Process Validation Lifecycle

QbD implementation is facilitated in Stage 1 (Process Design) of the Process Validation Lifecycle.

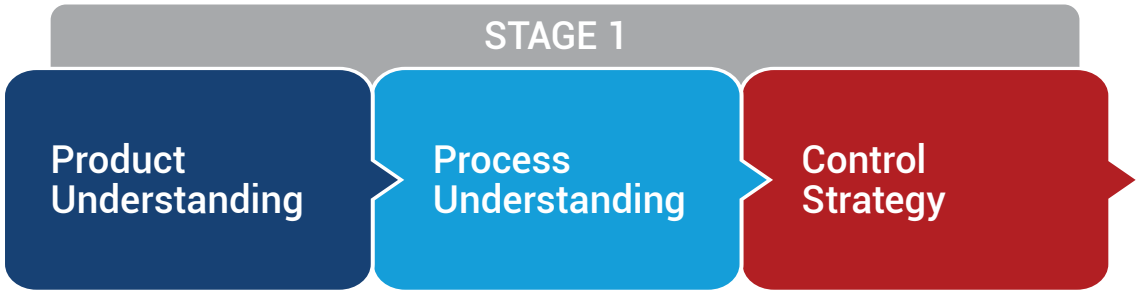

Figure 1: This figure outlines the three phases of stage one of the process validation lifecycle: product understanding, process understanding, and control strategy.

As an organization moves through each section of stage 1 (product understanding, process understanding, and control strategy), they must meet the multiple risk assessments and deliverables outlined in this workflow to develop a robust process and analytical control strategy.

Before making any steps toward QbD implementation, it's critical to understand each assessment and deliverable your organization will need to achieve along the way, as seen in Figure 2.

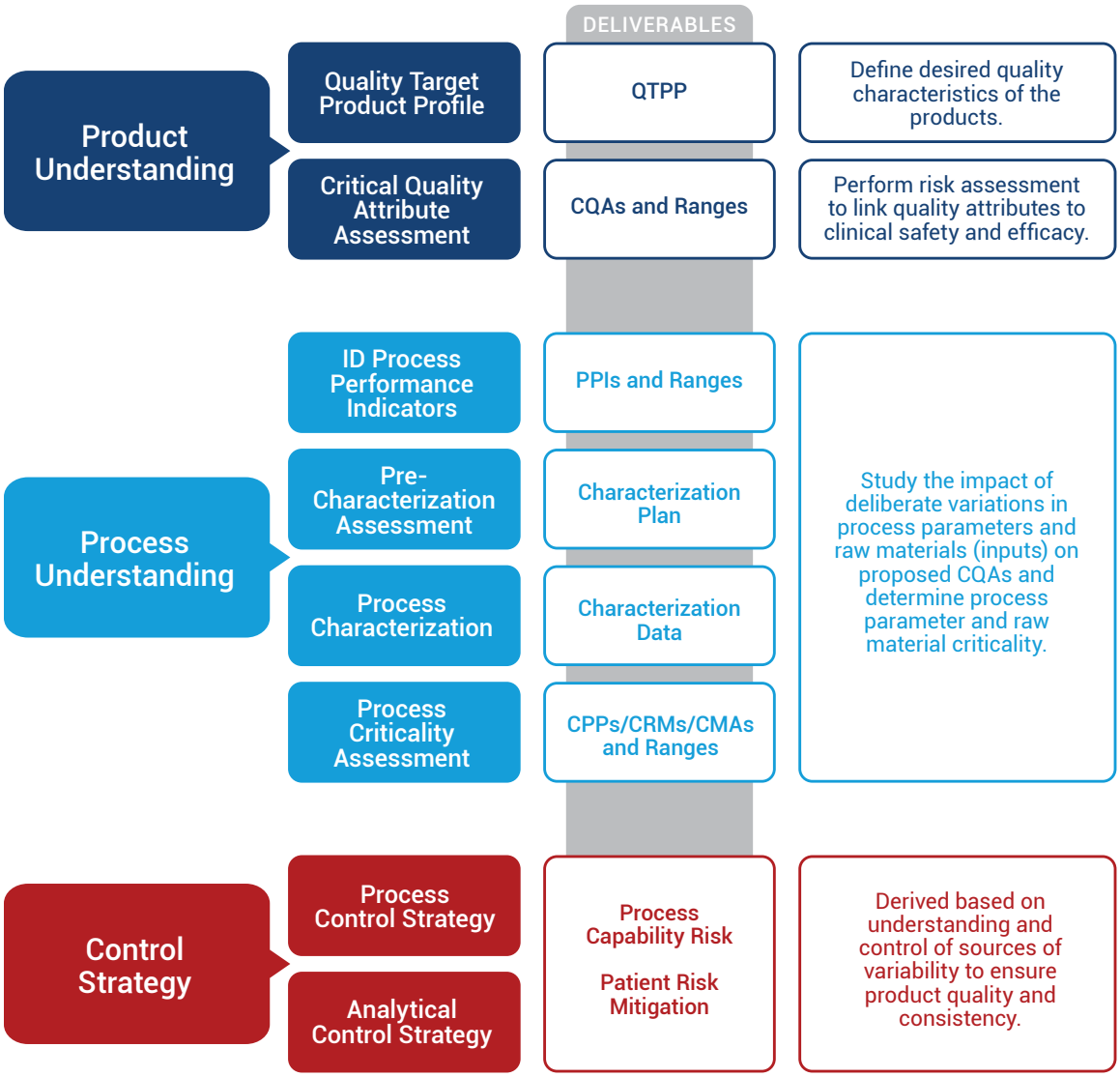

Figure 2: This figure outlines the various assessments and deliverables needed for each phase of stage one of the process validation lifecycle.

