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Review Article

Understanding Pharmaceutical Quality by Design

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Abstract. This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: (1) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; (2) product design and understanding including identification of critical material attributes (CMAs); (3) process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; (4) 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; and (5) process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and drug application review.

KEY WORDS: control strategy; critical quality attributes; pharmaceutical quality by design; process understanding; product understanding.

INTRODUCTION

Quality by design (QbD) is a concept first developed by the quality pioneer Dr. Joseph M. Juran (1). Dr. Juran believed that quality should be designed into a product, and that most quality crises and problems relate to the way in which a product was designed in the first place. Woodcock (2) defined a high-quality drug product as a product free of contamination and reliably delivering the therapeutic benefit promised in the label to the consumer. The US Food and Drug Administration (FDA) encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing, and regulation. FDA's emphasis on QbD began with the recognition that increased testing does not necessarily improve product quality. Quality must be built into the product.

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) (3–5). In addition, the ICH Q1WG on Q8, Q9, and Q10 Questions and Answers; the ICH Q8/Q9/Q10 Points to Consider document; and ICH Q11 (Development and Manufacture of Drug Substance) have been issued, as have the conclusions of FDA-EMA's parallel assessment of Quality-By-Design elements of marketing applications (6–9). These documents provide high level directions with respect to the scope and definition of QbD as it applies to the pharmaceutical industry.

Nonetheless, many implementation details are not discussed in these guidances or documents. There is confusion among industry scientists, academicians, and regulators despite recent publications (10–13). This paper is intended to describe the objectives of pharmaceutical QbD, detail its concept and elements, and explain implementation tools and studies.

PHARMACEUTICAL QUALITY BY DESIGN OBJECTIVES

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management (3). The goals of pharmaceutical QbD may include the following:

1. To achieve meaningful product quality specifications that are based on clinical performance
2. To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control
3. To increase product development and manufacturing efficiencies
4. To enhance root cause analysis and postapproval change management

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Under QbD, these goals can often be achieved by linking product quality to the desired clinical performance and then designing a robust formulation and manufacturing process to consistently deliver the desired product quality.

Since the initiation of pharmaceutical QbD, the FDA has made significant progress in achieving the first objective: performance-based quality specifications. Some examples of FDA policies include tablet scoring and bead sizes in capsules labeled for sprinkle (14,15). The recent FDA discussions on the assayed potency limits for narrow therapeutic index drugs and physical attributes of generic drug products reflect this trend (16). Nonetheless, it should be recognized that ICH documents (3–9) did not explicitly acknowledge clinical performance-based specifications as a QbD goal, although this was recognized in a recent scientific paper (10).

The second objective of pharmaceutical QbD is to increase process capability and reduce product variability that often leads to product defects, rejections, and recalls. Achieving this objective requires robustly designed product and process. In addition, an improved product and process understanding can facilitate the identification and control of factors influencing the drug product quality. After regulatory approval, effort should continue to improve the process to reduce product variability, defects, rejections, and recalls.

QbD uses a systematic approach to product design and development. As such, it enhances development capability, speed, and formulation design. Furthermore, it transfers resources from a downstream corrective mode to an upstream proactive mode. It enhances the manufacturer's ability to identify the root causes of manufacturing failures. Hence, increasing product development and manufacturing efficiencies is the third objective of pharmaceutical QbD.

The final objective of QbD is to enhance root cause analysis and postapproval change management. Without good product and process understanding, the ability to efficiently scale-up and conduct root cause analysis is limited and requires the generation of additional data sets on the proposed larger scale. FDA's change guidances (17,18) provide a framework for postapproval changes. Recently, the FDA issued a guidance intended to reduce the regulatory filing requirements for specific low-risk chemistry, manufacturing, and control (CMC) postapproval manufacturing changes (19).

ELEMENTS OF PHARMACEUTICAL QUALITY BY DESIGN

In a pharmaceutical QbD approach to product development, an applicant identifies characteristics that are critical to quality from the patient's perspective, translates them into the drug product critical quality attributes (CQAs), and establishes the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product with such CQAs to the patient. QbD consists of the following elements:

1. A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product
2. Product design and understanding including the identification of critical material attributes (CMAs)
3. Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs
4. 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
5. Process capability and continual improvement

Quality Target Product Profile that Identifies the Critical Quality Attributes of the Drug Product

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 (3):

- 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

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 (3). 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.

