QUALITY BY DESIGN (QbD)

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WHAT IS QUALITY BY DESIGN (QBD)?

- Quality by Design is a concept first outlined by Joseph M. Juran in various publications. He supposed that quality could be planned. The concept of QBD was mention in ICH Q8 guidelines, which states that, “To identify quality can not be tested in products, i.e. Quality should be built in to product by design.”
- Quality by Design (QbD) is a strategic approach employed in various industries, including pharmaceuticals, manufacturing, and product development, to ensure the consistent delivery of high-quality products.
- It involves a systematic and proactive process of integrating quality considerations throughout the entire product lifecycle, from conception to production.
- Over the years, pharmaceutical QbD has evolved with the issuance of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System)

WHY QbD?

- It enables manufacturers to better understand their processes, reduce variability, and mitigate risks.
- By integrating quality into the product development and manufacturing phases, potential quality issues can be identified and addressed early on, reducing the likelihood of post-production problems.
- Additionally, QbD facilitates continuous improvement by providing a framework for ongoing process optimization and innovation.

PRINCIPLE

- Quality by Design focuses on optimizing the development, manufacturing, and control processes of drugs to enhance their safety, efficacy, and overall quality. It requires a deep understanding of the product's critical quality attributes (CQAs), which are the measurable characteristics that determine its performance, and the critical process parameters (CPPs), which are the variables affecting the manufacturing process.
- The core principle of Quality by Design is to identify and understand the relationships between the product's CQAs and the CPPs that influence them. This knowledge is gained through a combination of scientific experimentation, risk assessment, and statistical analysis. By thoroughly studying these relationships, manufacturers can establish a design space within which the product can consistently meet the desired quality standards.
- The design space defines the range of CPPs that ensure the product's CQAs are within acceptable limits. It provides flexibility for process optimization while maintaining the required quality attributes. Within this design space, manufacturers can establish appropriate process controls, monitoring techniques, and quality assurance systems to ensure consistency and predictability in product performance.

OBJECTIVES

To achieve meaningful product quality specifications that are based on clinical performance

To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control

To increase product development and manufacturing efficiencies

To enhance root cause analysis and post approval change management

ELEMENTS OF PHARMACEUTICAL QUALITY BY DESIGN

A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product

Product design and understanding including the identification of critical material attributes (CMAs)

Process design and understanding including the identification of critical process parameters (CPPs)

Design space

A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process

QUALITY TARGET PRODUCT PROFILE

- QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP forms the basis of design for the development of the product.

- Considerations for inclusion in the QTPP could include the following:

✓ Intended use in a clinical setting, route of administration, dosage form, and delivery system(s)

✓ Dosage strength(s)

✓ Container closure system

✓ Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (*e.g.*, dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed

✓ Drug product quality criteria (*e.g.*, sterility, purity, stability, and drug release) appropriate for the intended marketed product

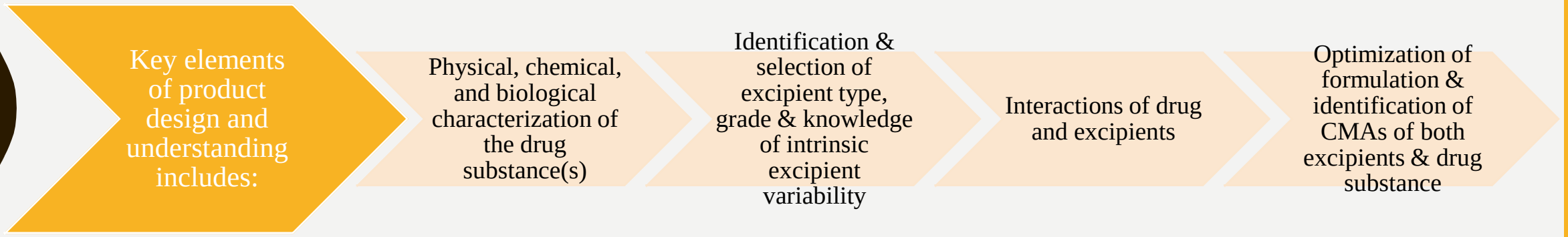
CRITICAL QUALITY ATTRIBUTES

- Identification of the CQAs of the drug product is the next step in drug product development.
- A CQA is a physical, chemical, biological, or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits, and physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical.
- Criticality of an attribute is primarily based upon the severity of harm to the patient should the product fall outside the acceptable range for that attribute.
- Probability of occurrence, detectability, or controllability does not impact criticality of an attribute.