PRODUCT UNDERSTANDING

Quality Target Product Profile

As defined in ICHQ8(R2), the quality target product profile (QTTP) is a prospective summary of quality characteristics of a drug product that organizations will ideally achieve to ensure desired quality, taking into account the safety and efficacy of the drug product. It forms the basis of design for the development of a product.

There are many considerations a pharmaceutical organization should make when creating its QTTP, such as:

- Intended use in a clinical setting, route of administration, dosage form, delivery systems
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery
- Attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form
- Drug product quality criteria (e.g., sterility, purity, stability, drug release) appropriate for the intended marketed product

Defining and documenting QTPP early in the lifecycle of clinical development of the product is highly recommended.

Critical Quality Attribute Assessment

Critical quality attributes (CQAs) are physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality [ICH Q8 (R2)].

The first step to creating a CQA assessment is to create a quality attribute (QA) list. Organizations can establish these lists based on knowledge from product research reports, preclinical research reports from animal studies, human clinical studies, and relevant scientific literature and publications.

Then, CQV professionals will measure QAs using analytical assays. It's important to note that there is not necessarily a one-to-one correspondence between a QA and an analytical assay. Some may use multiple assays to measure a single QA; conversely, a single assay may measure multiple QAs.

Organizations can classify QAs according to:

- Structure and variants
- Product-related degradants and impurities
- Manufacturing process-related impurities
- Drug product related
- Adventitious agents
- Container closure
- Diluents

Different product modalities may not have QAs in all categories. Or, organizations may need additional categories and should define them based on a particular product modality.

Another essential aspect of CQA assessment is classifying QAs as either CQA or non-CQA based on two aspects.

The first aspect is the potential severity of the impact of a QA on the safety, potency/efficacy, and pharmacokinetics of the final product. A CQV professional will assign a QA a severity score based on different criteria. Depending on its score, it will fall into one of four levels: negligible, minor, moderate, or major.

Level	Guidance on Definition
Major	Potentially serious impact to a patient that results in death, a permanent impairment, or a life-threatening injury. There is a direct link between the potency/efficacy and these impacts. A minor change in QA would significantly impact potency, efficacy, and pharmacokinetics.
Moderate	Moderate impact on a patient that results in adverse event(s) that require professional medical intervention, but it is reversible. There is a moderate link between these results and the potency, efficacy, and/or pharmacokinetics.
Minor	Low impact on patients that results in temporary inconvenience or impairment.
Negligible	No patient harm.

Figure 3: Example quality attribute severity score definitions, ranging from negligible to major.

The second aspect is the uncertainty associated with each severity rating. If the uncertainty is low and the level of confidence is high, that indicates that there are scientifically sound data points for a specific product. If the uncertainty score is moderate and the level of confidence is medium, there may be some legitimate data, but knowledge may be experience-based. Lastly, if the uncertainty score is high and the level of confidence is low, there may be no sound data for referencing.

Once a team defines its CQAs, they are considered equally critical for defining a control strategy. Initiating CQAs and initial acceptance criteria early in the development process is imperative as they enable the development of assays and process understanding.

PROCESS UNDERSTANDING

Process Performance Indicators

Process performance indicators (PPIs) are measurable outputs or characteristics to verify that a process consistently performs as expected.

Pharma companies should identify PPIs during process development based on platform experience and understanding. They can monitor PPIs during routine manufacturing.

PPIs are not classified; however, organizations can define different types of limits for PPIs, such as acceptance criteria and action limits.

It's important to note that PPIs are indicators of process performance in addition to CQAs.

Pre-Characterization Assessment and Process Characterization

The goal of pre-characterization assessment (PCA) is to identify process parameters (PPs), material attributes (MAs), and raw materials (RMs) with potential impact on CQAs and/or PPIs, to determine which may be further evaluated during process characterization studies.

Pharma organizations identify PPs by analyzing manufacturing batch records, development batch records, process descriptions, or similar documentation. Examples of PPs include temperature, pressure, and flow rate.

Next, they can create an initial list of raw materials using similar documentation to those used to identify PPs: manufacturing batch records, development batch records, process descriptions, and a bill of materials. An organization should perform a raw material pre-selection assessment to select which raw materials they need to include as part of the PCA.

