Pharmaceutical Research, Vol. 25, No. 4, April 2008 (© 2007)
DOI: 10.1007/s11095-007-9511-1

Research Paper

Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control

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Received September 9, 2007; accepted November 26, 2007; published online January 10, 2008

Purpose. The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and describe how it can be used to ensure pharmaceutical quality.
Materials and Methods. The QbD was described and some of its elements identified. Process parameters and quality attributes were identified for each unit operation during manufacture of solid oral dosage forms. The use of QbD was contrasted with the evaluation of product quality by testing alone.
Results. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include:

- Defining target product quality profile
- Designing product and manufacturing processes
- Identifying critical quality attributes, process parameters, and sources of variability
- Controlling manufacturing processes to produce consistent quality over time

Conclusions. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry, manufacturing, and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment.

KEY WORDS: pharmaceutical quality by design; pharmaceutical quality by testing; process control; process design; process parameter; process variability; product design; quality attribute; question-based review.

INTRODUCTION

The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question-based review (QbR) for its chemistry, manufacturing, and controls (CMC) evaluation of abbreviated new drug applications (ANDAs). QbR is a new quality assessment system that is focused on critical pharmaceutical quality attributes. It is a concrete and practical implementation of some underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the twenty-first century and quality by design (QbD) initiatives (1).

This new QbR system incorporates some elements of QbD (2). It recommends that ANDAs be submitted using the common technical document (CTD) and include the quality overall summary (QOS) that addresses all the QbR questions. The main benefits of this QbR system are to (1) assure product quality through design and performance-based specifications, (2) facilitate continuous improvement and reduce CMC supplements, (3) enhance the quality of CMC reviews through standardized review questions, and (4) reduce CMC review time when applicants submit a QOS that addresses the QbR questions.

This commentary focuses on the QbD for generic drugs. The concept of QbD was mentioned in the ICH Q8 guidance (3), which states that "quality cannot be tested into products, i.e., quality should be built in by design". This paper discusses the pharmaceutical quality by design and describes how it can be used to ensure pharmaceutical quality with emphasis on solid oral dosage forms of small molecules.

PHARMACEUTICAL QUALITY BY TESTING

Figure 1 shows a simplified quality control diagram under the current quality by testing (QbT) regulatory framework for generic drugs. In this system, product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing.

The quality of raw materials including drug substance and excipients is monitored by testing. If they meet the manufacturer's proposed and FDA approved specifications or other

The views presented in this article do not necessarily reflect those of the Food and Drug Administration.

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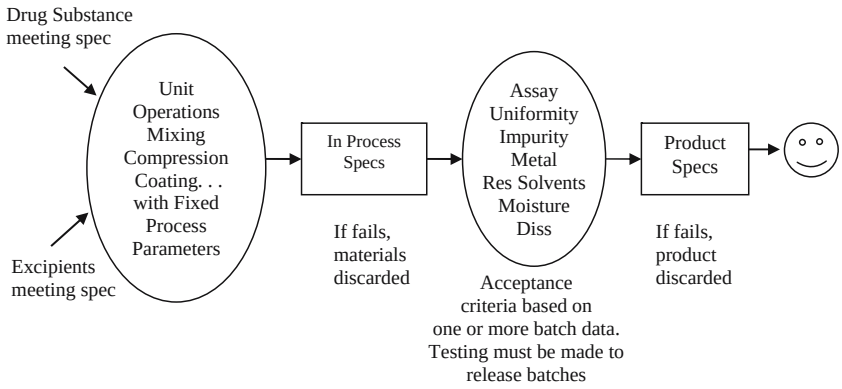


Fig. 1. A simplified quality control diagram using QbT.

standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Because of uncertainty as to whether the drug substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. A change to the drug substance manufacturing process may require the drug product manufacturer to file supplements with the FDA.

Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specifications. If not, they are discarded. Root causes for failure are usually not well understood. The manufacturers risk ongoing losses of the product until the root causes of failure are understood and addressed or FDA approves supplements to revise (e.g., widen) the acceptance criteria to pass the previously failed batches. Typical specifications for an immediate release oral solid dosage form, for example, include assay, uniformity, impurities, moisture, and dissolution. Under the current paradigm, the specification is tight because it is used to assure consistency of manufacturing processes. The stringent specification has resulted in recalls and drug shortages (4).