PRODUCT DESIGN AND UNDERSTANDING

- Over the years, QbD's focus has been on the process design, understanding, and control, as discussed in the ICH Q8 (R2) guidance. It should be emphasized that product design, understanding, and control are equally important. Product design determines whether the product is able to meet patients' needs, which is confirmed with clinical studies. Product design also determines whether the product is able to maintain its performance through its shelf life, which is confirmed with stability studies. This type of product understanding could have prevented some historical stability failures.

- The key objective of product design and understanding is to develop a robust product that can deliver the desired QTPP over the product shelf life. Product design is open-ended and may allow for many design pathways.



PROCESS DESIGN AND UNDERSTANDING

- Process parameters are referred to as the input operating parameters (*e.g.*, speed and flow rate) or process state variables (*e.g.*, temperature and pressure) of a process step or unit operation.

- A process parameter is critical when its variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

PROCESS DESIGN AND UNDERSTANDING

Steps to establish process understanding are very similar to those of product understanding and include the following:

- Identify all possible known process parameters that could impact the performance of the process
- Use risk assessment and scientific knowledge to identify potentially high-risk parameters
- Establish levels or ranges of these potentially high-risk parameters
- Design and conduct experiments, using DoE when appropriate
- Analyze the experimental data and, when possible, determine scalability and apply first principle models to determine if a process parameter is critical.
- Develop a control strategy. For critical parameters, define acceptable ranges. For noncritical parameters, the acceptable range is the range investigated. When more than one process parameter or material attribute is involved, these defined acceptable ranges may be termed process design space

DESIGN SPACE

- ICH Q8 (R2) defines design space as the multidimensional combination and interaction of input variables (*e.g.*, material attributes) and process parameters that have been demonstrated to provide assurance of quality.

- Parameter movements that occur within the design space are not subjected to regulatory notification.

- However, movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

- Design space is proposed by the applicant and is subject to regulatory assessment and approval.

CONTROL STRATEGY

Control strategy as a planned set of controls, derived from current product and process understanding that ensures process performance and product 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.

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (*e.g.*, drug substance, excipient, in process material, and primary packaging material) based on an understanding of their impact on processability or product quality
- Product specification(s)
- Controls for unit operations that have an impact on downstream processing or product quality (*e.g.*, the impact of drying on degradation and particle size distribution of the granulate on dissolution)
- In-process or real-time release testing in lieu of end-product testing (*e.g.*, measurement and control of CQAs during processing)
- A monitoring program (*e.g.*, full product testing at regular intervals) for verifying multivariate prediction models

CONTINUAL IMPROVEMENT

Continuous improvement is a set of activities that the applicant carries out in order to enhance its ability to meet requirements.

- Continual improvements typically have five phases as follows:
- Define the problem and the project goals, specifically
- Measure key aspects of the current process and collect relevant data
- Analyze the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of the defect if any.
- Improve or optimize the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Control the future state process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

DESIGN TOOLS

Prior Knowledge

Risk Assessment

Mechanistic Model, Design of Experiments, and Data Analysis

Process Analytical Technology

PRIOR KNOWLEDGE

- The term “prior knowledge” has been extensively used in workshops, seminars, and presentations. In regulatory submissions, applicants often attempt to use prior knowledge as a “legitimate” reason for substitution of scientific justifications or conducting necessary scientific studies.

- Knowledge may be defined as a familiarity with someone or something, which can include information, facts, descriptions, and/or skills acquired through experience or education. The word “prior” in the term “prior knowledge” not only means “previous,” but also associates with ownership and confidentiality, not available to the public.

- Prior knowledge can only be obtained through experience, not education.

- Prior knowledge in the QbD framework generally refers to knowledge that stems from previous experience that is not in publically available literature.

- Prior knowledge may be the proprietary information, understanding, or skill that applicants acquire through previous studies.

RISK ASSESSMENT

- The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development. However, the risk assessment tools identified in ICH Q9 are applicable to risk assessment in product development also.