During the raw material pre-selection assessment, teams should ask these questions to determine if they need to evaluate a raw material during PCA:

- Does the raw material have animal-derived inputs?
- Does the raw material have the potential to impact CQAs or PPIs?

Then, companies can identify MAs using the certificate of analysis (COA) of each raw material and excipient used in the manufacturing process.

Another critical step in the PCA is determining the assessment range, normal operating range (NOR), and proven acceptable range (PAR).

An assessment range is wider than the NOR. Organizations should choose their assessment range based on platform understanding of similar process parameters, understanding of manufacturing equipment, and the desired design space.

This range is the basis for selecting characterization ranges, and teams should perform the recommended process characterization studies for process parameters and material attributes over this range.

The general guidance is that, if possible, the assessment range should land between 1.5-2.0 times the NOR.

Range	Definition
Normal Operating Range (NOR)	A defined range within (or equal to) the proven acceptable range (PAR) specified in manufacturing instructions as the target and range at which a process parameter is controlled, while producing unit operation material or final product meeting release criteria.
Proven Acceptable Range (PAR)	A characterized range of a process parameter (or a material attribute) that, while keeping other parameters constant, will produce a material meeting relevant quality criteria.

Then, for a given unit operation, a team will assess each PP, RM, and MA for its potential impact on each relevant CQA and PPI. These assessments build the foundation for characterization studies and plans.

Characterization studies and plans use the estimated impact of PPs, RMs, and MAs on CQAs and PPIs and gather data to inform the process critically assessment.

Process Criticality Assessment

The goal of process criticality assessment (PrCA) is to classify PPs, RMs, and MAs as critical or non-critical.

CQV professionals classify PPs, RMs, and MAs based on data gleaned from process characterization studies, pilot scale runs, experiments for supporting deviations and investigations, and at-scale engineering or clinical supply runs along with any process excursion data.

Then, they can classify them based on the extent of the observed impact on CQAs due to variation within the characterization range.

CONTROL STRATEGY

Process Control Strategy

ICHQ10 defines a control strategy as a planned set of controls derived from current product and process understanding that assures process performance and quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

The process control strategy (PCS) is the heart of QbD. The primary goal of a PCS is to minimize the risk of CQAs and PPIs going out of acceptable ranges based on variations in PPs and RMs.

Organizations can avoid this by determining the process capability risk.

Determining process capability risk includes:

- PPs, RMs, and MAs that have an impact on CQAs and PPIs (from PrCA)
- Relationship of Proven Acceptable Range (PAR) and Normal Operating Range (NOR)
- Controls commensurate with the extent of impact and design space such as alarms, automation, batch record, raw material testing

These elements enable organizations to predict process capability risk, also known as lot rejection risk, at commercialization.

Analytical Control Strategy

Once the process control strategy is finished, teams can create an analytical control strategy (ACS) for all CQAs and PPIs.

An ACS has three main goals. The first is to mitigate patient risk by analytical testing based on any residual risk due to suboptimal process capability scores for CQAs from PCS. For example, an analytical test at product release can identify if a CQA is out of acceptable range before patient exposure.

The second goal is to meet established regulatory requirements. For example, if a CQA is related to the product's safety, it must be tested.

The third goal is to mitigate process performance risk posed by any residual risk caused by suboptimal process capability risk scores for PPIs from the PCS assessment.

Advantages of QbD

1. Continuous Improvement

Continuous improvement is a core focus of QbD. Through this approach, you gain a deeper understanding of your product as it moves through its lifecycle, making it much easier to spot areas of concern.

Once you identify aspects that need improvement, you can adapt your techniques to create a safer product and more efficient manufacturing process. The QbD approach allows for ongoing fine-tuning of your operations, even when scaling up from the lab to commercial manufacturing.

2. Consistency

Using QbD helps companies achieve greater batch-to-batch consistency. Maintaining this type of consistency leads to desirable outcomes not only from regulatory bodies but also from consumers.

Regulators will gain more confidence in you, which may reduce the intensity of their oversight. Consistency also helps companies maintain a high level of pharma manufacturing operational readiness.

From the consumers' end, they will experience fewer or no recalls, resulting in increased trust and credibility.

3. Reduced Controls

The QbD approach builds quality into the manufacturing process by design, reducing the need for controls.

Because of this, developers have a good idea of quality even prior to testing. In the end, this can save companies time and money.

4. Failure Prevention

The QbD approach sets manufacturing teams up for success by providing a clear and comprehensive understanding of the parameters involved in the development process and how they work together. This deep understanding helps teams assess risk and act accordingly—significantly reducing the likelihood of failure.

Achieving QbD

Considering the various assessments and deliverables required for QbD, it's safe to say it's not an overnight process—it's an iterative process that takes time and resources. However, the benefits of building quality into every aspect of your processes far outweigh any upfront efforts.

Implementing QbD means assessing and considering virtually every detail of your product's lifecycle, which may seem overwhelming, but it doesn't have to be. Biopharma and life sciences companies can partner with CQV firms that will walk your organization through every step of the process.

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