Mitigating the Risks of Generic Drug Product Development: An Application of Quality by Design (QbD) and Question based Review (QbR) Approaches.

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ABSTRACT

This paper discusses the challenges and advantages of implementing Quality by Design (QbD) and Question based Review (QbR) when developing solid dosage formulations and manufacturing processes for generic drugs. Formulation and process development of a drug product is challenging due to the inherent variability of the processes. Regulatory agencies, such as the Food and Drug Administration (FDA) in the USA, demand a QbD approach when developing formulations and processes for new and existing medicinal products. The QbD approach is described in the International Conference on Harmonization (ICH) Guidance Q8 (R2). The regulatory reviewers follow the QbR approach during the review of Chemistry, Manufacturing, and Controls (CMC), which have also adopted some of the elements of the QbD guidance. A systematic application of scientific principles for developing the formulations and processes for generic drug products following the QbD approach is outlined below in three main categories. The categories are product understanding, process understanding, and control strategy. The concept of predefined objectives, quality risk management, and CMC considerations together with the prior knowledge are discussed in detail. The discussions and explanations provided in this paper are based on sound scientific principles, as well as, practical experience applied to resolve product quality and manufacturing issues. Emphasis is given to streamlining formulation and process development that complies with current QbD and QbR principles in order to prevent commonly cited deficiencies. Examples are provided as guiding tools for generic formulation and process development.

KEY WORDS: Generic formulation development, Quality by Design, QbD, Quality based Review, QbR, product and process understanding, Chemistry Manufacturing and Controls, CMC

INTRODUCTION

Formulation and process development of drug products are challenging for the generic pharmaceutical industry because of the need to get them quickly to the market because of inherent process and material variabilities and cost of development. The inherent variability associated with formulation and development is driven by several factors. Some of the factors are (i) patent expiration of a number of medicinal products within a short span of time, (ii) increased competition from new entrants as well as generic versions of the innovator drug products, (iii) enhanced scrutiny by regulatory

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bodies, (iv) increasingly lower prices due to government mandated price cuts to make healthcare more affordable, and (v) existing patents of drug substances, drug formulations and their manufacturing processes.

The two greatest challenges facing the generic pharmaceutical industry today are a trend in decreasing drug prices and increasing regulatory scrutiny. Regulatory bodies, such as the FDA, now require the generic pharmaceutical industry to adopt QbD when developing formulations and processes for a drug product. ICH Q8 (R2) Guidance states that QbD "is a systemic approach to pharmaceutical development and manufacturing that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." The question is, how can QbD and QbR be implemented without impacting time to market and cost of development?

The benefits of implementing QbD and QbR have been discussed previously (1). The McKinsey QbD Report stated that best practice in product and process development (PPD) could increase net profits by up to 20% (2). PPD directly determines production cost before and after commercial launch. It accounts for 15-50% of the total research time and development (R&D) expenditure. PPD can also improve overall equipment effectiveness (OEE), a standard operational performance measure which is about 35-50% for the pharmaceutical industry compared to 70-90% in other comparably regulated industries. Downtime in the manufacturing processes adds to production costs. The application of QbD in PPD ensures a reduction in wasted time thereby increasing overall profitability. In addition, the FDA has incorporated some elements of QbD in the QbR methodology for CMC for generic drugs (3).

The required elements for pharmaceutical development as described in the ICH QbD Guidance (4) are (a) defining the quality target product profile (QTPP) based on the route of administration, dosage form, bioavailability, strength, and stability, (b) identifying, studying and controlling potential critical quality attributes (CQAs) of the drug product, (c) determining the type and amount of excipients and their critical material attributes (CMAs), (d) selecting the appropriate manufacturing process, (e) establishing the critical process parameters (CPPs) and linking high risk CMAs and CPPs to drug product CQAs and its manufacturability using risk assessment tools, and (f) defining a control strategy.

The purpose of the guidance is to ensure a desired product performance. There are other elements, such as design space, and process analytical technology (PAT), which are not discussed in this paper. Therefore, an increased level of product and process understanding is required to fulfil the objectives of the QbD and QbR approaches. Product and process understanding are achieved by a systematic application of scientific principles to formulations and process design. The question remains, what does product and process understanding mean and how can it be demonstrated?

Product and process understanding is described in the QbR methodology. Product understanding is related to the input materials' (e.g. drug substance, excipients, and container and closures) critical attributes. The critical attributes of the input materials are those which affect drug product performance. Process understanding is related to process attributes, which are sometimes influenced by the input materials and hence affect drug product performance. The acceptable norms in demonstrating product and process understanding are (a) identification of all possible attributes of the materials and process

parameters that could impact the drug product performance, (b) determination of high risk attributes of the materials and process parameters using risk assessment tools, (c) determination of level, range of the high risk materials attributes and process parameters, (d) performing actual trials, and (e) analysis of experimental data to determine appropriate range for CQAs, CMAs, and CPPs. Prior knowledge from developing similar formulations and processes together with design of experiments (DoE) can be accepted as a demonstration of product and process understanding. Prior knowledge and how it can be demonstrated is discussed later in this paper.

The QbD concepts, terminology, and differences between the typical *versus* QbD approach have been discussed previously (5, 6). This paper focuses on the development of formulations and manufacturing processes for generic solid dosage forms, as well as, reviews questions and deficiencies. Analytical method development is considered outside the scope of this paper. A schematic of the QbD approach in developing the generic formulations and manufacturing process is illustrated in Figure 1.

This paper discusses the techniques with relevant examples to fulfill the requirements of the QbD and QbR approaches and the science behind the required elements. The explanations provided in this paper are based on practical experience and approaches applied to resolve product quality issues with scientific rationale. The definitions of some important terms used in this paper are provided below.

DEFINITIONS

AUC (area under the curve) is a method of measuring the bioavailability of a drug based on a plot of blood concentrations sampled at frequent intervals. It is directly proportional to the total amount of unaltered drug in the patient's blood (7).

C_{max} (maximum plasma concentration) is the peak concentration that a drug achieves in a specified compartment after the drug has been administrated and before administration of a second dose (7).

Control Strategy is 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 (4).

CPPs is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (4).

CQAs is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (4).

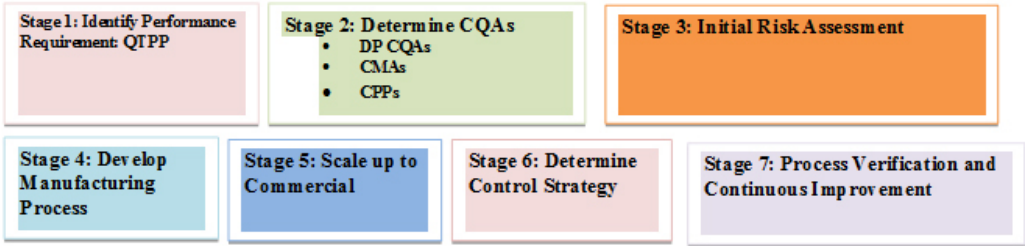

Figure 1 QbD approach for generic formulation and manufacturing processes

Process robustness is the ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality (4.)

Quality Risk Management is a systematic approach for assessing, controlling, communicating and reviewing risks to the quality of the drug (medicinal) product across the product lifecycle (8). Risk based assessment is proportionate to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and the capability of process control strategies to prevent or mitigate the risk of producing a poor quality 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 the safety and efficacy of the drug product (4).

T_{max} is the time after the administration of a drug when the maximum plasma concentration is reached i.e., when the rate of absorption equals the rate of elimination (7).

QbD and QbR approaches together with commonly cited deficiencies and the concept of prior knowledge are described as Product Understanding, Process Understanding, Control Strategy and Prior Knowledge expanded further below.

PRODUCT UNDERSTANDING

The typical components of product understanding are (i) analyzing the reference listed drug (RLD) product, (ii) determining the QTPP, (iii) defining drug product CQAs, (iv) characterizing the drug product components, and (v) assessing the risk associated with the input materials and the drug product. The components of drug product understanding are discussed below.

RLD Analysis

Generic drug product development begins with a predefined objective. The objective is to develop a product, which is therapeutically equivalent to the RLD. Therefore, the starting point for successful development of a generic drug product is the complete understanding of the RLD properties. The major components of the RLD analysis, such as composition, physicochemical characteristics and its CQAs, dissolution, and biological properties are described below with relevant examples.

Composition

Drug product formulation and process development begins with a description of the components and composition of the RLD. The descriptions of the components include references to the quality standard of each material and their functional category. The functional aspect of each material is crucial to the formulations and process development rationale. The quantitative/qualitative composition of the RLD is available in the literature, such as in the product monograph, the label and patents. An example of describing the components and composition is outlined in the manufacturing process development section.

Physicochemical Characterization

Physicochemical characterization of the RLD is carried out to identify potential pitfalls in the proposed product. Recent and near the end of the shelf life batches of the reference drug product are characterized to understand the physical and chemical attributes. Analysis of a near the end of the shelf life batch is critical for establishing an impurity profile and dissolution, and for preventing an out-of-specification (OOS) situation. Typical elements of the physicochemical characteristics of the RLD are listed below. These elements are in line with the

presentation titled "Quality Target Product Profile with Examples" (9).

- Brand name
- Description
- Batch Number
- Strength
- Expiry date
- BCS (Biopharmaceutics Classification System) Class
- Tablet shape and dimension
- Appearance (description with image)
- Tablet weight
- Thickness
- Hardness
- Disintegration time (without discs)
- Uniformity of dosages unit
- Assay (%)
- Dissolution
- Tablet pH
- Tablet surface area and porosity
- Tablet water vapor sorption
- Impurity (A, B, C, D)
- Highest Unknown Impurity

The critical physicochemical attributes of RLDs are disintegration and dissolution, which are discussed in the section on RLD dissolution. Additionally pH, surface area, porosity, and hygroscopicity of the RLD tablet are typically analyzed to gain information on the specific properties of the drug product. For example, changes in pH can significantly influence the solubility of some drugs. Therefore, a pH modifying excipient may be used with free base or salt to adjust the micro-environmental pH. The pH in tablets is generally measured using a pH meter by dissolving the tablet into water. Tablet surface area and porosity of some drugs influence dissolution and degradation. Surface area, morphology, and porosity are critical attributes for BCS (biopharmaceutical classification system) Class II and IV drugs as dissolution is the rate limiting step for such drugs. Surface area and porosity are generally analyzed using the BET (Brunauer, Emmett, Teller) method. The water adsorption/ desorption nature of the drug product and drug substance is helpful in designing the formulations and processes of the hygroscopic and hydrolytic molecules. Water vapor sorption is a gravimetric technique that measures how quickly and how much of a solvent is absorbed by a sample.

Dissolution

The dissolution profile of the proposed drug product must be similar to the RLD. A discriminatory dissolution test method is used to demonstrate the similarity between the proposed drug product and the RLD. Discriminatory dissolution test methods could be used to detect from higher to a lower soluble forms and/or transitions from metastable to a stable form of a drug substance in a drug product. A biorelevant dissolution test is also performed on a case-by-case basis. The purpose is to demonstrate *in vitro/in vivo* correlations (IVIVC) and to develop *in vitro* dissolution specification (10). *In vitro/in vivo* correlations are generally accepted for BCS Class II, III and some BCS Class II drugs. The common factors associated with dissolution tests are apparatus, dissolution media, pH of the dissolution media, solubility and stability of the drug substance in the dissolution media, and discriminatory power of the dissolution test method.

In general, United States Pharmacopeia (USP) dissolution apparatus are preferred for dissolution testing. The four types of USP dissolution apparatus (1-4) for testing solid dosage forms are discussed below.

USP Apparatus 1 is a rotating basket type apparatus for which the recommended agitation rate is between 50 and 150 RPM and the compendial preference is 100 RPM. It is generally used for testing the dissolution rate of capsules and tablets. The USP apparatus 1 is preferred for testing immediate release (IR) and modified release (MR) dosage forms. The

agitation ranges are usually used for the development of IVIVCs (11, 12).

USP Apparatus 2 is a rotating paddle type apparatus for which the recommended agitation rate is between 25 and 100 RPM and the compendial preference is 50 RPM. It is generally used for testing the dissolution of tablets and capsules. Similarly to the USP apparatus 1, it is used for testing IR and MR dosage forms. The agitation ranges are usually used for developing IVIVCs (11,12). The USP apparatus 2 is the most preferred apparatus for developing dissolution test methods.

USP Apparatus 3 is a reciprocating cylinder bio-dis type apparatus and recommended dip rate is between 10 and 15 RPM. It is generally used for testing poorly soluble drugs and MR dosage forms. The USP apparatus 3 is not accepted by the Japanese Pharmacopeia.