It seems obvious that a new product should be adequately defined before any development work commences. However, over the years, the value of predefining the target characteristics of the drug product is often underestimated. Consequently, the lack of a well-defined QTPP has resulted in wasted time and valuable resources. A recent paper by Raw

et al. (12) illustrates the significance of defining the correct QTPP before conducting any development. Also, QbD examples exemplify the identification and use of QTPPs (20–22).

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 (3). 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. Key elements of product design and understanding include the following:

- Physical, chemical, and biological characterization of the drug substance(s)
- Identification and selection of excipient type and grade, and knowledge of intrinsic excipient variability
- Interactions of drug and excipients
- Optimization of formulation and identification of CMAs of both excipients and drug substance

To design and develop a robust drug product that has the intended CQAs, a product development scientist must give serious consideration to the physical, chemical, and biological properties of the drug substance. Physical properties include physical description (particle size distribution and particle morphology), polymorphism and form transformation, aqueous solubility as a function of pH, intrinsic dissolution rate, hygroscopicity, and melting point(s). Pharmaceutical solid polymorphism, for example, has received much attention recently since it can impact solubility, dissolution, stability, and manufacturability. Chemical properties include pKa, chemical stability in solid state and in solution, as well as photolytic and oxidative stability. Biological properties include partition coefficient, membrane permeability, and bioavailability.

Pharmaceutical excipients are components of a drug product other than the active pharmaceutical ingredient. Excipients can (1) aid in the processing of the dosage form during its manufacture; (2) protect, support, or enhance stability, bioavailability, or patient acceptability; (3) assist in product identification; or (4) enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use (23). They are classified by the functions they perform in a pharmaceutical dosage form. Among 42 functional excipient categories listed in USP/NF (24), commonly used excipients include binders, disintegrants, fillers (diluents), lubricants, glidants (flow enhancers), compression aids, colors, sweeteners, preservatives, suspending/dispersing agents, pH modifiers/buffers, tonicity agents, film formers/coatings, flavors, and printing inks. The FDA's inactive ingredients database (25) lists the safety limits of excipients based on prior use in FDA-approved drug products.

It is well recognized that excipients can be a major source of variability. Despite the fact that excipients can alter the stability, manufacturability, and bioavailability of drug products, the general principles of excipient selection are not well-defined, and excipients are often selected *ad hoc* without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 (R2) recommends drug-excipient compatibility studies to facilitate the early prediction of compatibility (3). Systematic drug-excipient compatibility studies offer several advantages as follows: minimizing unexpected stability failures which usually lead to increased development time and cost, maximizing the stability of a formulation and hence the shelf life of the drug product, and enhancing the understanding of drug-excipient interactions that can help with root cause analysis should stability problems occur.

Formulation optimization studies are essential in developing a robust formulation that is not on the edge of failure. Without optimization studies, a formulation is more likely to be high risk because it is unknown whether any changes in the formulation itself or in the raw material properties would significantly impact the quality and performance of the drug product, as shown in recent examples (26,27). Formulation optimization studies provide important information on the following:

- Robustness of the formulation including establishing functional relationships between CQAs and CMAs
- Identification of CMAs of drug substance, excipients, and in-process materials
- Development of control strategies for drug substance and excipients

In a QbD approach, it is not the number of optimization studies conducted but rather the relevance of the studies and the utility of the knowledge gained for designing a quality drug product that is paramount. As such, the QbD does not equal design of experiments (DoE), but the latter could be an important component of QbD.

Drug substance, excipients, and in-process materials may have many CMAs. A CMA is a physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of that drug substance, excipient, or in-process material. For the purpose of this paper, CMAs are considered different from CQAs in that CQAs are for output materials including product intermediates and finished drug product while CMAs are for input materials including drug substance and excipients. The CQA of an intermediate may become a CMA of that same intermediate for a downstream manufacturing step.