- The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product. It helps to prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which facilitates the establishment of a control strategy. The outcome of the risk assessment is to identify the variables to be experimentally investigated.

RISK ASSESSMENT

ICH Q9 provides a non exhaustive list of common risk assessment tools as follows:

- Basic risk management facilitation methods (flowcharts, check sheets, *etc*.)
- Fault tree analysis
- Risk ranking and filtering
- Preliminary hazard analysis
- Hazard analysis and critical control points
- Failure mode effects analysis
- Failure mode, effects, and criticality analysis
- Hazard operability analysis
- Supporting statistical tools

DESIGN OF EXPERIMENTS

- DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a prespecified design. The DoE also reveals relationships between input factors and output responses. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a predefined output are then assessed.

- The strength of DoE is the ability to properly uncover how factors jointly affect the output responses. DoE also allows us to quantify the interaction terms of the variables. DoE is important as a formal way of maximizing information gained while minimizing the resources required. DoE studies may be integrated with mechanism-based studies to maximize product and process understanding.

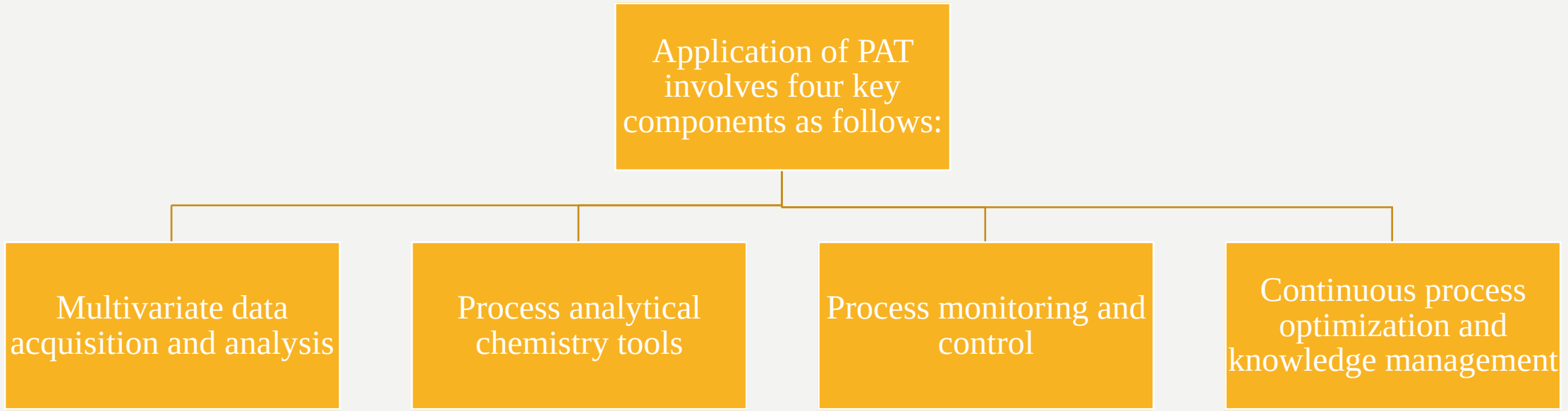
- When DoE is applied to formulation or process development, input variables include the material attributes (*e.g.*, particle size) of raw material or excipients and process parameters (*e.g.*, press speed or spray rate), while outputs are the critical quality attributes of the in-process materials or final drug product (*e.g.*, blend uniformity, particle size or particle size distribution of the granules, tablet assay, content uniformity, or drug release).

- DoE can help identify optimal conditions, CMAs, CPPs, and, ultimately, the design space.

PROCESS ANALYTICAL TECHNOLOGY

- ICH Q8 (R2) identifies the use of PAT to ensure that the process remains within an established design space.
- PAT can provide continuous monitoring of CPPs, CMAs, or CQAs to make go/no go decisions and to demonstrate that the process is maintained in the design space.
- In-process testing, CMAs, or CQAs can also be measured online or inline with PAT.
- Both of these applications of PAT are more effective at detecting failures than end-product testing alone.
- In a more robust process, PAT can enable active control of CMAs and/or CPPs, and timely adjustment of the operating parameters if a variation in the environment or input materials that would adversely impact the drug product quality is detected.

PROCESS ANALYTICAL TECHNOLOGY



THANK YOU!!!