USP Apparatus 4 is flow-through cell apparatus which is generally used for testing multiparticulate dosage forms.

The dissolution media are selected based on the drug solubility screening. The media should be capable of dissolving 3 times the drug substance and must be stable in the media for at least 24 hours. The recommended pH range of the dissolution media for IR and MR formulations is 1.2-6.8 and 1.2-7.5 respectively (10, 11). Typically, a dissolution test (n=12) is performed using 2 to 3 dissolution media. The purpose is to establish the discriminatory power of the dissolution test method.

An aqueous medium with a pH range of 1.2 to 6.8 is commonly used for dissolution tests (11, 12) of IR dosages forms. Use of water as a dissolution medium is discouraged because test conditions, such as pH and surface tension, can vary depending on the source of water. In addition, the pH and surface tension may change during the dissolution test due to the influence of the drug substance and excipients. A dissolution medium of pH 6.8 is used to simulate intestinal fluid (SIF). A higher pH (NMT 8.0) is used on a case-by-case basis, however, a justification is required if using a higher pH. To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 is used without enzymes. On a case-by-case basis, enzymes, such as pepsin with SGF, and pancreatin with SIF can be used with justification. For example, pepsin is used with SGF for dissolution testing of some gelatin capsule products. It is reported that storage conditions, formulation as well as analytical test methods influence gelatin crosslinking (13).

Gelatin crosslinking can be caused by extremely hot and humid storage conditions, intense ultraviolet (UV) or visible lights. Gelatin crosslinking is caused by the presence of corn starch, aldehydes, imines, ketones, saccharides (glucose and aldose sugar) calcium carbonate, hydrogen peroxide, and dyes (FD&C Red No. 3 or 40 and Blue No. 1) in the formulation or in the empty gelatin capsules. A barrier film is formed during storage due to gelatin crosslinking. The barrier film prolongs the disintegration time and a subsequent decrease in dissolution rate. Pepsin in the dissolution medium breaks down the crossed-linked barrier film quicker than acid alone, and hence permits the release of the drug. Therefore, USP <711> (Dissolution) recommends the addition of an enzyme (e.g. pepsin) to the dissolution medium. However, it is required to demonstrate that a decrease in dissolution is directly related to crosslinked gelatin shells rather than the degradation of the drug product. A surfactant, such as sodium lauryl sulfate (SLS) can be used for water insoluble or sparingly water soluble drug products. However, a justification for the need and the amount of the surfactant is required.

The dissolution test of highly soluble (largest dose dissolved in ≤ 250 ml of water over a pH

range of 1.2 – 6.8) and highly permeable (extent of absorption is > 90%) drugs (classified as BCS Class I) could be replaced by a simple disintegration test. The ICH Guidance (14) also permits the use of a disintegration test as a surrogate for the conventional compendial dissolution test provided that (i) the drug is highly soluble, (ii) the intrinsic rate of solubilization is rapid, and (iii) the overall drug release rate is dominated by cohesive properties of the formulation. However, a justification for the selection of dissolution *versus* a disintegration test, as well as, the development and suitability of the chosen test is required. This is generally carried out by establishing a relationship between disintegration and dissolution. The relationship proves that disintegration is more discriminating than dissolution and therefore a simple disintegration test could replace the dissolution test.

Drug substance solubility, formulations and process variables often influence the dissolution of hydrophobic and poorly water soluble drugs (BCS Class II and IV). The typical formulations and process variables are excipient attributes (hydrophilic/hydrophobic), levels and grades, tablet hardness, surface area and porosity of the drug product. In addition to these factors, the physiological conditions of the gastrointestinal tract (GI) affect drug product dissolution (15). Therefore, a discriminatory dissolution test method is used to analyze the proposed and referenced drug product. The purpose is to assess the impacts of the excipients CMAs and levels, and tablet hardness on dissolution rate. An example of the RLD dissolution study is discussed below.

The dissolution study for an RLD (e.g. a brand named Risedronate sodium 150 mg tablet, batch XYZ, expiry date month/year of the USA market) was carried out across the four physiological pH ranges. The media used were USP purified water (deaerated), 0.1N HCl, 0.05M phosphate buffer pH 4.5 and pH 6.8. During the study, USP Apparatus 2, using an agitation rate of 50 RPM and a volume of 900 ml dissolution medium was used. The USP dissolution specification for Risedronate sodium is NLT 80% (Q) dissolved in 30 minutes for tablets labeled to contain at least 75 mg. The drug release profile of the RLD in these four dissolution media is illustrated in Figure 2.

The RLD (i.e., the brand named drug) exhibits very rapid dissolution profiles, ≥ 85% of the drug substance dissolved within 15 minutes, in water. Therefore, the dissolution profile of the

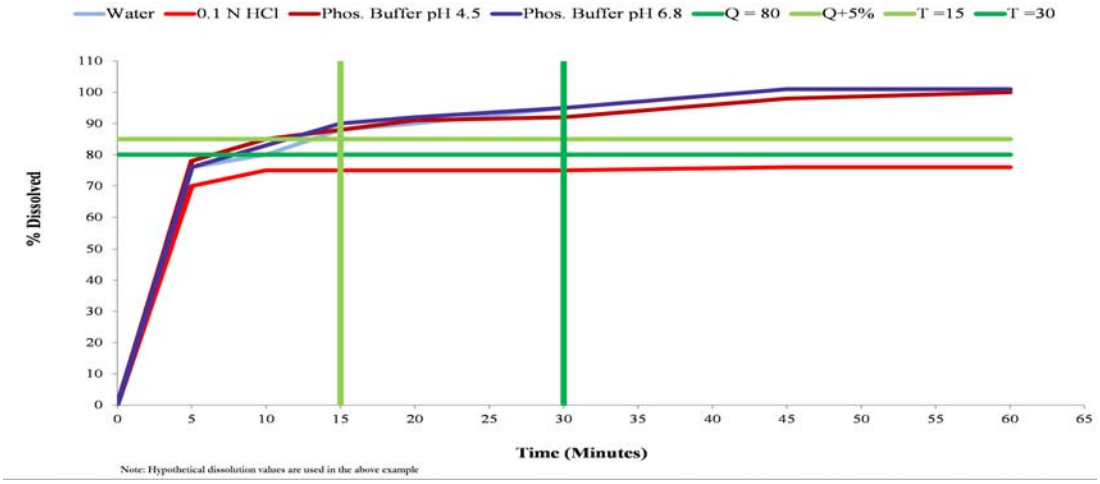

Figure 2 pH dissolution profiles of a brand named Risedronate Sodium 150 mg tablets (batch XYZ) in USP Purified Water, 0.1N HCl, and 0.05 M Phosphate Buffer pH 4.5 and pH 6.8.

proposed generic drug product considered similar and no mathematical evaluation (i.e., f2 calculation) is required.

Biological Properties

The RLD biological properties must be described according to clinical and pharmacokinetics {ADME: absorption (AUC, C_{max}, T_{max}), distribution, metabolism, and elimination}. The bioequivalency of the drug product depends on the absorption site which for oral dosage forms is the GI tract. The criticality of the C_{max} and AUC depends on the solubility of the drug (based on BCS Class).

Drugs classified as BCS Class I (High solubility/High permeability, amphiphilic in nature) are well absorbed in the GI tract. However, the absorption of such drugs is controlled by gastric emptying. Highly permeable drugs are rapidly absorbed in the GI tract. Therefore, C_{max} is the critical *in vivo* parameter for such drugs and is indicative of overall AUC. Compounds belonging to BCS Class I are eligible for biowaiver, if the dissolution of the compound is >85% within 30 minutes at pH 1.2 to 6.8 when tested using USP dissolution apparatus 1 without adding lecithin, bile salts or enzymes in the dissolution media.

The absorption of BCS Class II (Low solubility/High permeability, lipophilic in nature) drugs in the GI tract is good and controlled by dissolution. C_{max} is the critical *in vivo* parameter for such drugs. According to the World Health Organization (WHO), certain BCS Class II compounds are eligible for biowaiver, if the compound is a weak acid with a dose:solubility ratio of <250 ml at pH 6.8, and the dissolution is > 85% within 30 minutes at pH 6.8 tested at 75 RPM. However, in the USA the FDA and the EMA (European Medicines Agency) in Europe do not allow for a biowaver for BCS Class II drugs.

The absorption of BCS Class III (High solubility/Low permeability, hydrophilic in nature) drugs in the GI tract is limited and controlled by permeability. C_{max} and AUC are the critical *in vivo* parameters for such drugs. BCS Class III compounds are eligible for biowaiver if the compound dissolves within 15 minutes at pH of 1.2 to 6.8 tested at 75 RPM.

The absorption of BCS Class IV (Low solubility/Low permeability, hydrophobic in nature) drugs in the GI tract is poor. C_{max} and AUC are the critical *in vivo* parameters for such drugs.

The physiology of the GI tract, for example pH, residence time, and various bile salts can influence the biological properties (e.g. C_{max} and AUC) of the drug molecule. The small intestine has a high concentration of bile salts with a large surface area due to its villi and micro-villi structures. This area serves as the primary site for drug absorption. Therefore, the knowledge of where in the GI tract the drug is absorbed facilitates formulation design. In addition, it is useful to understand the impact of food on drug absorption, bioavailability (BA) and bioequivalence (BE) when developing the formulation. The dissolution of weakly basic drugs is slower at a higher pH because more drugs exist in its unionized form. On the other hand, weakly acidic drugs dissolve faster at higher pH due to the fact that more drugs exist in its ionized form. Therefore, meals that elevate gastric pH can decrease the dissolution of a weak base by increasing the proportion of drug existence in its un-ionized state. For example, Indinavir, a weak base with pKa (dissociation constant) of 3.7 and 5.9 forms precipitate when gastric pH is elevated during a meal. The formation of precipitates causes a significant reduction in AUC and C_{max} values of the Indinavir in fed versus fasted human subjects (16). The biological properties of the RLD are generally available in the product monograph and/or in literature.

Determining the QTPP

The QTPP is a prospective summary of the quality characteristics of a drug product and forms the basis of the development design. The RLD analysis determines the QTPP of the proposed drug product. An example for determining the drug product QTPP (17) is outlined in Table 1, which is in line with the presentation entitled "Quality Target Product Profile with Examples (9).

Table 1 Quality Target Product Profile (QTPP)

ELEMENT	QTPP TARGET	RATIONALE
Dosages Form	Tablet	Same Dosage Form.
Dosage Design	IR/DR Tablet	IR/DR design, meet label claims.
Route of Administration	Oral	Same route of administration.
Dosage Strength (mg)	x and xx	Same Strength.
Physical Attributes	Weight Thickness Friability Hardness Disintegration	Similar to the RLD.
Drug Product Quality Attributes	Identification Assay Dosages uniformity Dissolution Degradation products Residual solvents	Pharmaceutical Equivalence Requirement: meet compendia, ICH or other applicable quality standards. Dissolution in acid and buffer medium provides idea about the absorption.
Pharmacokinetics (pK)	IR enabling T_{max} in 2 hours or less. Bioequivalent (BE) to RLD.	Bioequivalence requirement. $C_{max,}$ AUC, and T_{max} similar to the RDL. Ensures rapid onset and efficacy.
Contraindication	Situations in which the drug might be contraindicated.	Same as the RLD.
Use in specific populations	Not to specific group.	No plan to study the drug in a specific population as it is intended for all groups.
Stability	At least 24 months at room temp.	For commercialization
Container Closure System	HDPE Bottles/Blisters	Commercial requirement

DR= Delayed release
IR = Immediate release

Determining Drug Product CQAs

The QTPP defines the critical and non-critical attributes of the proposed drug product. The formulations and/or process variables can potentially alter the critical quality attributes of the drug product. An example of determining the drug product CQAs is presented in Table 2.

Table 2 Drug Product Critical Quality Attributes (DP CQAs)

DP QUALITY ATTRIBUTES		TARGET	CQA	RATIONALE
Identification		Positive for drug substance	No	Formulation and process unlikely to have any impact identity
Physical Attributes	Appearance (color and shape)	To match RLD	No	Not critical for IR product
	Size	Similar or > RLD	No	Not critical for IR product
	Hardness	To be defined	Yes	
	Friability	NMT 0.8 % @ 100 rev NMT 1.2% @ 200 rev. 500 rev. for info only	Yes	Influenced by formulation and compression process parameters
	Disintegration (without discs)	NMT xx min	Yes	
	Scoring/ divisibility	Unscored tablet	No	Not critical as there is no score
Chemical Attributes	Degradation products	Meets ICH requirement	Yes	Influenced by CMAs, mfg. process and container & closure.
	Assay	Compendia specs	Yes	
	Dosages Uniformity	USP <905>	Yes	
	Drug Release/ Dissolution	Similar as RLD	Yes	Influenced by formulation, CMAs, mfg. process & parameter

Characterizing drug product components

The drug product components, such as drug substance and excipients are discussed below.