Since there are many attributes of the drug substance and excipients that could potentially impact the CQAs of the intermediates and finished drug product, it is unrealistic that a formulation scientist investigate all the identified material attributes during the formulation optimization studies. Therefore, a risk assessment would be valuable in prioritizing which material attributes warrant further study. The assessment should leverage common scientific knowledge and the formulator's expertise. A material attribute is critical when a realistic change in that material attribute can have a

Table I. Typical Input Material Attributes, Process Parameters, and Quality Attributes of Pharmaceutical Unit Operations

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
	Blending/mixing	
• Particle size • Particle size distribution • Fines/oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Moisture content	• Type and geometry of mixer • Mixer load level • Order of addition • Number of revolutions (time and speed) • Agitating bar (on/off pattern) • Discharge method • Holding time • Environment temperature and RH	• Blend uniformity • Potency • Particle size • Particle size distribution • Bulk/tapped/true density • Moisture content • Flow properties • Cohesive/adhesive properties • Powder segregation • Electrostatic properties
	Size reduction/comminution	
• Particle/granule size • Particle/granule size distribution • Fines • Particle/granule shape • Bulk/tapped/true density • Adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content • Granule porosity/density	Ribbon milling • Ribbon dimensions • Ribbon density • Ribbon porosity/solid fraction Impact/cutting/screening mills • Mill type • Speed • Blade configuration, type, orientation • Screen size and type • Feeding rate Fluid energy mill • Number of grinding nozzles • Feed rate • Nozzle pressure • Classifier Granule/ribbon milling • Mill type • Speed • Blade configuration, type, orientation • Screen size and type • Feeding rate	• Particle/granule size • Particle/granule size distribution • Particle/granule shape • Particle/granule shape factor (*e.g.*, aspect ratio) • Particle/granule density/Porosity • Bulk/tapped/true density • Flow properties • API polymorphic form • API crystalline morphology • Cohesive/adhesive properties • Electrostatic properties • Hardness/Plasticity • Viscoelasticity • Brittleness • Elasticity
	Wet granulation	
• Particle size distribution • Fines/Oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content	High/low shear granulation • Type of granulator (High/low shear, top/bottom drive) • Fill level • Pregranulation mix time • Granulating liquid or solvent quantity • Impeller speed, tip speed, configuration, location, power consumption/torque • Chopper speed, configuration, location, power consumption • Spray nozzle type and location • Method of binder excipient addition (dry/wet) • Method of granulating liquid addition (spray or pump) • granulating liquid temperature • granulating liquid addition rate and time • Wet massing time (post-granulation mix time) • Bowl temperature(jacket temperature) • Product temperature • Post mixing time • Pump Type: Peristaltic, Gear type • Granulating liquid vessel (*e.g.*, pressurized, heated) Fluid bed granulation • Type of fluid bed • Inlet air distribution plate • Spray nozzle (tip size, type/quantity/ pattern/configuration/position) • Filter type and orifice size	• Endpoint measurement (*e.g.*, power consumption, torque, *etc.*) • Blend uniformity • Potency • Flow • Moisture content • Particle size and distribution • Granule size and distribution • Granule strength and uniformity • Bulk/tapped/true density • API polymorphic form • Cohesive/adhesive properties • Electrostatic properties • Granule brittleness • Granule elasticity • Solid form/polymorph