Since a few tablets out of several million are tested, drug manufacturers are usually expected to conduct extensive in-process tests, such as blend uniformity, tablet hardness, etc, to ensure the outcome of in-process testing also meets the FDA approved in-process testing specifications. Manufacturers are also not permitted to make changes to the operating parameters specified in the batch record or other process changes without filing supplements with the FDA (5–8). As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years. For example, in 2005 and 2006, the FDA Office of Generic Drugs received over 3,000 CMC supplements annually.

This combination of fixed (and thus inflexible) manufacturing steps and extensive testing is what ensures quality under the traditional system. Limited characterization of variability, inadequate understanding to identify and quantify critical process parameters, and caution on the part of regulators leads to a very rigid and inflexible specifications that prohibit the release of products that may have acceptable clinical performance (9). Significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. Often these debates are concentrated on acceptance limits or statistical aspects. FDA reviewers' conservatism results from the fact that manufacturers may not understand how drug substance, excipients, and manufacturing processes affect the quality of their products or they do not share this information with FDA reviewers.

Under the traditional regulatory evaluation system, all products are treated equally without regard to the risk to the consumer (10). This has the effect of placing too much review time on low-risk products and more significantly, takes away needed resources from the review of high-risk products. CMC review assessments of complex dosage forms (modified release products, topicals, transdermals) as well as narrow therapeutic index (NTI) drugs, differ only marginally from those of simple dosage forms (many immediate release solid oral products). Further, all CMC information in applications are sometimes evaluated equally, without differentiation of criticality, resulting in the requirement of intensive resources for each application.

In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing. The present regulatory review system places little or no emphasis on how the design of an effective and efficient manufacturing process can ensure product quality. As a result, the complexities of process scale-up, particularly for complex dosage forms are often not recognized. Product specifications often are derived using test data from one or more batches (often not at production scale), and mechanistic understanding does not play a significant role in this process. Finally, the burdensome regulatory requirement of supplements imposed on manufacturers for executing minor and incremental changes to manufacturing processes and controls inhibits continuous improvement and strategies for the implementation of continuous "real time" assurance of quality.

PHARMACEUTICAL QUALITY BY DESIGN

ICH Q8 (3) defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." ICH Q6A (11) emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities." Woodcock (9) defined a high quality drug product as a product free of contamination and reproducibly delivering the therapeutic benefit promised in the label to the consumer. This definition of product quality focuses on the performance of the drug product while the ICH definition focuses on specifications. As Woodcock pointed out in her paper (9) "this (ICH) definition can be

considered correct to the extent that the quality attributes represent, and the quality system controls variability of, the parameters that are important for clinical performance." Generally, the established drug quality attributes are adequate because they usually achieve much tighter control of the level of variability than could be detected in patients without extensive trials (Fig. 2).

Pharmaceutical QbD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control (12). It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives (9). QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics (13). In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time. Thus, some of the QbD elements may include:

- Define target product quality profile
- Design and develop product and manufacturing processes
- Identify critical quality attributes, process parameters, and sources of variability
- Control manufacturing processes to produce consistent quality over time

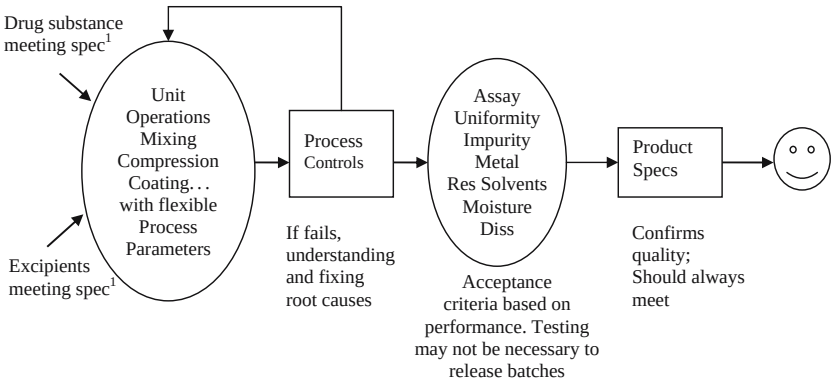
Under the QbD paradigm, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. Under QbT a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Under QbD consistency comes from the design and control of the manufacturing process and the specification of drug product under QbD should be clinically relevant and generally determined by product performance.