Drug substance

The ICH Guidance requirement is to identify and discuss the physicochemical and biological properties of the drug substance and their influence on drug product performance and its manufacturability (4). The required QbD

elements for drug substance are (a) physicochemical and biological properties, (b) degradation pathway (e.g. intrinsic stability), (c) chemical reactivity, and (d) risk assessment.

Some of the deficiencies in drug substances as cited by the FDA (18) are (i) multiple polymorphic forms are reported in the literature, provide the form used and a suitable control to ensure consistency in the drug substance, (ii) include a control for the relevant enantiomer and diastereomers if the drug substance is chiral and the enantiomers show differences in pharmacological effect and/or safety, and (iii) justify the specification for the full range of particle size distribution (PSD). Alternatively, it is possible to show that the PSD is not critical to the manufacturing process and drug product performance.

The physicochemical and biological properties of the drug substance usually examined include aqueous solubility (as a function of pH), water content, particle size, crystal properties (e.g. polymorphism), biological activity, and permeability. Other physicochemical and mechanical properties of the drug substance include melting point, particle shape, surface area, porosity, pKa, partition coefficient, stereoisomers, chemical stability, flowability, and compressibility. If they are interrelated some of these properties will be considered in combination. An explanation is required if a property is not included. For example, pKa may not be listed because there are no ionizable groups in the chemical structure. The product development report usually describes the polymorphism, solubility, and particle size of the drug substance.

Physicochemical and mechanical properties of the drug substance

Some of the physicochemical and mechanical properties of the drug substance and their influence on drug product performance and its manufacturability are discussed below with an example.

Polymorphism

Polymorphs of a drug substance that are generally recognized are amorphous, crystalline, hydrate and solvate (19). However, polymorphs refer to crystalline structure of a molecule. By definition, an amorphous material is not crystalline. Hydrates and solvates may, or may not, be crystalline and could have their own polymorphs. The physicochemical properties, for example, solubility, hygroscopicity, particle shape, density, flowability, and compactibility of different polymorphs of a drug substance are different. Therefore, polymorphic forms of the drug substance influence the performance of the drug product and its manufacturability.

The thermodynamically most stable polymorph should be chosen for the formulation to ensure optimum product performance and manufacturability. A thermodynamically stable polymorph is chemically stable and has the least potential for conversion to another polymorph when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray-drying, and compaction (20). However, occasionally, a metastable form is preferred over the stable form, since they have better solubility, and bioavailability/ bioequivalency. A metastable form has a high energy state, low melting point and high aqueous solubility.

Water in pharmaceutical hydrates is generally present in three different form, for example, residing in isolated lattice sites, in the lattice channel sites, which are also referred to as channel water and in the ion-coordinated sites (20, 21). In isolated lattice sites, water molecules are in contact with the drug molecule and therefore, isolated from other water molecules. Channel water is in contact with other water molecules of adjoining unit cells along an axis

of a unit cell and is mobile in nature. Therefore, channel water may migrate into and out of the crystal lattice as a function of ambient humidity. Ion-coordinated water participates in an ion water bond, which is usually stronger than hydrogen bonds present in the molecule. The removal of isolated lattice water generally compromises the crystal integrity. In contrast, crystal integrity remains relatively intact upon removal of channel water (21). However, upon the removal of channel water from some drug substances e.g. Risedronate Hemipentahydrate, the crystal integrity has been reported to be compromised. The hydrate, depending upon the nature of the water may, or may not, change over time with ambient humidity, temperature, or other drug product manufacturing and storage conditions (22). Therefore, the metastable polymorph or pharmaceutical hydrate requires special attention during the formulation design regarding the selection of, for example, excipients, as well as, the selection of the manufacturing processes. The influence of polymorphic forms on the performance of the drug product and its manufacturing processes are discussed below.

Solid state phase conversion (re-crystallization) of amorphous or metastable drug substances during manufacturing processing and/or storage has been observed. For example, a roller compaction process can influence the degradation of acetylsalicylic acid, and milled Carbamazepine anhydrate converts to dihydrate at least four times faster than the unmilled material during a wet granulation process (23). Mechanical treatments, such as milling, tend to accelerate the kinetics of dehydration by generating surface defects and local heating which causes phase conversion.

Phase conversion of a drug substance may take place immediately or, over time, during storage, at accelerated conditions (40ºC/75% RH). This is a common occurrence for amorphous materials. Drug substance conversion was reported for an IR formulation containing a highly soluble drug (24). The drug content in the formulation was low (≤ 2 mg). The product was manufactured by wet granulation. The drug substance was dissolved during the wet granulation due to low drug content and high solubility. The completely dissolved drug substance converted to an amorphous form during the drying cycle. The phase conversion of the drug substance caused a loss in potency and an increase in related substances at accelerated storage conditions. The extent of conversion generally depends on the relative stability of the polymorphs, kinetic barriers to phase conversion, and applied stress (25).

Drug substance phase conversion, however, is generally not a serious concern provided that the conversion occurs consistently as part of a validated manufacturing process where critical manufacturing process parameters are well understood and controlled, and where drug product BA/BE has been demonstrated (19).

Drug product stability is affected by various other factors, including the formulation, manufacturing processes and packaging. Therefore, stability is an important quality parameter. The effect of polymorphism on the drug product manufacturing process also depends on the formulation and the manufacturing processes (26). For example, the impact of the drug's physical and mechanical properties on direct compression for low or high drug content formulations can be significant compared to dry granulation. Therefore, paying close attention to the drug's polymorphism is critical as it is related to the manufacturing processes.

If different polymorphic forms are known, it is required to specify which polymorphic form was chosen and provide supporting evidence for the claim. The identification of the polymorphic form is usually determined using different analytical methods, for example, using

a Fourier Transform Infrared Spectroscopy (FTIR). It collects simultaneously high spectral resolution data over a wide spectral range and measures how well a sample absorbs light at each wavelength). X-ray Powder Diffraction (XRPD) is a rapid analytical technique primarily used for phase identification of a crystalline material. Differential Scanning Calorimetry (DSC) determines where the energy of a sample is absorbed or released as it is heated, cooled, or held at a constant temperature. Thermogravimetric Analysis (TGA) measures the change in weight of a sample as it is heated. Information on drug substance polymorphism is generally available in the Drug Master File (DMF) and/or in the literature. An example of the selection of a polymorphic form is given below.

A drug substance such as Carbamezepine is known to exhibit polymorphism and four anhydrous polymorphs and a hydrate, as well as, other solvates have been reported in the literature (27, 28, 29, 30). The four polymorphic forms of Carbamezapine have been identified through XRPD analysis (27). Among the four polymorphs, Form III is the most stable form at room temperature, and is therefore commonly used in tablet formulations (31). The manufacturing process is a direct compression/ dry granulation process and is not expected to cause phase conversion during processing. Therefore, Form III was chosen for development, and was expected to be stable throughout its shelf life under normal environmental conditions. The XRPD data of the drug substance confirmed that the polymorph was Form III.

Solubility

Drug substance solubility is often referred to according to its BCS Class. The solubility of the drug substance influences the selection of the excipients and drug product manufacturing process, stability, and dissolution testing design. Several factors, for example, polymorphism (crystalline form), pKa, lipophilicity and high melting point of the drug substance, lack of solute-solvent interaction, changes in pH, fluid contents, and motility, as well as, the residence time in the GI tract influence the solubility and *in vivo* dissolution of an oral solid dosage forms. For example, a drug substance with an aqueous solubility of <100 μg/ml is reported to present dissolution and absorption limitations (32). Therefore, solubility screening of the drug substance is a pre-requisite of the formulation and process development, and for any application for a biowaiver. Solubility information of the drug substance is available in the literature, for example, in the Martindale, the Extra Pharmacopeia, the Merck Index, Florey's Analytical drug profiles and on the internet (aqueous solubility is available on Medline®).

However, there are concerns for using the solubility information from the literature or the internet because the reported solubility data is generally based on using water as the dissolution media at room temperature and at one pH only. Therefore, it is essential to determine the drug substance solubility experimentally. Solubility screening is performed using multiple media, such as, acid and buffer. The media usually represents all physiologically relevant pH ranges, for example, pH 1.1, pH 2-3, pH 4-5, pH 6.8, and pH 7.5 at 37ºC. To determine the dose:solubility ratio, the highest single dose strength is divided by the solubility of the compound over the pH range of 1.1 to 7.5 at 37°C. The drug substance is considered "highly soluble," if the dose:solubility ratio is <250 ml. The reason for comparing the solubility < 250 ml or > 250 ml is that typically, 250 ml of fluid is present in the upper GI-tract when administering the drug in a fasted state. The goal is to determine the optimal solubility and stability of the drug substance and to meet the FDA BCS classification system (33). The solubility screening decision tree is illustrated in Figure 3.

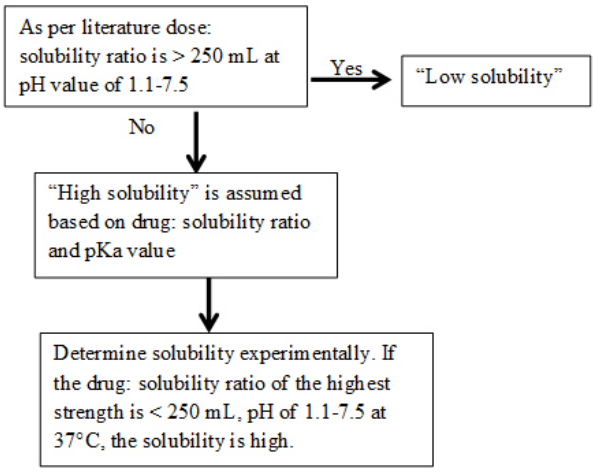

Figure 3 Solubility screening diagram

The solubility in media with different pH also indicates the pH dependent release nature of the drug substance. The solubility information guides the selection of excipients and manufacturing processes together with the stability of the drug substance. For example, Poloxamer 470 (a nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene), Meglumine (an amino sugar derived from sorbitol with pKa value of 9.60) is used as a solubilizing agent for poorly water soluble drugs, and potassium bitartrate (the potassium acid salt of tartaric acid) is used as a buffering agent to ensure optimal release of the pH dependent drug substance. An example of aqueous solubility as a function of the pH of a drug substance is shown in Table 3.

Particle size and particle size distribution

A discussion about the drug substance particle size is mandatory irrespective of the impact on the drug product performance and its manufacturability. The criticality of the drug substance particle size depends on (i) drug substance solubility, drug product dissolution, and bioavailability/bioequivalence (ii) dosage strength (iii) drug content in the formulation and (iv) manufacturing process, such as, direct compression >dry granulation >wet granulation.

Particle size and its distribution influence the dissolution and absorption (C_{max} and AUC) of the drug product, as well as, its manufacturability. For example, C_{max} and AUC of a drug product containing a drug substance with 100 µm particle size were significantly lower compared to the <50 µm (34). Particle size is indicative of compressibility and flowability i.e., flow and cohesiveness. Therefore, particle size usually impacts quality parameters, such as assay and dosage uniformity in formulations with a low drug content, as well as, the compression force of formulations with a high drug content. The particle size of a cohesive/milled/micronized drug substance is of greater concern. For example, the mean particle size of the micronized Griseofulvin has been reported to increase during the com-paction process based on drug loading (35). The surface area of a particle decreases with increasing particle size leading to a decrease in the dissolution rate. In addition to an increase in particle size, the author experienced excessive wafer build up in the granulation chamber during dry granulation (roller compaction) process of a micronized drug substance.

Therefore, for some drugs, particle size specification and its test method is a mandatory requirement. In general, laser diffraction, image and sieve analysis techniques are employed to examine the particle size of a drug substance. However, different particle sizes have been obtained for a specific batch when analyzed using different techniques. In addition, different particle sizes can be obtained based on the method used for measuring the particle size.