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
	• Fill level • Bottom screen size and type • Preheating temperature/time • Method of binder excipient addition (dry/wet) • Granulating liquid temperature • Granulating liquid quantity • Granulating liquid concentration/viscosity • Granulating liquid holding time • Granulating liquid delivery method • Granulating liquid spray rate • Inlet air, volume, temperature, dew point • Atomization air pressure • Product and filter pressure differentials • Product temperature • Exhaust air temperature, flow • Filter shaking interval and duration	
	Drying	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture content	Fluidized bed • Inlet air volume, temperature, dew point • Product temperature • Exhaust air temperature, flow • Filter type and orifice size • Shaking interval and duration • Total drying time Tray • Type of tray dryer • Bed thickness/tray depth (depth of product per tray) • Type of drying tray liner (*e.g.*, paper, plastic, synthetic fiber, *etc.*) • Quantity carts and trays per chamber • Quantity of product per tray • Drying time and temperature • Air flow • Inlet dew point Vacuum/microwave • Jacket temperature • Condenser temperature • Impeller speed • Bleed air volume • Vacuum pressure • Microwave power • Electric field • Energy supplied • Product temperature • Bowl and lid temperature • Total drying time	• Granule size and distribution • Granule strength, uniformity • Flow • Bulk/tapped/true density • Moisture content • Residual solvents • API polymorphic form or transition • Purity profile • Moisture profile (*e.g.* product temperature *vs.* LOD) • Potency • Cohesive/adhesive properties • Electrostatic properties
	Roller compaction/chilsonation	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity	• Type of roller compactor • Auger (feed screw) type/design (horizontal, vertical or angular) • Deaeration (*e.g.*, vacuum) • Auger (feed screw) speed • Roll shape (cylindrical or interlocking). • Roll surface design (smooth, knurled, serrated, or pocketed) • Roll gap width (*e.g.*, flexible or fixed) • Roll speed • Roll pressure	• Ribbon appearance (edge attrition, splitting, lamination, color, *etc.*) • Ribbon thickness • Ribbon density (*e.g.*, envelop density) • Ribbon porosity/solid fraction • Ribbon tensile strength/breaking force • Throughput rate • API polymorphic form and transition

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
• Solid form/polymorph	• Roller temperature • Fines recycled (yes or no, # of cycles)	
	Extrusion–Spheronization	
• Particle size, distribution • Fines/oversize • Particle shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph	• Type of extruder (screw or basket) • Screw length, pitch, and diameter • Screw channel depth • Screw blade configuration • Number of screws (single/dual) • Die or screen configuration (*e.g.*, radial or axial) • Die length/diameter ratio • Roll diameter (mm) • Screen opening diameter (mm) • Screw speed (rpm) • Feeding rate (g/min) • Type and scale of spheronizer • Spheronizer load level • Plate geometry and speed • Plate groove design (spacing and pattern) • Air flow • Residence time	• Extrudate • Density • Length/thickness/diameter • Moisture content • API polymorphic form and transition • Content uniformity • Throughput • Pellets after spheronization • Pellets size and distribution • Pellets shape factor (*e.g.* aspect ratio) • Bulk/Tapped density • Flow properties • Brittleness • Elasticity • Mechanical strength • Friability
	Hot melt extrusion	
• Particle size, distribution • Fines/oversize • Particle shape • Melting point • Density • Solid form/polymorph • Moisture content	• Screw design (twin/single) • Screw speed • Screw opening diameter (mm) • Solid and liquid feed rates • Feeder type/design • Feed rate • No. of zones • Zone temperatures • Chilling rate	• Extrudate density • Length/thickness/diameter • Polymorphic form and transition • Content uniformity • Throughput
	Tabletting	
• Particle/granule size and distribution • Fines/oversize • Particle/granule shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness • Elasticity • Solid form/polymorph • Moisture	• Type of press (model, geometry, number of stations) • Hopper design, height, angle, vibration • Feeder mechanism (gravity/forced feed, shape of wheels, direction of rotation, number of bars) • Feed frame type and speed • Feeder fill depth • Tooling design (*e.g.*, dimension, score configuration, quality of the metal) • Maximum punch load • Press speed/dwell time • Precompression force • Main compression force • Punch penetration depth • Ejection force • Dwell Time	• Tablet appearance • Tablet weight • Weight uniformity • Content uniformity • Hardness/tablet breaking force/ tensile strength • Thickness/dimensions • Tablet porosity/density/solid fraction • Friability • Tablet defects • Moisture content • Disintegration • Dissolution
	Encapsulation	
• Particle/granule size and distribution • Fines/oversize • Particle/granule shape • Cohesive/adhesive properties • Electrostatic properties • Hardness/plasticity • Bulk/tapped/true density • Viscoelasticity • Brittleness	• Machine type • Machine fill speed • Tamping Force • No. of tamps • Auger screw design/speed • Powder bed height	• Capsule appearance • Weight • Weight uniformity • Content uniformity • Moisture content • Slug tensile strength • Disintegration • Dissolution