The specifications for assay and dissolution often evaluate the most important characteristics drug products must have to ensure their effectiveness. It is interesting to note that the assay limit is currently determined in a manner that is closer to the QbD approach than to the QbT approach. The assay limit is normally set to be 90–110% with the exception a few selected drugs where there are clinical reasons for narrower acceptance limits, for example, 95–105% (14). Assay limits are not routinely set by using batch data. A sponsor that routinely produced drug product with an assay of 98–100% would still expect an assay limit of 90–110%.

However current dissolution acceptance limits are selected based on data from a small number of batches in the context of their ability to distinguish batches with limited regard to clinical relevance. Under the QbD, the dissolution tests should be developed to reflect *in vivo* performance as much as possible. For example, the acceptance criteria for BCS Class I and III IR tablets may be much wider than that from batch data because, for these BCS classes, dissolution is highly unlikely to be the rate limiting step *in vivo* (15,16). Similarly, dissolution tests for BCS Class II and IV drugs may need to be carefully examined to better reflect *in vivo* dissolution (17).

The specification for impurities assesses another important characteristic a drug product must have to ensure its safety. Under the QbD, the acceptance criterion of an impurity should be set based on its qualification/biological safety level instead of the actual batch data. The biological safety level is generally determined by safety and/or clinical studies although it may be also determined by toxicity studies (18). Therefore, the acceptance criteria for impurities are usually those found in clinical study materials or reference listed drugs for generic drugs (18,19).

It should be noted that although there is a specification for a drug product under both the QbT and QbD paradigms, the roles that the specification plays are completely different. Under the QbT, each batch has to be tested against the



Note:

[1]Drug substance and excipient specifications only contain critical attributes that will impact performance and processing of the product

Fig. 2. A simplified quality assurance diagram under the QbD for generic drugs.

specification to ensure its quality and manufacturing consistency. Under the QbD, batches may not be actually tested against the specification as the process understanding and/or process control provides sufficient evidences that the batches will meet the specification if tested, which allows the real time release of the batches. Further, the specification under the QbD is solely used for the confirmation of product quality, not manufacturing consistency and process control.

Define Target Product Quality Profile

The target product profile (TPP) is generally accepted as a tool for setting the strategic foundation for drug development—"planning with the end in mind." More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The target profile is a summary of the drug development program described in the context of prescribing information goals (20,21). The TPP can play a central role in the entire drug discovery and development process such as: (1) effective optimization of a drug candidate, (2) decision-making within an organization, (3) design of clinical research strategies, and (4) constructive communication with regulatory authorities. TPP is currently primarily expressed in clinical terms such as clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, overdosage, etc. Thus, it is organized according to key sections in the product's label. TPP therefore links drug development activities to specific statements intended for inclusion in the drug's label.

Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical TPQP of an immediate release solid oral dosage form would include (22):

- Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability, and
- Dissolution

The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available information from the scientific literature and possibly the pharmacopeia, the TPQP can be used to define product specifications to some extent even before the product is developed. Predefined, high quality product specifications make the product and process design and development more objective and efficient.

Design Product and Manufacturing Processes

Product Design and Development

In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties (23). Physical properties include physical description (particle size, shape, and distribution), polymorphism, aqueous solubility as function of pH, hygroscopicity, and melting points. Pharmaceutical solid polymorphism, for example, has received much attention recently. Its impact on product quality and performance has been discussed in recent review articles (24–26). Chemical properties include p*K*a, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and/or oral bioavailability. Biopharmaceutical properties should be assessed for every form for which there is an interest in development and every form that can potentially be created during processing (e.g., hydrates, anhydrates) or *in vivo* (e.g., less soluble salts, polymorphic forms, hydrates) (27). The investigation of these properties is termed preformulation in pharmaceutical science. The goal of preformulation studies is to determine the appropriate salt and polymorphic form of drug substance, evaluate and understand its critical properties, and generate a thorough understanding of the material's stability under various processing and *in vivo* conditions, leading to an optimal drug delivery system. Pharmaceutical preformulation studies need to be conducted routinely to appropriately align dosage form components and processing with drug substance and performance criteria.