For example, different particle size are obtained for a specific batch when analyzed using wet or dry methods by a Malvern particle size analyzer. Therefore, it is required to use validated test method to analyze particle size. Particle fragility, nature of agglomeration and particle habits of the material influence the selection of particle size test method. An example of drug

Table 3 Aqueous Solubility

SOLUBILITY	USP TERMINOLOGY	AQUEOUS SOLUBILITY AS A FUNCTION OF pH AT 37°C		
		Solvent	Final pH[a]	Sol.[b] (mg/ml)
>1 g/ml	Very soluble	0.1 N, HCl, pH = 1	1.0	47.2 mg/ml
100-1000 mg/ml	Freely soluble	0.05 N HCl, pH = 2	1.7	49.2 mg/ml
33.3-100 mg/ml	Soluble	0.15 M acetate buffer, pH = 4	3.7	56.8 mg/ml
10-33.3 mg/ml	Sparingly soluble	0.15 M phosphate buffer, pH = 6	5.8	60.8 mg/ml
1-10 mg/ml	Slightly soluble	0.15 M phosphate buffer, pH = 8	7.8	56.0 mg/ml
0.1-1 mg/ml	Very slightly soluble			
<0.1 mg/ml	Practically insoluble			

[a] Refers to the pH of aqueous media following addition of drug substance.
[b] Solubility measures were carried out on polymorphic Form I (the most stable form)

Note: hypothetical values are used for dose/solubility calculation.
The calculated dose/solubility volume: 32 mg (highest strength) ÷ 47.2 mg/ml (minimum concentration of drug) = 0.68 ml. Based on the BCS Classification system the drug is highly soluble as the dose/solubility volume is less than 250 ml. Considering the strength (low and high), a drug substance could be classified as high soluble or low soluble, for example, Acyclovir 200 mg tablet belongs to BCS class III (high solubility - low permeability), whereas Acyclovir 800 mg tablet belongs to BCS class IV (low solubility - low permeability).

substance particle size discussion is outlined below.

When the water solubility of a drug substance (e.g. Captopril) is 160 mg/ml at 25°C (CAS 62571-86-2), it is categorized as a highly soluble drug (BCS Class III). The drug content in the formulation is 27.0% $^{W}/_{W}$. The highest dosage strength is 100 mg tablet. The manufacturing process is dry granulation. The particle size of a highly soluble drug is not critical to the drug product performance (14). Therefore, the particle size specification of the drug substance (e.g. Captopril) is not proposed based on the drug content in the formulation, manufacturing process (dry granulation), and particle size of the dug substance will not be controlled during routine release test.

Permeability

The permeability of a drug substance influences its absorption. Information on permeability for some drug substances can be found in the literature, e.g.,, the Martindale, the Merck Index and Florey's Analytical drug profiles and on the internet (permeability or bioavailability is available on Medline). A drug substance is considered "highly" permeable, if the permeability is >90%, measured in humans/animals or a suitable cell line (e.g., Caco 2 cells). However, determination in Caco 2 cells is only applicable to passively absorbed substances and is used for additional confirmation. Permeability data from humans is preferred and animal data is only used if no other data can be found. The probable reasons for below 90% bioavailability are degradation in the GI-tract, first pass effect, solubility limited bioavailability, and poor absorption.

Lipinski's "The Rule of 5" can be used to predict the permeation of a drug substance. 'The Rule of 5' predicts that poor absorption or permeation of a drug substance is more likely, when (i) there are more than 5 H-bond donors, (ii) there are more than 10 H-bond acceptors, (iii) the molecular weight is greater than 500 g/mol, and (iv) the Log P (Clog P) is greater than 5 (or Mlog P > 4.15) (36). An example of the drug substance permeability discussion is provided below.

A drug substance, e.g., Clopidogrel bisulfate has 2 H-bond donor and 8 H-bond acceptor. Its partition coefficient, Log P is 3.89 in octanol/water, pH 7.4 at 25°C and it has a molecular weight of 419.90 g/mol (37). Therefore, according to "The Rule of 5" the permeability of Clopidogrel bisulfate is good.

However, following an oral administration, the bioavailability of Clopidogrel bisulfate is reported to be about 50% due to its poor water solubility (38).

Water content and hygroscopicity

It is expected to include a test (e.g. Karl Fischer titration) for water content when appropriate. Water exists as bound and free water in a molecule. Generally, the free water associated with the drug molecule and excipient can influence dissolution, stability (chemical degradation e.g., hydrolysis), pow-der flow, manufacturability and microbial growth. Typically water is not a reactant except in ester hydrolysis, however, it accelerates most reactions by bringing the molecules together due to an increase in plasticity and molecular mobility in the system. Highly soluble and highly hygroscopic drugs have a tendency to change polymorphic forms during storage at ambient conditions. A partial change in the polymorphic form (e.g. crystalline to amorphous) generally causes faster dissolution. Tablets and excipients in the formulation are examined using a XRPD method to confirm the change in polymorphic form, if any. The acceptance criteria for water content in such drugs are usually justified by the effects of hydration or water absorption. In some cases, a loss on drying analysis is also adequate. Drug substance hygroscopicity is usually used to justify the selection of the excipients grade, level, and manufacturing process together with the packaging. The hygroscopicity of the drug substance is generally analyzed using a dynamic vapor sorption (DVS) method and is available in the DMF (drug master file) and/or in the literature.

Flowability

Drug substance flowability influences blend uniformity (BU), uniformity of dosages unit (DU), assay, and granulate compressibility. The flowability property is used to justify excipient selections and manufacturing processes. For example, direct compression is selected based on the measured angle of repose (AoR is < 30°) and the compressibility index (CI is <10%) of the drug substance and drug content (i.e., 40% $^{W}/_{W}$) in the formulation. Therefore, no adverse impact on the drug product quality attributes and its manufacturability is anticipated.

Compactability

Together with other factors e.g., formulation composition and compression press speed, drug substance compactability influences compression force and tablet hardness. Drug substance bulk density is one of the indicators for compactability. Compactability is critical for high drug content formulations especially when compressibility of the drug substance is poor or moderate.

The physical properties of the drug substance have the least impact in a wet granulation. The physical and mechanical properties of the drug substance are often masked during the wet granulation process (19).

DS Degradation Pathways: Forced Degradation/ Stress Testing

It is required to describe the degradation pathways of the drug, generally demonstrated through forced degradation studyes/stress testing. A stress test is performed in both solution and solid state for a specific storage time or until a certain degradation is observed. The purpose of such a test is (i) to demonstrate the intrinsic stability of the drug substance, (ii) to identify environmental factors (ambient temperature, humidity, light) and oxygen affecting the stability of the drug product, (iii) to determine the potential degradates and assess if they can be formed during manufacture or storage of the drug, (iv) to validate the stability indicating power of the analytical method, and (v) to justify the selection of primary packaging

material that protects the drug product during storage and transportation.

The four main degradation mechanisms are hydrolytic, oxidative, heat, and photolytic degradation. Therefore, typically the drug substance is subjected to these conditions during forced degradation studies. The preferred level of degradation depends on the (i) suitable reagents, (ii) concentration of the reagents such as acid, base, or oxidizing agent, (iii) test conditions e.g. varying temperature and humidity, and (iv) length of exposure. During stress testing, degradation is controlled to a desired level to ensure that the drug substance is not subject to over- or under- stressing. Over-stressing a sample may lead to the formation of secondary degradants that would not be seen in formal shelf-life stability studies and under-stressing may not serve the purpose of stress testing. Therefore, a generic approach for stress testing is applied to achieve purposeful degradation that is predictive of long-term and accelerated storage conditions, which is between 5-20% degradation (39, 40, 41, 42). The 5 – 20% range covers the generally permissible 10% degradation for small molecule drug products. The typical stability limits for small molecule drug product is 90 to 110% of the label claim (43). Generally, 10% degradation is preferred by some pharmaceutical scientists to validate the analytical method for small drug molecules. The stress conditions are selected based on prior knowledge of a compound. For instance, low concentration of a base is generally used for a compound containing an ester group as the compound is very labile to base hydrolysis. The samples are analyzed at different time intervals as it generally provides information on the progress of degradation and help to distinguish primary degradants from secondary ones.

Acid and base hydrolysis

Acid and base hydrolytic stress testing are carried out for drug substances and drug products in solution at ambient temperature or at elevated temperatures. The selection of an acid or a base and their concentration depends on the stability of the drug substance. The drug substance solution is subjected to various pH values e.g., 2, 7, 10–12 at room temperature for two weeks or up to a maximum of 15% degradation (40) to assess the hydrolytic degradation. Typically, hydrochloric acid or sulfuric acid at a concentration of 0.1 M to 1 M for acid hydrolysis and sodium hydroxide or potassium hydroxide at a concentration of 0.1 M to 1 M for base hydrolysis is used (43). For lipophilic drugs e.g., thiopental, inert co-solvents are generally used to solubilize the drug substance. The selection of cosolvent depends on the functional groups present in the drug molecule.

Oxidation

Oxidative degradation is complex. Hydrogen peroxide is used predominantly for oxidation degradation tests because it mimics the possible presence of peroxides in the drug and/or excipients. Other oxidizing agents such as metal ions, oxygen and light are also used. The selection of an oxidizing agent, its concentration, and conditions depends on the drug substance. Typically the drug substance solution is subjected to 0.1%-3% hydrogen peroxide at neutral pH and room temperature for seven days or up to a maximum of 20% degradation (42). Metals ions e.g., iron and copper are found in some drug substances and some excipients. Therefore, metal ions are added to the solution of the drug substance to determine whether the drug substance will be catalytically oxidized or not. Oxidative degradation influenced by light is discussed below in the photostability section.

Heat

Thermal stress testing e.g., dry or wet heat is generally more strenuous than recommended in the ICH Q1A accelerated testing conditions. Samples of solid-state drug substances and drug

products are exposed to dry or wet heat, whereas liquid drug products are exposed to dry heat. Generally, the effect of temperature is studied in 10°C increments at 75% or greater relative humidity (44). In the event that the stress conditions produce little or no degradation due to the stability of a drug molecule, it is required to ensure that the stress applied is in excess of the energy applied by accelerated conditions (40°C for 6 months) before terminating the stress study.

Photostability

Testing photostability is an integral part of stress testing, especially for photolabile compounds. The recommended conditions for photostability testing are described in ICH Q1B Photostability Testing of New Drug Substances and Product (45). Samples of a solid/liquid drug product, are exposed to a minimum of 1.2 million lux hours and 200 watt hours per square meter light. The same samples are exposed to both white and UV light. The temperature is controlled to minimize the effect of temperature changes during exposure. The light-exposed samples are examined for any changes in physical properties e.g. appearance, clarity, color of solution, and for assay and degradants. The information is used to specify the appropriate storage conditions on the container labels.

Understanding common degradation pathways helps in designing stable formulations and processes and to avoid OOS situations. A discussion about the common degradation pathways (e.g. hydrolysis/thermolytic, oxidation, and photolytic) is not required. However, the three common degradation pathways of the drug substance or drug product are briefly discussed below.

Hydrolysis

Hydrolysis accounts for the majority of reported drug degradations. Hydrolysis is common for a broad category of organic molecules derived from weak functional groups such as carboxylic acids. Moisture, temperature, and pH may greatly impact the rate of hydrolysis. Drug substances containing functional groups such as amide (Acetaminophen, Oxazepam), carbamic ester (Loratidine), lactone (Warfarin), imide (Barbiturates), acetal (Erythromycin), imine (Diazepam, Oxazepam) are susceptible for hydrolytic degradation.

Oxidation

Oxidation reactions are often catalyzed by oxidizing agents such as peroxides, metals, atmospheric oxygen, light, and free-radical. The reactive impurities in excipients play a key role in oxidation either as a primary source of oxidants, trace amounts of metals, or other contaminants. Three primary mechanisms for oxidative degradation are nucleophilic and electrophilic, electron transfer, and autoxidation. Peroxides are a common impurity in many excipients, such as Povidone, Crospovidone, Hydroxypropylcellulose (HPC) etc. Nucleophilic and electrophilic oxidation is generally initiated by the peroxides present in the drug substance and in the excipients. Electron transfer oxidation is typically mediated by the transition metal ions presents in the excipients. Oxidizing agents can produce free radicals in the presence of atmospheric oxygen and light. The free radicals then react with oxygen to form peroxy radicals. The peroxy radicals then react with the oxidative substrate to yield further complex radicals affecting the stability of the drug product. A free radical often initiate chain reaction called autoxidation, which could be autocatalytic and non- Arrhenius.