Table I. (continued)

Pharmaceutical unit operation		
Input material attributes	Process parameters	Quality attributes
• Elasticity • Solid form/polymorph • Moisture		
	Pan coating	
• Tablet dimensions • Tablet defects • Hardness/plasticity • Density • Porosity • Moisture content	• Type of pan coater (conventional or side-vented) • Pan (fully perforated or partial perforated) • Baffle (design, number, location) • Pan load level • Pan rotation speed • Spray nozzle (type, quantity, pattern, configuration, spray pattern) • Nozzle to bed distance • Distance between nozzles • Nozzle orientation • Total preheating time • Inlet air flow rate, volume, temperature, dew point • Product temperature • Individual nozzle spray rate • Total spray rate • Atomization air pressure • Pattern air pressure • Exhaust air temperature, air flow • Total coating, curing time and drying time	• Coating efficiency • Core tablet weight before and after preheating • Moisture (gain/loss) during preheating • Environmental equivalency factor • Coated drug product (*e.g.*, tablet or capsule) appearance • % weight gain • Film thickness • Coating (polymer and /or color) uniformity • Hardness/breaking force/Tensile strength • Friability • Moisture (gain/loss) during overall process • Residual solvent(s) • Disintegration • Dissolution • Tablet defects • Visual attributes
	Fluid bed coating	
• Tablet dimensions • Tablet defects • Hardness/plasticity • Density/porosity moisture content	• Type of fluid bed coater • Fluid bed load level • Partition column diameter • Partition column height • Number of partition columns • Air distribution plate type and size • Filter type and orifice size • Filter differential pressure • Filter shaking interval and duration • Spray nozzle (type, quantity, pattern, configuration) • Nozzle port size • Total preheating time • Spray rate per nozzle • Total spray rate • Atomization air pressure • Inlet air flow rate, volume, temperature, dew point • Product temperature • Exhaust air temperature, air flow • Total coating, curing and drying time	• Coating efficiency • Core tablet weight before and after preheating • Moisture (gain/loss) during preheating • Environmental equivalency factor • Coated drug product (*e.g.*, tablet or capsule) appearance • % weight gain • Film thickness • Coating (polymer and /or color) uniformity • Hardness/breaking force/tensile strength • Friability • Moisture (gain/loss) during overall process • Residual solvent(s) • Disintegration • Dissolution • Tablet defects • Visual attributes
	Laser drilling	
• Size/dimensions • Polymer type membrane thickness	• Conveyor type • Conveyor speed • Laser power • Number of pulses • Type(s) of lens(es) • One or two sided • Number of holes	• Opening diameter (internal and external) • Depth • Shape of the opening

significant impact on the quality of the output material. Product understanding includes the ability to link input CMAs to output CQAs. The steps taken to gain product understanding may include the following:

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

Process Design and Understanding

A pharmaceutical manufacturing process usually consists of a series of unit operations to produce the desired quality product. Unit operations may be executed in batch mode or in a continuous manufacturing process. A unit operation is a discrete activity that involves physical or chemical changes, such as mixing, milling, granulation, drying, compression, and coating. A process is generally considered well-understood when (1) all critical sources of variability are identified and explained, (2) variability is managed by the process, and (3) product quality attributes can be accurately and reliably predicted (28).

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. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Table I lists the typical manufacturing unit operations, material attributes, process parameters, and quality attributes for solid oral dosage forms.

Process robustness is the ability of a process to deliver acceptable drug product quality and performance while tolerating variability in the process and material inputs (29). The effects of variations in process parameters and material attributes are investigated in process robustness studies. The analysis of these experiments identifies CPPs that could affect drug product quality and establishes limits for these CPPs (and CMAs) within which the quality of drug product is assured. The relationship between input CMAs and CPPs and output CQAs is shown in Fig. 1.