Biopharmaceutical assessment provides the information needed to select a solid form, to evaluate the developability of a drug candidate, and to determine its classification according to the Biopharmaceutics Classification System (BCS) (28–30). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility, dose, and intestinal permeability (31,32). The BCS guidance is generally considered to be conservative with respect to the class boundaries of solubility, permeability, and the dissolution criteria. Thus, the possibility of modification of these boundaries and criteria has received increasing attention (33,34).

Table I shows how the BCS can help focus efforts on developability and dosage form options to overcome limitations of poor solubility, poor permeability, or poor stability (23). In general, BCS Class I drugs present fewer development challenges. BCS Class III can be easily formulated. The poor absorption of BCS Class II drugs can be overcome with various formulation technologies (29). The delivery of BCS Class IV drugs is very challenging. Class V drugs, a new class established by Amidon for developability purposes (23), consist of drugs with significant presystemic degradation in the GI tract. While the enteric coating technique is reasonably successful in protecting drug from degradation in the stomach, it can result in significant variability of plasma concentration profiles. The other techniques listed in Table I are being investigated and/or developed.

Mechanical properties, though not often studied in detail, can have a profound impact on solid dosage form development and processing (35). A sound understanding of mechanical properties of the drug and excipients can be useful in (1) developing a processing method such as granulation or direct compression, (2) rationally selecting excipients whose properties can compensate for the properties of the drug substance, and (3) helping assess critical material attributes and

Table I. Impact of Biopharmaceutics Classification System on Formulation Dosage Form Design

Classifications	Impacts
Class I: High Solubility High Permeability	No major challenges for immediate release dosage forms Controlled release dosage forms may be needed to limit rapid absorption profile
Class II: Low Solubility High Permeability	Formulations designed to overcome dissolution rate problems: Particle size reduction Salt formation Precipitation inhibitors Metastable forms Solid dispersion Complexation Lipid Technologies
Class III: High Solubility Low Permeability	Approaches to improve permeability: Prodrugs Permeation Enhancers Ion Pairing Bioadhesives
Class IV: Low Solubility Low Permeability	Formulation would have to use a combination of approaches identified in Class II and Class III to overcome dissolution and permeability problems Strategies for oral administration are not often viable. Use of alternative delivery methods, such as intravenous administration may be most effective
Class V: Metabolically or Chemically Unstable Compounds[a]	Approaches to stabilize or avoid instability: Prodrugs Enteric Coating (protection in stomach) Lipid Vehicles (micelles or emulsions/microemulsions) Enzyme Inhibitor Lymphatic delivery (to avoid first pass metabolism) Lipid prodrugs P-gp efflux pump inhibitors

[a] Class V compounds do not belong to BCS. Compounds in this class may have acceptable solubility and permeability, but can still pose significant absorption challenge if they undergo luminal degradation and significant pre-systemic elimination.

root cause analysis during process scale-up or failure. Pharmaceutical materials can be elastic, plastic, viscoelastic, hard, soft, tough, or brittle. There exist various methods in the literature (36) to evaluate these mechanical properties. The knowledge of mechanical properties of the drug and excipients are expected to play a more significant role in product design and development in the future.