Photolytic

Drug substances containing functional groups such as carbonyl, nitro-aromatic, aryl, vinyl, thiol, or halogens are susceptible for photo labile degradation (46). Photo labile degradation is also influenced by the intrinsic photosensitivity of the counter ions present in

the salt form. Aromatic (toluenesulfonic acid) and/or carbonyls (oxalic acid) counter ions shows higher photo degradation compared to non-aromatic counter ions (47). The explanation is that oxalic acid, the carbonyl counter ions and toluenesulfonic acid, the aromatic counter ions have the higher tendency for photo degradation due to the inherent property. Hydrated salts are more susceptible to photo labile degradation compared to their anhydrous counterparts. Anhydrous salts containing aromatic/carbonyl counter ions are also susceptible to photo labile degradation. Solid-state photo degradation of amlodipine camsylate is lower compared to that of amlodipine besylate (48). The photostability of prazosin salts are prazosin hydrochloride anhydrous >prazosin camsylate anhydrous~ prazosin-free base >prazosin hydrochloride polyhydrate >prazosin tosylate anhydrous >prazosin oxalate dihydrate~ prazosin tosylate monohydrate (49).

Chemical reactivity

Generally, excipients facilitate the release of the drug substance, as well as, stabilize it against degradation. However, excipients can also accelerate the degradation of the drug product. The interaction between the drug substance and excipients influences the instability and bioavailability/bioequivalency of the drug product. The reactive impurities of the excipients as well as the moisture content of the drug substance and excipients often influence the instability of the drug product. Some of the known incompatibilities between the excipients and drug substance are Meglumine with Glipizide (50) and Magnesium Stearate with Clopidogrel (51). Therefore, regulatory bodies require evidence of compatibility between the drug substance and excipients.

Typically, the binary mix of the drug substance and excipient are analyzed to examine the chemical reactivity between the drug substance and excipients. The binary mix of the drug substance and the excipient is stored at different conditions, such as non-stress, thermal, heat and humid, and light. After the defined time, the stored sample is analyzed using a stability indicating test method to determine the percent impurities and remaining potency. The common methods to examine the chemical reactivity are: (i) chromatographic analysis e.g. HPLC, (ii) DSC, and (iii) TGA. However, an orthogonal confirmatory technique is required with DSC to determine the chemical reactivity. Sometimes the information from literature is used to justify chemical reactivity between the drug substance and excipients instead of performing the experiment.

Determining DS critical material attributes (CMAs)

The critical attributes of a drug substance are generally identified by their physicochemical and mechanical properties, intrinsic stability, and chemical reactions with the excipients. The typical critical attributes of the drug substance affecting drug product CQAs and its manufacturability for explicit tracking in risk assessment are: (i) polymorphism, (ii) solubility (BCS Class), (iii) particle size, (iv) intrinsic stability, and (v) water content and hygroscopicity.

Excipients

Excipients affects critical attributes of a drug product such as bioavailability and stability, as well as, manufacturability. Mannitol may influence drug absorption and thus the bioavailability of a drug product. The probable explanation is that Mannitol influences gastro-intestinal motility due to contraction and can decrease the transit time in the small intestine which may impact drug absorption and thus its bioavailability (52, 53). Excipients such as surfactant (Poloxamer) and polymers (Povidone/Polyvinylpyrrolidone) can impact the metabolizing cytochrome p-450 enzymes.

The requirements for excipients as stated in the ICH QbD Guidance (4) are:

a) The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g. stability, bioavailability) or manufacturability are discussed. Compatibility of excipients with other excipients, if relevant, should be established. Excipient compatibility with other excipients is specific to the preservative.
b) The intended functionality of the excipients throughout the drug product shelf life should be demonstrated. The excipients for which the functionality should be demonstrated are antioxidants, penetration enhancers, disintegrants, and release controlling agents.
c) The information on excipient performance can be used to support the justification of the drug product specification.
d) Information to support the safety of excipients, when appropriate, should be cross referenced.

Formulations and process design protocols must capture the above points. The experimental trial outcomes are discussed in the development report required for the CMC review. Usually, drug substances and drug product attributes and its manufacturability are used to justify the appropriateness of excipient selection. An understanding of pharmaceutical hydrates as excipients and their impact on product quality and its manufacturing process is often helpful. Some of the commonly used hydrates as excipients are, magnesium stearate, lactose, glucose, dextrose or calcium diphosphate. Use of magnesium stearates in the solid dosage formulation is always critical. Differences in the hydration state i.e., water of crystallization between batches of magnesium stearate impacts its lubrication properties (54). The physical properties of magnesium stearate vary between batches due to its hydration state and thus affects powder beds mechanical properties and tablet die wall friction. Physical attributes, such as particle size, surface area, porosity, surface morphology, and viscosity of excipients have the potential to impact drug product manufacturing process and quality attributes. Sometimes commonly used excipients such as, starch is modified by chemical or mechanical methods to enhance its functionality. For example, starch can be modified chemically through carboxy-methylation to enhance hydrophilicity and crosslinking to reduce solubility. The source of starch, particle size, amount of sodium chloride (reaction by-product), viscosity, degree of substitution and cross-linking effect the functionality of the modified starch e.g. pregelatizied starch, sodium starch glycolate etc. The author has observed differences in disintegration, and experienced capping during compression due to differences in liquid uptake and settling volume (15 *versus* 30) of disintegrants e.g., Croscarmellose sodium.

All possible excipients that could be used in the proposed formulation are typically categorized into soluble, insoluble, and hydrophobic materials. The purpose is to ensure the quality and robustness of the proposed formulation and its manufacturability. For example, inorganic/ insoluble/hydrophobic excipients are generally avoided in formulating BCS Class II and IV drugs. Instead hydrophilic excipients together with solubilizers/surfactants are chosen to optimize dissolution and drug absorption. The dissolution profile of the RLD and the proposed drug product are frequently used to rationalize the selection of the disintegrant and control releasing agents used in the proposed formulation. An example of excipient description is described below.

Croscarmellose Sodium NF

Croscarmellose sodium NF is a crosslinked polymer of carboxymethyl cellulose sodium

(NaCMC) and is an odorless, white or grayish white powder. It is an anionic water insoluble compound which is highly alkaline, and hygroscopic in nature. The pKa of Croscarmellose Sodium NF is 4.17. It swells to 4 to 8 times its original volume in contact with water in less than 10 seconds. It has a bulk density of 0.529 g/cc, and specific surface area of 0.81–0.83 m^2/g (55).

In general, Croscarmellose Sodium NF is nontoxic and nonirritant in nature. However, oral consumption of large amounts of Croscarmellose Sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such a problem. The reactive impurities present in Croscarmellose Sodium are nitrite (NO_2) and nitrate (NO_3). These reactive impurities can react with functional groups, such as dialkyl, alkylaryl, diaryl, cyclic secondary amines, *N*-alkylureas, *N*-alkylcarbamates, and *N*-alkylamides to form *N*-nitroso compounds (e.g. nitrosamines or nitrosamides). The nitrosamines or nitrosamides are the drug substance degradates. Drug substance potency decreases due to the formation of nitrosamines or nitrosamides. In addition to the potency loss, nitrosation at trace levels can also be carcinogenic (56). Croscarmellose Sodium also reacts with weakly basic drugs in the presence of moisture causing loss in disintegration capacity. Therefore, the ability of the disintegrant to fully push apart the tablet matrix is reduced and hence dissolution is slowed down. The change in interparticulate bonding of the disintegrant is believed to cause a decrease in dissolution rate. Croscarmellose Sodium is not compatible with strong acid or with soluble salts of irons and other metals, such as aluminum, mercury, and zinc. It loses its disintegration capacity when used in wet granulation or in direct compression with other hygroscopic ingredients e.g. sorbitol (57).

It is one of the so called super disintegrants and used at a concentration up to 5% $^{W}/_{W}$ of tablet weight. The disintegration mechanism of Croscarmellose Sodium is swelling and wicking. It is suitable for both direct compression and dry granulation. In addition to its disintegrant property, the addition of a large amount of this super disintegrant in the formulation of micronized drugs prevents the agglomeration of the drug substance during compression.

Risk assessment

The ICH QbD Guidance requirements for risk assessment of the input materials, as well as, process parameters are summarized below (4):

a) Critical material attributes (CMAs) and critical process parameters (CPPs) impacting drug product CQAs is linked.
b) Risk assessment is typically performed early in the pharmaceutical development process and repeated as more information becomes available and greater knowledge is obtained. The risk assessment tools mentioned in the guidance are the Ishikawa (fishbone) diagram and the failure mode and effects analysis (FMEA).
c) Risk assessment could be based on prior knowledge and initial experimental data.

The two basic elements of risk assessment are the identification of hazards and evaluation of risk associated with exposure to those hazards. Three fundamental questions are often helpful in defining risk. The questions are (i) what might go wrong (ii) what is the likelihood (probability) that it will go wrong and (iii) what are the consequences (severity)? (8)

The CMAs of the drug substance are determined considering the impact on the biological properties (e.g. bioavailability), drug product critical quality attributes and its manufacturing process. The typical CMAs of the drug substance for explicit tracking in risk

assessment are: polymorphism, particle size, chemical reactivity, impurity, and water content. Generally, the drug product development report describes the impacts of the drug substance CMAs on drug product CQAs and its manufacturability. A control strategy needs to be outlined to control the identified CMAs of the drug substance. An example of the quantitative risk assessment is outlined in Table 4, considering the impacts of the drug substance CMAs on drug product CQAs and its manufacturability. A risk priority number (e.g. low/medium/high) is used for the assessment.

PROCESS UNDERSTANDING

The common elements of process understanding are: (i) manufacturing process selection, (ii) drug product and manufacturing process development, and (iii) risk assessment.

The elements of process understanding along with the container and closures system are discussed below.

Manufacturing process selection

The requirement is to select an appropriate manufacturing process based on scientific rationale. The purpose is to mitigate the potential effects of the drug substance and excipients attributes on drug product performance as well as on unit operations. Sometimes the manufacturing process of the RLD is referred to justify the manufacturing process selection of the proposed drug product. The manufacturing process of the RLD could be available in the literature or patents. Sometimes reverse engineering study is also performed to determine the manufacturing process of the RLD. Some of the examples of manufacturing process selection are: (i) since the solubility of the drug substance is poor, a solid dispersion/hot melt extrusion process is employed to improve the dissolution and absorption of the drug product, (ii) a dry/wet granulation process is suitable when the flow property of the drug substance is poor; however, dry granulation is preferred for reasons of cost, (iii) a hot melt/wet granulation process is selected as the drug substance shows

Table 4 Risk assessment of DS attributes on DP CQAs

DS CMA	DP CQA					MANUFACTURING
	DU	ASSAY	DT	DISSOLUTION	STABILITY	
Polymorphism						
Chemical Stability						
Degradant/Impurity						
Particle Size						
Hygroscopicity/ Water Content						

Low: No investigation is required or not applicable

Medium: Investigation may be required

High: Investigation is required

DU: Uniformity of Dosages Unit
DT: Disintegration

reduced crystallinity after processing (e.g. milling, micronization), (iv) a direct compression/dry granulation process is selected because the drug substance is susceptible to hydrolytic degradation, and (v) encapsulation approach is chosen as the drug substance has a low melting point. Besides formulation optimization, stringent environment and process controls are required for any drug substance susceptible to hydrolysis/ oxidation/photolytic degradations to ensure desired drug product performance and its manufacturability.

Drug product development

The ICH QbD Guidance requires an initial formulation risk assessment to identify the focus of the drug development. The goal is to meet the QTPP. Formulation parameters, such as pH dependent solubility of the drug substance, drugs forming insoluble complexes with the GI contents, instability in the GI tract, and physicochemical interaction that could affect *in vivo* absorption (58). In general, the drug is micronized to increase the dissolution rate and thereby the absorption of BCS Class II and IV drugs.

The micronized/fine particles have a large specific surface area and hence dissolve at a faster rate leading to improved drug absorption. However, micronized/fine particles have a greater tendency to form agglomerates which can decrease the dissolution rate. Therefore, an initial risk assessment of the proposed formulation is performed to identify potential problems that could affect the CQAs of the drug (e.g. assay, dosage uniformity, disintegration, dissolution, and impurities). The typical ways to perform an initial formulation risk assessment are a cause-and-effect diagram, such as the Ishikawa (fishbone) diagram and quantitative risk mapping. A risk priority number, such as low, medium, or high is employed for quantitative risk assessment. Initial formulation risk assessments are often based on prior information of the input materials' attributes together with knowledge of developing similar dosage forms, as well as, the unit operations. An example of an initial formulation risk assessment is shown in Table 5.