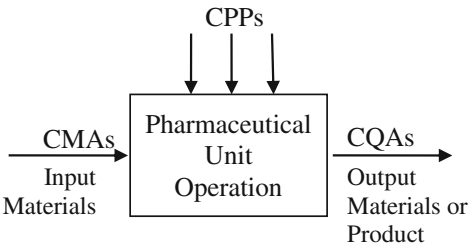
Steps to establish process understanding are very similar to those of product understanding and include the following:

1. Identify all possible known process parameters that could impact the performance of the process
2. Use risk assessment and scientific knowledge to identify potentially high-risk parameters
3. Establish levels or ranges of these potentially high-risk parameters
4. Design and conduct experiments, using DoE when appropriate
5. Analyze the experimental data and, when possible, determine scalability and apply first principle models to determine if a process parameter is critical. Link CMAs and CPPs to CQAs when possible.
6. 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

While developing a strategy for investigating both product design and understanding and process design and understanding, studies can be designed in such a way that both the objectives of product and process understanding are achieved simultaneously. In addition, an interactive (or interdependent) relationship among material attributes, process parameters, and product attributes can be more easily developed when such analyses are performed in carefully planned and designed experimental studies.

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 (3). 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 postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Thus, design space is the direct outcome of analysis of the DoE data or validated models such as first-principle models.

Design space may be scale and equipment dependent. Therefore, the design space determined at laboratory scale may need to be justified for use at commercial scale. Approaches for justification may include geometric considerations, kinematic considerations, heat and mass transfer, or dimensionless numbers as well as continual verification during commercial manufacturing. Justification is needed because the mechanistic understanding of pharmaceutical unit operations may be limited and scale-up is largely based on general rule of thumb and trial-and-error approaches; however, when mechanistic understanding or reliable



$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Fig. 1. Link input critical material attributes (*CMAs*) and critical process parameters (*CPPs*) to output critical quality attributes (*CQAs*) for a unit operation

empirical models (*i.e.*, extensive process understanding) exists, then the design space can be translated across scale.

Pharmaceutical products are frequently manufactured by a combination of unit operations. For example, tablets prepared by direct compression may simply involve blending and compression. However, when tablets are prepared by wet granulation, unit operations may involve blending, granulation, wet milling, drying, dry milling, blending for lubrication, compression, coating, and packaging. In such cases, the output of the first unit operation becomes an input of subsequent unit operations. Process understanding could be conducted on each unit operation or a combination of unit operations to determine CMAs, CPPs, and CQAs. Figure 2 shows an example how the CMAs and CPPs were determined, using an example of an immediate release dosage form (20).

Control Strategy

The knowledge gained through appropriately designed development studies culminates in the establishment of a control strategy. As shown in Fig. 3, control strategy could include three levels of controls as follows:

Level 1 utilizes automatic engineering control to monitor the CQAs of the output materials in real time. This level of control is the most adaptive. Input material attributes are monitored and process parameters are automatically adjusted to assure that CQAs consistently conform to the established acceptance criteria. Level 1 control can enable real-time release testing and provides an increased level of quality assurance compared to traditional end-product testing. It should be noted that adoption of process analytical technology (PAT) is not the only way to implement real-time release testing (*e.g.*, the use of predictive models as a surrogate for traditional release test, where the model may be defined in terms of traditional in-process measurements).

Level 2 consists of pharmaceutical control with reduced end-product testing and flexible material attributes and process parameters within the established design space. QbD fosters product and process understanding and facilitates identification of the sources of variability that impact product quality. Understanding the impact that variability has on in-process materials, downstream processing, and drug product quality provides an opportunity to shift controls upstream and to reduce the reliance on end-product testing (3).

Level 3 is the level of control traditionally used in the pharmaceutical industry. This control strategy relies on extensive end-product testing and tightly constrained material attributes and process parameters. Due to limited characterization of the sources of variability and inadequate understanding of the impact that CMAs and CPPs have on the drug product CQAs, any significant change in these requires regulatory oversight. Significant industry and regulatory resources are spent debating issues related to acceptable variability, the need for additional controls, and the establishment of acceptance criteria.