Drug-excipient compatibility has been identified as one of the most frustrating, troubling, and perplexing formulation challenges (37). Despite the fact that excipients can alter stability and bioavailability of drugs, the general principles of selecting suitable excipients for dosage forms are not well-defined, and excipients are often selected without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 recommends drug-excipient compatibility studies to gain early prediction of drug-excipient compatibility (3). Systematic drug-excipient compatibility studies offer several advantages: minimizing unexpected stability problems which usually lead to increases in time and cost; maximizing the stability of a formulation; and enhancing understanding of drug-excipient interactions that can help with root cause analysis if stability problems occur. Despite its significance, however, there is no universally accepted way to conduct drug-excipient compatibility studies in this evolving area. One method is thermal analysis (38), where a physical property of a substance (e.g., melting point) and/or reaction products is measured as a function of temperature while the substance is subject to a controlled temperature program. Another method utilizes isothermal stress (39–41). This method typically involves storing the drug-excipient blends or compacts with or without moisture at elevated temperature and determining drug content or degradation product formation as a function of time. Both methods can be used together to evaluate the compatibility of drugs with the selected excipients.

Process Design and Development

Strictly speaking, process and product design and development can not be separated since a formulation can not become a product without a process. A formulation without a process is, for example, a pile of powder (K. Morris, 2005, personal communication). Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified on paper, including the intended scales of manufacturing. This should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables (42). Other factors to consider for process design are the target product quality profiles. Depending upon the product being developed, type of process, and process knowledge the development scientists have, it may be necessary to conduct preliminary feasibility studies before completing the process design and development.

The selection of type of process depends upon the product design and the properties of the materials. For

example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed (43). When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor.

Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing (44). Process simulation has been successfully used in the chemical and oil industries since the early 1960s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. Currently, CAPD and process simulation are largely used in drug substance manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized. With the emphasis of QbD by the FDA and industry and drug product cost pressures, this trend is expected to change. The use of CAPD and process simulation should result in more robust processes developed faster and at a lower cost, resulting in higher quality products.

Identify Critical Quality Attributes, Process Parameters, and Sources of Variability

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture (45). The quality and quantity of drug substance and excipients are considered as attributes of raw materials.

During process development, raw materials, process parameters and quality attributes[1] are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Table II (46) (G. E. Amidon, 2006, personal communication. 2006) lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training, standard of operation (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly. Therefore, risk assessment should be used to reduce variables to be investigated.

Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time (47). In process robustness studies, effects of variations in process parameters for a candidate process are evaluated. The analysis of these experiments identifies critical process parameters that could potentially affect product quality or performance, and establishes limits for the critical process parameters within which the quality of drug product is assured. Ideally, data used to identify process parameters should be derived from commercial scale processes to avoid any potential impact of scale-up. However, in reality, these studies are often conducted on laboratory or pilot-scale batches. If results from the small-scale batches have not been shown to be size independent, any conclusion from small scale studies may need to be verified in the actual commercial production batches. At the end, the effect of raw material attributes and critical process parameters on product quality or product variability is fully understood and established. Ideally, the interactions between materials attributes and critical process parameters should be understood so that critical process parameters can be varied to compensate for changes in raw materials.

To demonstrate the reproducibility and consistency of a process, process capability should be studied. Process capability is a statistical measure of the inherent process variability for a given characteristic. The most widely accepted formula for process capability is six sigma. Process capability index is the value of the tolerance specified for a particular characteristic divided by the process capability, which is defined as follows:

$$\text{Process capability index } (C_pK) = \frac{\text{Upper limit of specification} - \text{lower limit of specification}}{6 \text{ standard deviation}}$$

If the C_pK value is significantly greater than one, the process is deemed capable. If the process capability is low, Rath and Strong (48) recommend an iterative five-step procedure to progressively reduce the variability of the process. These five steps are:

1. Define: The intended improvement should be clearly stated.
2. Measure: The critical product performance attributes should be measured to see if they are out of specification.

[1] This may be defined as material attributes.

