The AAPS Journal, Vol. 16, No. 4, July 2014 (© 2014)
DOI: 10.1208/s12248-014-9598-3

Review Article

Understanding Pharmaceutical Quality by Design

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Received 17 November 2013; accepted 24 March 2014; published online 23 May 2014

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

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