The QbR requirements for the drug product developments are: (i) what attributes the drug product should possess, (ii) how the drug product was designed to have these attributes, (iii) how alternative formulations or mechanisms were investigated, (iv) how the excipients and their grades were selected, and (v) how the final formulation was optimized.

Table 5 Initial formulation risk assessment using prior knowledge

DP QA	INPUT MATERIAL					MANUFACTURING PROCESS				
	DS PS	Excipient Grade and Ps	Major Excipient Ratio	Disintegraton Level	Magnesium Stearate Level	Blending	Lubrication	Compacting	Coating	Pkg.
Physical Attributes										
Hardness										
Assay										
DU										
Dissolution										
Degradation/ Stability										

Low: No investigation is required or not applicable

Medium: Investigation may be required

High: Investigation is required

Formulation development

The required elements of the formulation development as detailed in the ICH QbD guidance (4) are:

a) The drug product CQAs is identified.
b) The evolution of the formulation design from initial concept up to the final design should be summarized.
c) The excipient ranges, if any, included in the batch formula should be justified; this justification can often be based on the experience gained during development or manufacture.
d) Formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and the formulation(s) used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.
e) Information from comparative *in vitro* studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) that links clinical formulations to the proposed commercial formulation should be summarized and a cross-reference to the studies (with study numbers) should be provided. The results of the *in vitro/in vivo* correlation (when performed) and a cross-reference to the studies (with study numbers), should be provided.
f) Any special design features of the drug product should be identified and a rationale should be provided for their use. The special design features include tablet score line, overfill, and anti-counterfeiting measures.

Overages

a) Use of an overage of a drug substance is discouraged.
b) The information required for using an overage are: (i) the amount of overage (ii) the reason for the overage (e.g. to compensate for expected and documented manufacturing losses) and (iii) a justification for the amount of overage.
c) The overage should be included in the batch formula.

Typical formulation related deficiencies (59) are: (i) Ethylcellulose is listed as a binder instead of a rate controlling agent, provide data to demonstrate that the amount of Ethylcellulose used has no impact on the drug release profile, (ii) it was concluded that high polymer content can prevent the drug substance from undergoing physical changes, such as re-crystallization, clarify if the drug substance remains as crystalline form or transforms to amorphous form, (iii) provide the excipient compatibility (chemical and physical changes) study report performed during the pharmaceutical development, and (iv) clarify the difference in the acceptance criteria of the excipient (name) between the vendor's and yours.

Therefore, the formulations and process design protocol must integrate the QbD requirements and the possible QbR deficiencies discussed above. The findings are discussed in the development report to expedite the CMC review and to thereby reduce the approval time. One of the main goals of formulation design is to overcome the identified limitations of the drug substance, such as poor solubility or susceptibility to degradation.

The solubility of some drugs is pH dependent, and sometimes the drug has a tendency to crystallize or precipitate during dissolution. For example, dissolution of some weakly basic drugs (e.g. Quetiapine Fumarate) slows down due to its pH dependent solubility. The probable reasons for this release problem are the variable

pH of the GI tract and/or precipitation or crystallization of the free base during dissolution. Sometimes the pH of the GI tract increases as a result of antacid or food consumption. The slow or incomplete drug release impacts drug bioavailability/ bioequivalence. Therefore, the formulation is often optimized to mitigate the described degradation pathways of such drugs. The common ways to improve the performance of such drugs is to modify the micro-environmental pH or to add an antioxidant in the formulation to limit oxidative degradation. Acidic excipients, such as Tartaric Acid/Citric Acid/Fumaric Acid are often used in the formulations of such drugs to overcome gastric pH interaction. The addition of these excipients in the formulation of such drugs ensures optimal bioavailability/bioequivalence. Therefore, the choice of pH modifying excipients along with its levels for such drug is critical.

Several formulations around the target are usually examined through initial trials. The trials are performed to determine the robustness and sensitivity of the formulation and its impact on drug product CQAs. In general, the formulation variables are identified based on prior knowledge and/or using the design of experiment (DoE). The other typical considerations for initial formulation design are the patent on the drug substance, drug product formulations, and its manufacturing process. The common components of formulation development are identification of lead formulation, determination of excipient CMAs, and risk assessment. These elements are outlined below.

Identifying the lead formulation

In general, laboratory and pilot scale experiments are performed to determine the lead formulation(s). The quality attributes that are examined during the lab scale trials are tablet hardness and dissolution. The prospective formulation(s) are determined based on the lab scale trials. The prospective formulation(s) are then scaled up to a 5 to 20 kg batch size or more, depending on tablet weight and the experimental design. Typical evaluations performed at the pilot scale trials are: (i) blending time and blender speed (ii) granulate physical and chemical (blend uniformity) quality attributes (iii) compression force and (iv) tablet physical and quality attributes. The evaluations of blend characteristics include particle size distribution, bulk density (BD), tapped density (TD), and blend uniformity of 6 or 10 locations from the blender, and granules flowability. The evaluations of the tablet physical attributes include tablet weight (n=20), hardness, thickness, and friability (6 g or more). The quality attributes that are examined at this stage are dosage uniformity (n=10 or 20), impurity profile, and dissolution (n=12). Composite samples from the beginning, middle, and end of the operation are generally analyzed for evaluation purpose.

The lead formulation(s) is often selected based on tablet hardness, dosage uniformity, impurity profile, and dissolution rate. Typically statistical assessment is performed to compare the quality attributes of the experimental batches and RLD. One of the statistical assessments is to calculate the p value. The p values must > 0.05 to demonstrate that quality attributes of the experimental batches is comparable to the RLD. Statistical analyses are performed to justify that the proposed formulation is comparable to the RLD.

The development report documents the summary of each unit operations along with the equipment and the process parameters used. It also documents the in-process and quality attributes obtained from all the trial batches. The report identifies the processing problems observed and the actions taken to overcome the problems. This information is often useful for investigating future deviations. The activities

Table 6 Screening study

	PATTERN	DS*	DILUENT 1	DILUENT 2	BINDER	DISINTEGRANT	LUBRICATION
1	– – – – + +	-1	-1	-1	-1	+1	+1
2	– – + + – –	-1	-1	+1	+1	-1	-1
3	– + – + – +	-1	+1	-1	+1	-1	+1
4	– + + – + –	-1	+1	+1	-1	+1	-1
5	000000	Target	Target	Target	Target	Target	Target
6	+ – – + + –	+1	-1	-1	+1	+1	-1
7	+ – + – – +	+1	-1	+1	-1	-1	+1
8	+ + – – – –	+1	+1	-1	-1	-1	-1
9	+ + + + + +	+1	+1	+1	+1	+1	+1

*Theoretical low (-) and high (+) assay

performed at this stage are generally used to justify formulation robustness and sensitivity.

Determining excipients CMAs

Excipient grade and level influence drug product performance and its manufacturability. Therefore, experimental trials are performed to evaluate the impact of different grades and levels of excipients on product quality and unit operations. Experimental trials determine the CMAs of the major excipients affecting drug product performance and its manufacturability. Prior knowledge of CMAs of the selected excipients and manufacturing process in question is often used as QbD checklist for excipient.

Excipient Grades

Physical properties, for example, particle size, loss on drying, and flow of different grades of the same excipients are different. Formulations are designed and performed using at least two grades of the major excipients to evaluate the impact on product quality attributes and its manufacturability. The in-process quality attributes that are examined during the trials include weight (n = 20), hardness, thickness, and friability (6 g or more), capping, cracking, and disintegration. Dosage uniformity (n = 10), the impurity profile, and dissolution (n= 6 or 12) are analyzed to evaluate the product performance. The product development report describes the impact of the excipient grades on drug performance and its manufacturability. The report is also expected to document equipment and process parameters used for each trial. The evaluated result is used to justify the grades of the excipients.

Excipient Levels

Experimental trials are designed and performed to assess the effect of the generally used excipients, for example, diluent, binder, disintegrant/solubilizer, glidant, and lubricant levels on drug product in-process and quality attributes and on unit operations. The experimental trials are designed based on the worst case scenario of the drug substance assay (theoretical low and high assay values) or using the design of experiment (DoE) model e.g. screening study. In a worst case scenario, the major excipient levels are calculated based on the drug substance theoretical low and high assay values. The other technique that can be used is a screening study. An example of a screening study based on low (-) and high (+) levels of excipients is outlined in Table 6.

The summary report documents the trial findings and describes the impact of excipient levels on the drug product quality attributes (physical and chemical). It also describes the manufacturability of the drug and the equipment and process parameters used. The evaluated result justifies the excipient levels with a target quantity that could be used in future.

Table 7 Risk assessment of formulation variables

ELEMENT	DP CQAs					MANUFACTURING	JUSTIFICATION
	DU	Assay	DT	Dissolution	Stability		
Excipient compatibility							Influence scale up Impact unit operations, tablet hardness, BU, DU, DT and dissolution
Major excipient PS							
Excipient Impurity							
Major excipient Grade & Level							
Glidant Level							
Lubricant Level							

The goal is to keep an option for continual improvement.

Risk assessment

Chemical reactivity, excipient grades and levels trials identify the risks of the CMAs on drug product quality and its manufacturability. Generally recognized CMAs of the excipients for explicit tracking in risk assessments are particle size, flow, hygroscopicity, and reactive impurities. An example of assessing the risks of formulation variables is described in Table 7.

The formulation development studies and the risk assessment together determine the most likely formulation that will ensure problem free scale-up and subsequent process validation. Therefore, the prospective formulation is used during the manufacturing process development study to finalize the ranges for the critical process parameters of each unit operation.

Manufacturing process development

The elements of the manufacturing process development as expressed in the ICH QbD Guidance are listed below (4).

a) The selection, the control, and any improvement of the manufacturing process should be explained.
b) The selection of the manufacturing process, appropriateness of the components and equipment used should be discussed.
c) Critical process parameters are identified, monitored and controlled.
d) Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, and bioequivalence) or primary stability studies and the process for commercial manufacturing should be discussed. The information should include, for example, (i) identity (e.g. batch number) and use of the batches produced (e.g. bioequivalence study batch number), (ii) manufacturing site, (iii) batch size, and (iv) any significant equipment differences (e.g. different design, operating principle, or size).
e) A description of the measurement systems applied during monitoring and collection of CQAs/CMAs/ CPPs.
f) An assessment of the ability of the process to reliably produce a product of the intended quality e.g. the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment.

The purposes of the manufacturing process development are to (i) enable scale-up and decrease variations in drug product quality and its manufacturability using a science-based approach, (ii) provide flexibility for future process improvement, (iii) enhance process understanding, (iv) to reduce risk through risk assessment, and (v) justify the drug product specification.

A manufacturing process development study for non-problematic drug substances and noncritical dosage forms is optional. For example, an immediate release dosage form is manufactured using a direct compression process. The formulation contains a drug substance that is highly soluble, stable, and flows well. The other components, for example, diluent, binder, disintegrant, and lubricant are commonly used grades and are recognized in the national formulary or other acceptable quality standards. Their levels in the formulation are supported by the the Inactive Ingredient Database (IID) limits. The drug load in the formulation is between >10% to <50% $^{W}/_{W}$. In such cases, a manufacturing process development study may not be required provided that it could be justified based on prior knowledge.

Typical deficiencies pertaining to the manufacturing process development (59) are (i) to clarify how the critical process parameters (CPPs) were identified, monitored, and/or controlled for each unit operation, provide a summary table to adds clarity and facilitates review, (ii) drug content in the final blend is low, the manufacturing process is a direct compression process, provide available information regarding the segregation potential of the blend under your manufacturing conditions, and the possible impact on the content uniformity, (iii) for the pre-lubrication and lubrication blending of the commercial batch, establish your mixing time in relation to the scale-up effect from a 5 cu. ft. to a 80 cu. ft. blender, and (iv) provide data to justify your tablet hardness range, especially its impact on friability, shipping, and dissolution at the extremes of the proposed hardness range.

A scale-up plan should be based on the risk assessment of each variable and the process understanding gained during pilot scale and prior knowledge. One of the considerations for scale-up manufacturing is the design and operating principle of the equipment. Special attention is required if the manufacturing equipment is not within the same SUPAC (scale up and post approval changes) equipment class of the bio or submission batch. The factors considered in blending scale-up are (i) geometric similarity: ratio of all lengths constant (constant fill ratio), (ii) dynamic similarity: maintenance of forces (Froude number), and (iii) kinematic similarity: maintaining a consistent number or revolutions. Experimental trials examine the impacts of the process parameters of each unit operations on drug product quality attributes (in-process and CQAs) and its processability. Trial findings determine the ranges of the critical process parameters of each unit operations. Identification of the CPPs of different unit operations is summarized below.