Table II. Typical Unit Operations, Process Parameters, and Quality Attributes for Tableting[a]

Pharmaceutical Unit Operation	Example Process Parameter	Potential Quality Attributes
Mixing	Type and geometry of mixer	Blend uniformity
	Order of addition	Particle size distribution
	Mixer load level	Bulk/tapped density
	Number of rotations (time and speed)	Moisture content
	Agitating bar (on/off pattern)	Flow properties
Milling	Impact/cutting/screening mills	Particle size
	Mill type	Particle size distribution
	Speed	Particle shape
	Blade configuration and type	Bulk/tapped density
	Screen size and type	Flow properties
	Feeding rate	Polymorphic form
	Fluid energy mill	
	Number of grinding nozzles	
	Feed rate	
	Nozzle pressure	
	Classifier	
Wet Granulation	High shear granulation	Power consumption (process control)
	Pre-binder addition mix time	Blend uniformity
	Impeller speed, configuration, and location	Flow
	Chopper speed, configuration	Moisture content
	Spray nozzle type and location	Particle size and distribution
	Method of binder addition	Granule size and distribution
	Binder fluid temperature	Granule strength and uniformity
	Binder addition rate and time	Solid form
	Post-granulation mix time	
	Bowel temperature	
	Fluid bed granulations	
	Mixing time	
	Spray nozzle (type/quantity/ pattern/configuration)	
	Method of binder addition	
	Binder fluid temperature	
	Binder fluid addition rate and time	
	Inlet air flow rate, volume, temperature, and dew point	
	Exhaust air temperature, flow	
	Filter properties and size	
	Shaking intervals	
	Product temperature	
Drying	Fluidized bed	Granule size and distribution
	Inlet air volume, temperature, dew point	Granule strength, and uniformity
	Exhaust air temperature, flow	Particle size
	Filter properties	Flow
	Shaking intervals	Bulk/tapped density
	Product temperature	Moisture content
	Total drying time	Residual solvents
	Tray	
	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	
	Vacuum strength	
	Microwave potency	
	Electric field	
	Energy supplied	
	Product temperature	
Roller compaction	Roll speed	Appearance
	Gap setting	Ribbon/particle size and shape
	Roll pressure	Ribbon density, strength, and thickness

Table II. Continued

Pharmaceutical Unit Operation	Example process parameter	Potential Quality Attributes
	Auger screw rate	Solid form
	Roller type	
Compaction[b]	Compression speed and force	Target weight
	Pre-compression force	Weight uniformity
	Feed frame type and speed	Content uniformity
	Hopper design, height, and vibration	Hardness
	Tablet weight and thickness	Thickness
	Depth of fill	Tablet porosity
	Punch penetration depth	Friability
		Visual attributes
		Moisture content
Coating[b] Fluid bed, Pan	Product temperature	Weight of core tablets
	Total pre-heating time	Appearance
	Spray nozzle (type/quantity/ pattern/configuration)	Visual attributes
	Individual gun spray rate	% Weight gain
	Total spray rate	Film thickness
	Pan rotation speed	Color uniformity
	Atomization air pressure	Hardness
	Pattern air pressure	Thickness
	Inlet air flow, temperature, dew point	Friability
	Exhaust air temperature, air flow	
	Product temperature	
	Total coating time	

[a] By no means this table is comprehensive
[b] Dissolution (disintegration) is considered as an *in vitro* performance test. It depends upon, among others, quality attributes such as particle size and tablet hardness.

The out of specification data should be analyzed and used to the sigma level of the process.

3. Analyze: When the sigma level is below the target, steps should be taken to increase it, starting by identifying the most significant causes of the excessive variability.
4. Improve: The process should be redesigned and/or process controls should be incorporated to eliminate or attenuate the significant root causes of variance.
5. Control: The improved manufacturing process should be evaluated and maintained.

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined.

When considering scale-up, however, additional experimental work may be required to confirm that the model generated at the small scale is predictive at the large scale. This is because some critical process parameters are scale-dependent while others do not. The operating range of scale-dependent critical process parameters will have to change because of scale-up. Prior knowledge can play a very significant role in this regard as most pharmaceutical companies use the same technologies and excipients on a regular basis. Pharmaceutical scientists can often take advantage of past experience to define critical material properties, processing parameters and their operating ranges.

Control Manufacturing Processes to Produce Consistent Quality over Time

Under the QbD for generic drugs, the effects of raw materials including both drug substance and excipients, and process parameters on the product quality are well understood. This means that manufacturers have knowledge of the operating range as well as the proven range of critical raw material attributes and process parameters. The operating range is defined as the upper and/or lower limits for raw material attributes and process parameter values between which the attribute and parameter are routinely controlled during production in order to assure reproducibility. The proven range is defined as the upper and/or lower limits for process parameter values between which the parameter is known to produce a high quality product that delivers the therapeutic benefit claimed on the label (46). The proven range can be established based on historical and/or experimental data. It can also be established based on scientific and operational judgment and expertise.