In reality, a hybrid approach combining levels 1 and 2 can be used. ICH Q8 (R2) (3) defines a 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 (3):

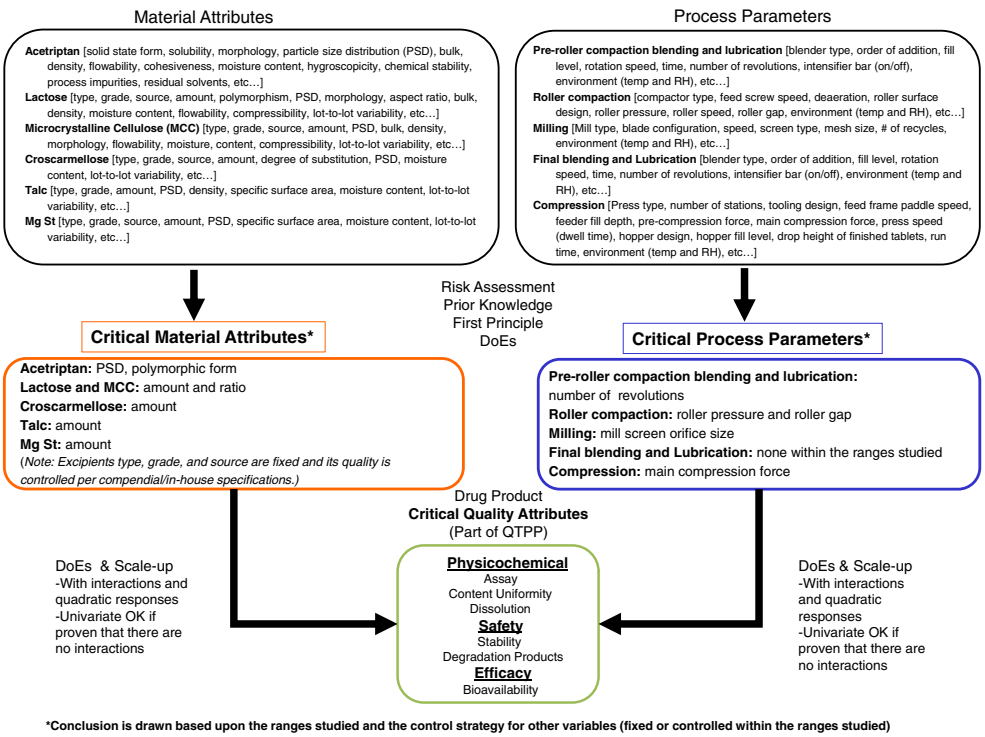


Fig. 2. Product and process understanding: an example for immediate release dosage forms

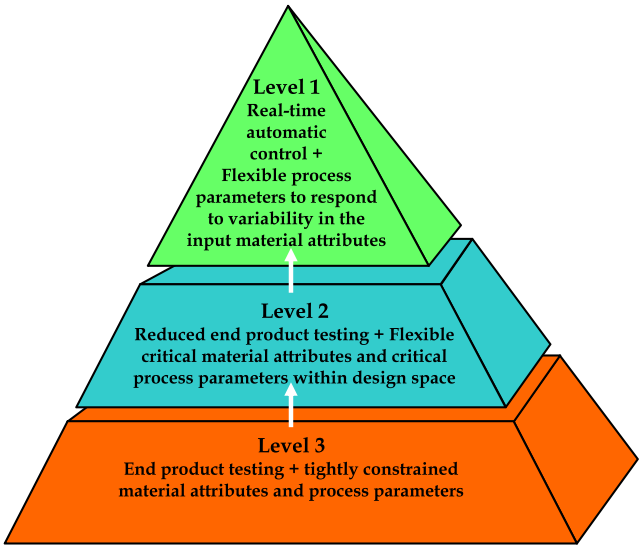


Fig. 3. Control strategy implementation options

- 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

Process Capability and Continual Improvement

Process capability measures the inherent variability of a stable process that is in a state of statistical control in relation to the established acceptance criteria. Table II shows the definition, calculation formula, and description of process capability indices (30) that are useful for monitoring the performance of pharmaceutical manufacturing processes. Calculations based on the inherent variability due to common cause of a stable process (*i.e.*, in a state of statistical control) result in process capability (C_p and C_{pk}) indices. When the process has not been demonstrated to be in a state of statistical control, the calculation needs to be based on sample standard deviation of all individual (observed) samples taken over a longer period of time; the result is a process performance index (P_p and P_{pk}). A state of statistical control is achieved when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process (31).