Identifying the critical process parameters (CPPs)

Typical CPPs of different unit operations and their probable impact on the drug product in-process quality attributes and CQAs, and the drug's manufacturability are discussed below.

De-agglomeration or milling

Screen size and impeller speed used during milling can affect the drug substance (e.g. phase conversion of metastable drugs) and the segregation of low drug content formulation. In general, smaller screen size and moderate impeller speed is used to de-agglomerate the cohesive/micronized drug substance. The objective is to ensure uniform dispersion of the drug substance without impacting its crystal structure.

Blending

Critical parameters of the blending process are bin fill, mixing order, blending time, and blender speed. The bin fill depends on several factors, for example, (i) drug substance and excipients flowability (ii) drug content in the formulation

and (iii) the manufacturing process. The bin fill is especially critical for the direct compression process which depends on drug content in the formulation. The recommended bin fill for mixing the cohesive/micronized/ fines and free flowing drug substance and excipients is 60% and 80% respectively of the blender working capacity. A blend time analysis method is used to evaluate blending time. Blend time analysis is performed by collecting the blend sample from the identified dead spots of the blender at different time points. The collected blends are usually examined for density, flow, blend uniformity, compressibility, and dosage uniformity.

Dry Granulation (Roller Compaction)

The purpose of compaction is to produce quality granules to ensure optimum flow and compressibility. Compaction process parameters control the physical quality attributes of the granules, such as particle size and their distribution, bulk and tapped density and flow. Particle size and shape along with the density influence the flow and compressibility of the granules. Granules flow and compressibility influence blend and dosage uniformity, and compression force and speed, and thereby impact drug product quality attributes, such as tablet weight, hardness, friability, disintegration, and dissolution. Generally recognized critical parameters of the compaction process are compaction force (CF), roller speed (RS), and roller gap (RG). An example of identifying the CPPs of the roller compaction process is outlined in Table 8 using a partial factorial design of experiment (DoE) model.

Table 8 Partial factorial DOE design: compaction parameter evaluation

TRIALS	PATTERN	CF (kN/cm) – X1	RG (mm) – X2	RS (rpm) – X3
1	--+	-1	-1	+1
2	-+-	-1	+1	-1
3	000	Target	Target	Target
4	+--	+1	-1	-1
5	+++	+1	+1	+1

The granule produced using each experimental trial is analyzed for physical characterization. The physical characteristics analyses determine the compaction parameters as well as the in-process acceptance limits of particle size distribution (sieve analysis), density, and flow.

Compression

Typical critical parameters of the compression process are compression speed and compression force. In addition, sometimes feeder speed may influence the segregation of low drug content formulation leading to OOS dosage uniformity and assay. Compression speed influences blend flow and thereby impacts tablet weight, hardness, and dosage uniformity. Compression force influences tablet hardness, disintegration, and dissolution. Trial plans, such as low weight – high weight (LW – HW), low speed – high speed (LS – HS) and low hardness – high hardness (LH – HH) are designed and performed to determine the ranges of the compression parameters. The analysis of the tablet physical quality attributes, for example, weight, hardness, thickness, friability, and disintegration of each experiment determines the tablets in-process quality attributes along with the compression speed. This also provides a guideline for pre and main compression force.

Coating

There are two types, i.e., functional and non-functional film coating. The degree of criticality of the non-functional coating is less compared to the functional coating. Sometimes, a seal coat is applied based on the drug substance and the coating solution/dispersion attributes. The objective of a seal coat is to ensure the robustness of the product. Triethyl citrate (TEC) is commonly used as a plasticizer in aqueous based delayed release coating. TEC is slightly acidic in nature, and so can influence the degradation of the drug substance (e.g. Pantoprazole) during the coating process (60).

Table 9 Delayed release coating process parameters

PARAMETERS	RANGES	CONTROLS	COMMENTS
Coating Dispersion			
Dry polymer on the tablet per cm^2 area	Yes	Yes	Ensure delayed release
Plasticizer on dry polymer	Yes	Yes	Provides elasticity to polymer.
Total quantity of insoluble excipients	Yes	Yes	Ensure film mechanical strength
Total solid contents	Yes	Yes	Governs solidification, impacts film mechanical strength
Mixing time	Yes	Yes	To ensure dispersion quality.
Coating Process			
Pan Load	Yes	Yes	Ranges based on study
Spray Rate	Yes	Yes	Ranges based on study
Gun Distance	No	Yes	Fixed for specific pan load
Gun Angle	No	Yes	Fixed
Pan Speed	Yes	Yes	Machine controlled in Auto Mode
Atomizing and Pattern Air Pressure	No	Yes	Fixed based on study
Exhaust Air Temp.	Yes	Yes	Based on study
Inlet Air Humidity	Yes	Yes	Impact film mechanical strength of hygroscopic core.

High susceptibility to hydrolysis coupled with an acidic environment influence the degradation. Therefore, a seal coat is applied to protect the tablet core of such drug substances. In this case, the seal coat does not contain TEC as a plasticizer. The goal is to ensure that the reactive ingredient, for example, TEC, in the final coating formulation does not come into contact with the core tablet. An example of identifying the critical parameters of the delayed release coating process is described in Table 9.

Worst case scenarios, e.g., extreme low and extreme high together with risk assessments are used to establish the ranges of the critical process parameters of each unit operation.

Risk assessment: impact of the CPPs on DP CQAs

The risk assessment tools for pharmaceutical manufacturing process development are described in the guidance (4, 8). They are failure mode effects analysis (FMEA), failure mode effects criticality analysis (FMECA), and hazard operability analysis (HAZOP) (8). FMEA focuses on how and when a system will fail, not if it will fail. Regulatory bodies accept both approaches, such as worst case experiments and risk assessment tools to establish the CPPs and their impact on CQAs. However, establishing the critical process parameter ranges using a risk assessment tool is optional for non-problematic generic formulations and process development. An example of determining the impact of critical process parameter(s) of unit operations on drug product CQAs is presented in Table 10 using FMEA risk assessment tool.

The RPN and criticality number provides guidance for ranking potentials failures in the order they should be addressed.

Formulation and process selection

The formulation and manufacturing process development studies determine the final formulations and manufacturing processes for the bioequivalence/stability/submission batch. The drug product CQAs manufactured using the optimized formulation and processes are compared with the RLD. The QbR questions with respect to composition of the drug product are: (i) what are the components and composition of the final product and their quality standard? What is the function of each excipient, (ii) does any excipient exceed the Inactive Ingredients Database (IID) limit for this route of administration, and

Table 10 Risk Assessment: Impact of CPPs on DP CQAs

Unit Op	Failure Mode/ CPPs	Potential Effects of Failure	S	Potential Cause of Failure	O	Detection	D	RPN**	CRITICALITY	Design/Control Strategy	S	O	D	RPN	CRITICALITY
	Screen size	Poor de-agglomeration. Impact assay and DU.	5	Drug substance particle size is not considered.	1	Release test (Assay, DU)	5	25	5	Develop screen size guideline considering drug substance particle size, drug content and manufacturing process.	5	1	1	5	5
Blending	Bin fill, blender speed and blending time	Mixing is not uniform. Over or under compaction of the blend. Impact BU, DU, DT, hardness and dissolution	5	Scale up batch size is not considered during initial development. Equipment malfunctions due to motor problem. Timer malfunction. No instruction to check blender speed and time as the time is preset.	3	BU/DT/Hardness	3	45	15	Link development batch size to submission/clinical study batch size and to the commercial batch size. Check list to ensure preventive maintenance, calibration of the blender speed and time.	5	1	1	5	5
Roller Compaction	Compaction force (CF), Roller gap (RG), Roller speed (RS)	Ribbon density. High/low density granules. Irregular granules size (big and small). Segregation potential, Impact flow and compressibility (hardness)	5	Compaction parameters are not optimized with a range.	5	Sieve analysis BD and TD	3	75	25	Determine granules physical attributes (PSD, BD, TD) in-process criteria based on the impact of the target and extreme parameters.	5	1	3	15	5
Compression	Hardness/ compression force and speed	Impact tablet porosity and dissolution	5	Poor quality granules cause variation in compression force.	5	Dissolution test	5	125	25	Determine hardness ranges based on compression speed and dissolution test result.	5	1	5	25	5

	Ranking			
	1	**3**	**5**	**7**
Severity (S)	Low: Deviation	Reprocessing	Batch Rejected	Recall
Occurrence (O)	Unlikely: 1 out of 500	Occasional: 1 out of 100	Repeated: 1 out of 20	Regular: 1 out of 10
Detectability (D)	Always before operations	During in-process test or before the next unit operation	During the release test	During stability test

** Risk Priority Number RPN = S*O*D, Criticality = S*O

(iii) do the differences between this formulation and the reference listed drug (RLD) present potential concerns with respect to therapeutic equivalence? Therefore, the product and process development summary report describes the (i) component and compositions of the final product with reference to the quality standard (ii) function(s) of each excipient (iii) excipient levels with reference to the IID limit for the route of administration (iv) potential differences between the selected formulation and the RLD with respect to therapeutic equivalence, if any, and (v) comparative formulation of the proposed drug product and the RLD.

Regulatory bodies accept the differences in excipients with a justification. An example of component and composition, and a comparative formulation of the proposed drug product are presented in Tables 11 and 12 respectively.

Table 11 Components and composition of the proposed drug product

COMPONENT	QTY (mg/TAB)		IID QTY	FUNCTION	REFERENCE TO QUALITY STANDARD
	xx mg	xy mg			
DS	X	X1	--	Active	USP/BP/EP/ In-house
Excipient 1	X	X2	--	Diluent	NF/EP/ In-house
Excipient 2	X	X3	--	Binder	NF/EP/ In-house
Excipient 3	X	X4	--	Disintegrant	NF/EP/ In-house
Excipient 4	X	X5	--	Glidant	NF/EP/ In-house
Excipient 5	X	X6	--	Lubricant	NF/EP/ In-house
Tablet weight (mg)	Xx	xy			

Table 12 Comparative formulation of the proposed drug product

PROPOSED DP	RLD	FUNCTION	JUSTIFICATION
DS	DS	Active	Diluent, binder and disintegrant used in the proposed drug product and RLD are different. However, the diluent, binder and disintegrant used in the proposed drug product are established and recognized for solid dosages formulation. In addition, the desired drug product performance and its manufacturability have been established.
Excipient 1	Excipient x	Diluent	
Excipient 2	Excipient x	Binder	
Excipient 3	Excipient x	Disintegrant	
Excipient 4	Excipient x	Glidant	
Excipient 5	Excipient 5	Lubricant	
	Excipient 6	Diluent	

x is used to differentiate material differences between the proposed and RLD formulation.

Container and closures system

The ICH QbD Guidance requirements for the container and closures systems are (4):

a) The choice and rationale for selection of the container and closures system particularly the primary packaging for the commercial product are discussed.
b) The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure.
c) The choice of primary packaging materials should be considered e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included when relevant.

The QbR questions related to the container closures are: (i) rationale for choice of the container closure system i.e. what specific container closure attributes are necessary to ensure product performance, (ii) what container closure system(s) is proposed for packaging and storage of the drug product? Has the container closure system been qualified as safe for use with this dosage form, and (iii) is the container closures suitable for use with respect to performance, functionality and safety. Relevant compendial test and controls for the container closure are USP <381> (Elastomeric Closures for Injections), <87> (Biological Reactivity Tests, *In Vitro*), <660> (Containers – Glass), <661> (Containers- Plastics), and <671> (Containers – Performance Testing). These tests are intended to demonstrate the identity, performance, suitability, compatibility and safety of the container closures. Generally, deficiency is cited, if this information is not mentioned.

Environmental factors, such as moisture, oxygen, and light often influence the hydrolytic/oxidative/photo degradation of the drug product. Therefore, the drug must be protected by an effective barrier to prevent or control the negative influence of environmental factors. For example, the moisture ingress often influences the appearance (e.g. discoloration) and tablet softening or hardening as well as hydrolytic degradation. Degradations adversely affects assay; dissolution and impurity profile of

the drug product thereby compromising its safety, purity and efficacy. Therefore, in general, high humidity territories warrant extra precautions.