Within the QbD, design space is defined as the multidimensional combination and interaction of input variables

(e.g., material attributes) and process parameters that have been demonstrated to provide quality assurance (3). Working within the FDA approved design space is not considered a change. 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. At an October 2006 Advisory Committee for Pharmaceutical Science meeting (49), the following issues were raised on design space:

- How were design space and control space established for each unit operation?
- Is the design space for each unit operation independent of equipment design and batch size?
- How does control space relate to design space?
- How does control space relate to operational ranges in the Master Batch Record?

The design space for generic drugs is likely established at small scale batches using design of experiments (DOE) and prior knowledge, and may need to be verified at commercial scale. The design space is dependent upon the equipment design principle and batch size. The control space (or normal operating ranges) is defined as the upper and/or lower limits for the critical raw material attributes and process parameters between which the parameter and material are routinely controlled during production in order to assure reproducibility. The control space should be within the design space. If the control space is much smaller than the design space, the process is then considered robust. Otherwise, stringent process control may be needed to assure that the process can be constantly operated within the design space.

The traditional techniques used in process monitoring apply a combination of mathematical and knowledge-based models. In-process testing has been playing a significant role in monitoring and controlling pharmaceutical processes. If any in-process testing result fails to meet predefined limits, the batch is scrapped and the root cause of the failure is identified and remedied. If necessary, the process is modified and updated so that the in-process or end-process testing results will meet the predefined limits. The QbD approach is more proactive. During the design phase, process steps whose failure could result in failure to meet quality targets are identified. As a first step toward QbD, process monitoring can then be established to provide advance indication of potential failure. Full establishment of QbD requires process control of critical steps to ensure that quality is maintained.

Process control in Chemical Engineering is the active changing of the process based on the results of on-line process monitoring. Once process monitoring detects an out of control situation, the process will make changes to bring the process back into control through automatic feedback control systems. For pharmaceutical batch processes, process-wide and supervisory automatic control which prevents the propagation of disturbances, and assures safe, stable, and optimal operation, would be ideal (50). Such automatic control is currently difficult to put into practice because of limited availability of sensors, models, and automatic control systems. The FDA's Process Analytical Technology (PAT) initiative is intended to advance pharmaceutical process identification, simulation, and control. PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (51).

Pharmaceutical scientists have begun to use PAT for process understanding and process control (52). Examples for implementing PAT have been widely discussed through public workshops, conferences, meetings, and journal publications (53). The FDA has approved a number of applications which implemented PAT. These approvals span a variety of products and processes, including drug substance and drug product manufacturing processes for new drug products, generic products, and veterinary products. Therefore, PAT is an important tool focusing on improved process understanding and knowledge. The use of PAT is expected to assist the implementation of QbD and is strongly encouraged.

SUMMARY

This paper starts with the FDA OGD's new quality review system; QbR. It discusses pharmaceutical QbD for generic drugs, identifies its fundamental principles and elements, and discusses its utility in ensuring pharmaceutical quality with emphasis on solid oral dosage forms of small molecules. In contrast to the traditional regulatory system of quality by testing (QbT), pharmaceutical QbD is a systemic approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Understanding and implementing QbD will enhance and modernize the regulation of pharmaceutical manufacturing and product quality. It will transform the Chemistry, Manufacturing, and Controls (CMC) regulatory review into a modern science-based pharmaceutical quality assessment.

ACKNOWLEDGMENT

The authors would like to thank Drs. Gregory Amidon, Yihong Qiu, John Strong, Alan Parr, Mansoor Khan, Vincent Vilker, Robert Lionberger, Andre Raw, Lai Ming Lee, Lawrence Sau Lee, Wallace Adams, Doan Nguyen, Michelle Bryden, Gary Buehler, Helen Winkle, and Janet Woodcock for their valuable suggestions.

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