When a process is not in a state of statistical control, it is because the process is subject to special cause (source of intermittent variation in a process). Special causes can give rise to short-term variability of the process or can cause long-term shifts or drifts of the process mean. Special causes can also create transient shifts or spikes in the process mean. On the other hand, common cause is a source of inherent variation that is random, always present, and affects every outcome of the process. In a QbD development process, the product and process understanding gained during pharmaceutical development should result in early identification and mitigation of potential sources of common cause variation *via* the control strategy. The manufacturing process will move toward a state of statistical control, and, once there, the manufacturer will continue to improve process capability by reducing or removing some of the random causes present and/or adjusting the process mean towards the preferred target value to the benefit of the patient. In a non-QbD approach, common cause variation is more likely to be discovered during commercial production and may interrupt commercial production and cause drug shortage when it will require a root cause analysis.

Process capability can be used to measure process improvement through continuous improvement efforts that focus on removing sources of inherent variability from the process operation conditions and raw material quality. Ongoing monitoring of process data for C_{pk} and other measures of statistical process control will also identify when special variations occur that need to be identified and corrective and preventive actions implemented.

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 (32):

- 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.

Table II. Process Capability Indices and Their Measures

Index	Description
$C_p = \frac{(USL-LSL)}{6\widehat{\sigma}}$	Estimates process capability when the data mean is centered between upper and lower specification limits.
$C_{pkl} = \frac{(Mean-LSL)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of a lower limit only.
$C_{pku} = \frac{(USL-Mean)}{3\widehat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of an upper limit only.

USL upper specification limit, *LSL* lower specification limit, $\widehat{\sigma}$ (*sigma hat*) inherent variability due to common cause of a stable process

- 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.

In addition, continuous improvement can apply to legacy products. Legacy products usually have a large amount of historical manufacturing data. Using multivariate analysis to examine the data could uncover major disturbances in the form of variability in raw materials and process parameters. Continuous improvement could be achieved by reducing and controlling this variability. Newer processes associated with a design space facilitate continuous process improvement since applicants will have regulatory flexibility to move within the design space (ICH Q8).

PHARMACEUTICAL QUALITY BY DESIGN TOOLS

Prior Knowledge

Although not officially defined, 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. Thus, for the purpose of this paper, prior knowledge can only be obtained through experience, not education. Knowledge gained through education or public literature may be termed public knowledge. 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

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk.… The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk (4)." 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. ICH Q9 (4) provides a nonexhaustive 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

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality.

Mechanistic Model, Design of Experiments, and Data Analysis

Product and process understanding is a key element of QbD. To best achieve these objectives, in addition to mechanistic models, 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 over the traditional univariate approach to development studies 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. FDA scientists have shown the use of DoE in product and process design in recent publications (33–39).

Process Analytical Technology

The application of PAT may be part of the control strategy (28). ICH Q8 (R2) identifies the use of PAT to

ensure that the process remains within an established design space (3). 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.

Application of PAT involves four key components as follows (40):

- Multivariate data acquisition and analysis
- Process analytical chemistry tools
- Process monitoring and control
- Continuous process optimization and knowledge management

Multivariate data acquisition and analysis requires building scientific understanding about a process and identifying critical material attributes and process parameters that affect product quality and integrating this knowledge into the process control, which is essentially the same as the process understanding in the context of QbD. Process analytical chemistry tools provide real-time and *in situ* data about the status of the process. Multivariate data analysis takes the raw information from the PAT tools and connects it to CQAs. Based on the outcome of the data analysis, process controls adjust critical variables to assure that CQAs are met. The information collected about the process provides a basis for further process optimization. Studies in FDA laboratories indicated the promise of several PAT tools and chemometric approaches (41–44).

CONCLUSION

The goals of implementing pharmaceutical QbD are to reduce product variability and defects, thereby enhancing product development and manufacturing efficiencies and postapproval change management. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, product design and understanding, process design and understanding, and scale up, control strategy, and continual improvement. Prior knowledge, risk assessment, DoE, and PAT are tools to facilitate QbD implementation. Finally, product and process capability is assessed and continually improved postapproval during product lifecycle management.

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