A justification for the selection of the container and closures system is required. Intrinsic stability of the drug substance and distinctive quality attributes of the primary packaging component influence the selection of the container and closures system. The quality attributes of the container and closures are physicochemical stability and barrier property against environmental factors (e.g. moisture, oxygen, and light). The other two aspects of container and closures selection are its child resistance property and security (e.g. anti-counterfeiting, tamper evident). The child resistance property of the container and closures is a legal requirement for the USA and Canada with few exceptions. However, child resistance of the container and closures is not mandatory in all European countries. In some European countries, the requirement is product specific. In addition to protection against environmental factors, the selection of the container and closures system depends on the cost of goods (CoGs), market trend, and preferred pack size/patient compliance. Selecting the right container and closures from the beginning minimizes stability failure and regulatory review questions. It also ensures the best product shelf-life.

Stable products are not sensitive to environmental factors. Therefore, the relevant scientific data pertaining to the intrinsic stability of the drug product and barrier property of the container and closures are sufficient to show the acceptability of the drug product's physicochemical integrity during storage. However, for moisture/oxygen/light sensitive drugs (e.g. Pantoprazole), it is required to demonstrate that the container and closures provide an effective barrier. Stability data at different storage conditions supports the effectiveness of the container and closures barrier property.

The high density polyethylene (HDPE) bottle is the preferred packaging format for tablets and capsules in the USA and Canada. The most common packaging for Europe and the rest of the world (ROW) is blister. Understanding the container and closures barrier properties and the packaging processes provide the basis for selecting the right container and closures. The barrier properties of some commonly used container and closures and typical critical aspects of the packaging process are briefly discussed below.

HDPE Bottle package

Water vapor transmission rate (WVTR) and oxygen vapor transmission rate (OVTR) influence the selection of the HDPE bottles. Theoretical WVTR of a standard 60cc HDPE bottle when stored at 40ºC/75% RH (relative humidity) is equal to 1 mg of water per day. Therefore, RH conditions within a standard 60cc HDPE bottle could re-equilibrate to 50% within 1 day, even if a product is packaged under low water vapor conditions. The OVTR of the HDPE, Polypropylene (PP), and PVC (polyvinyl chloride) bottle is 102 {g.mm/(m^2.day)}, 89 g.mm {g.mm/(m^2.day)}, and 4 {g.mm/(m^2.day)}, respectively.

In addition to permeation through the walls, the key vulnerability in a HDPE bottle is the screw-topped closure even when a lid induction seal is used. Moisture and oxygen levels in the container head space can be significant enough to affect the stability of some drugs. The author experienced a decrease in the dissolution rate of weakly basic drugs (e.g. Domperidone Maleate, pKa of 13.4) in presence of Croscarmellose Sodium NF due to the presence of environmental moisture in the bottle head space. Therefore, desiccants are used to prevent moisture mediated degradations. The adsorb/ absorb capacity of the desiccant varies

depending on storage conditions. For example, silica gel is efficient in absorbing moisture at high RH, but inefficient at lower RH. However, it is the opposite for molecular sieve desiccants. The molecular sieve is approved for pharmaceutical products in the EU, but not in the USA for commercial products. The amount of desiccant required to maintain relative humidity within a specified range over the product's shelf-life can be calculated. The calculation uses the WVTR of the container's material of construction and the rate of moisture adsorbed by the desiccants. An oxygen-impermeable seal (e.g., induction heat seal) is used for oral solid dosage forms prone to oxidative degradation. The induction seal is also used to ensure security of the packaged drug product. A secondary pack component can augment light protection.

The opacity of the container does not necessarily mean that it will protect the product from light. HDPE bottles are generally opacified with titanium dioxide pigment to prevent light transmission. However, HDPE bottles still allow significant light transmission because the light is scattered both internally and externally. Therefore, HDPE bottles are not used to pack light sensitive drugs.

Blister packages

Three types of pharmaceutical blister package are commonly used. They are: (i) thermoform (ii) cold form and (iii) tropical blister. The two components of a blister are forming/base film and lid foil. The polymers influence the characteristics of the commonly used blister films and the critical aspects of the blister packaging parameters. The intrinsic moisture and oxygen transmission properties of commonly used single polymers are different. The intrinsic transmission rate is the characteristic of each polymer (grade) and represents the thickness independent barrier performance (commonly called "the transmission rate of a one micron thick film").

PVC is the most commonly used base film in blister packs. The WVTR of the PVC film of 250 microns is about 3.72 g/(m² d) at 38°C and 90% RH (61). The PVC film is commonly used to pack stable drugs. The use of PVC in some European countries is restricted by regulations due to its disposal concern. The common disposal method of PVC is incineration that produces toxic gas.

Other blister films with superior barrier properties are available on the market. Blister films with enhanced barrier properties are PVC/PVdC (polyvinyl dichloride), PVC/PCTFE (polychlorotrifluroethylene), and cold form.

For PVdC coated PVC film, PVdC layer is specified in gsm. The weights of commonly used PVdC coating are 40 gsm, 60 gsm, 90 gsm, and 120 gsm. The PVC/PVdC film is offered with or without a middle layer of polyethylene (25μ PE). The polyethylene is used with a heavier coating of 60 gsm, 90 gsm or 120 gsm to improve the thermoforming characteristics of the blister cavity. The PVC/PVdC coated film provides medium to high barrier protection. Depending on the weights of PVdC coating, the WVTR of the PVC/PVdC coated film is varied between 0.6 g/(m²d) to 0.2 g/(m²d) at 38°C and 90% RH (62). PVC/PVdC coated films are easy to form, but PVdC tends to release gas during blister forming. The released gas is sticky in nature and is also reported to damage the blister formats (63).

Depending on the thickness of the PCTFE film, the WVTR of the PVC/PCTFE film is between 0.05 g/(m²d) to 0.45 g/(m²d) at 38°C and 90% RH. Generally, sustained/controlled release products and rapidly dissolving drugs are packaged using PVC/PCTFE blister film. The draft angle of the blister mold for PVC/PCTFE film is generally designed to be 5° to avoid non-uniform blister formation. A plug assist is required if blister depth is >6 mm to

avoid malformation. The most common problem of the PCTFE film is the curl formation towards the PCTFE side of the blister. Therefore, during the blistering process low heat is applied to the PCTFE side to minimize curl formation.

The product contact requirements for PVC/PVdC and PVC/PCTFF are different for the USA and Europe. In the USA, the product contact may only br PVC whereas either PVC or PVdC is acceptable in Europe.

Commonly used lid foils are hard aluminum, soft aluminum, paper/aluminum, paper/PET/ aluminum. Hard aluminum is the most widely used push-through lid foil in Europe. Paper/PET/aluminum is predominantly used in the USA for peel-push (child resistant) blister. The product contact requirement for lid foil is that the heat seal lacquer must be non-reactive and non-toxic. The heat seal lacquer non-reactive and non-toxic information is available in the open part of the DMF.

The cold form blister provides a nearly absolute barrier against moisture, oxygen, and light. The cold form blister generally contains three layers. These are (i) OPA (oriented polyamide)/ aluminum/PVC (ii) OPA/aluminum/nylon and (iii) OPA/aluminum/PP. The presence of aluminum in the cold form blister ensures best protection from light. Cold form blister materials are mostly used to pack drug products that are extremely sensitive to moisture, oxygen, or light.

Some other critical aspects of blister packaging are: (i) blister tip thickness, (ii) sealing temperature, and (iii) outer seal width. The preferred blister tip thickness is one fourth of the base film original thickness. However for stable products, the tip thickness could be up to one sixth of the original thickness. An outer seal width of 3 mm is optimum for moisture/oxygen sensitive products. Generally, a channel is formed between the lid foil and base films due to overheating during sealing. The formed channel allows water/oxygen vapor to pass into the blister pockets, which facilitates the degradation of the drug product. Therefore, the sealing temperature is controlled to ensure optimum sealing, which is generally tested by performing a leak test.

The appropriate container and closures are selected based on the primary packaging materials quality attributes and the drug substance intrinsic stability. The developed drug products are packaged using the selected container and closures. The packaged product is then placed in stability following the ICH stability guideline (44, 64). The product placed in stability is then analyzed at different intervals to assess the integrity, safety, and purity of the drug product. The data is also used to demonstrate the suitability of the container and closures.

The science based analysis of the drug substance attributes, drug product formulation and manufacturing process, and the packaging components discussed above provide the highest confidence for product integrity.

CONTROL STRATEGY

The ICH QbD Guidance requires the design of control strategy to ensure consistent quality of the drug product. The elements of control strategy should describe and justify how in-process controls and the controls of input materials e.g., drug substance and excipients, intermediates e.g., in-process materials, container and closure system, and drug product contributes to final product quality. A control strategy can include, but is not limited to, the following as outlined in the Guidance (4).

a) Control of input material attributes (e.g. drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;

b) Product specification(s);
c) Controls for unit operations that have an impact on downstream processing or product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution);
d) In-process or real-time release testing in lieu of end-product testing, for example, analyzing CQAs (blend and dosage uniformity) during processing;
e) A monitoring program (e.g. full product testing at regular intervals) for verifying multivariate prediction models.

Control strategy pertaining to the test method and testing frequency of the input materials is out of the scope of this paper. Control strategy for the input materials, unit operations, and drug product is briefly discussed below.

Drug substance

The control strategy for a drug substance is determined based on the risk assessment pertaining to intrinsic stability, particle size, impurity, chemical reactivity, and their impact on drug product CQAs as well as its manufacturability. For example, sometimes, the oxidative degradates (>1%) derived from the drug substance are controlled to prevent or minimize the impact on drug product quality. The ways to control the oxidative degradates (>1%) of the drug substance and their interaction with peroxides and/or environmental factors are discussed below.

- Set a tighter limit for the oxidative degradates derived from the drug substance and the reactive impurities of the excipient based on the annual rate of change.
- Perform real time analysis (i.e. prior to use) of the excipient containing reactive impurity.
- Add Butylated hydroxyanisole (BHA), Butylated hydroxytoluene (BHT), Ethylenediaminetetraacetic acid (EDTA), Ascorbic acid, Thioglycerol, Propyl gallate in the formulation.
- Introduce an antioxidant (e.g. BHA or Tetrahydrofuran (THF)) as an impurity in the drug substance, if possible.
- Assign hold time for each unit operations to limit the exposure to environmental oxygen, moisture and temperature.
- Ensure minimum head space in the bottle by selecting the right size bottle for each count and use of desiccant.

The controls discussed above are generally included either in the master production document or in the release testing specification as appropriate. In general, drug specific tests (e.g. polymorphism, particle size, optical rotation, water content, impurities, and residual solvent) are captured in the control strategy.

The typical control strategy for stabilizing photo labile degradation is the addition of light absorbing agents, such as pigments, colorants, or UV absorbers in the formulation or use of appropriate packaging components. The effectivity of the light absorbing agents are pigments > colorants > UV absorbers. The ideal packaging component for extreme photo labile drugs is aluminum foil.

Excipients

The specifications for excipients are included USP/NF compendial monographs. Sometimes, additional specifications, such as particle size and viscosity are included in the release testing to control excipients with critical functional roles or specific grades (e.g. povidone, guar gum). For non-compendial excipients, the development report must provide a description of the tests performed to control identity and quality along with the validation of the test method. Special attention is given to control and monitor the reactive impurities of the

excipients to ensure the product purity, safety and efficacy.

Drug product

Usually the drug product specification includes the tests, procedures, and acceptance criteria used to control quality, identity, strength, and purity of the drug product.

The risk assessments are usually the basis for the control strategy. An example of determining the control strategy for input materials and unit operations using risk assessment and mitigating the risks is outlined in Table 13.

PRIOR KNOWLEDGE

Prior knowledge is one of the important elements of the QbD approach, which is generally the starting point for subsequent assessment. Prior knowledge could be used during the risk assessment of the drug substance, excipient selection, formulation and process design. However, it cannot be generalized as a standard set of information for all applications. It is relevant to the submission if it (i) clearly delineates similarities and differences, (ii) properly links CQA's with CMA's and CPP's, (iii) justifiable/qualifiable based on scientific rationale, (iv) supported by relevant data, and (v) can fill the gaps/missing-links, as applicable. Outside information and industry or in-house information could be used as prior knowledge. The typical sources of outside information are: published literature, research articles, review papers, patents/intellectual properties, reference books, RLD label, and suppliers (equipment/material) technical data sheets. The pertaining industry or in-house information are capability (equipment and technology available, process know-how), dosage form/drug delivery system specific prior submissions, dosage form/drug delivery system specific expertise, specialized material attributes/utilization expertise, drug product specific expertise, and policies/procedures in place. An example to justify the use of prior knowledge is provided in Table 14.

CONCLUSION

There are challenges in implementing QbD and QbR when developing formulations and processes for generic drugs. However, there are benefits when adopting QbD, for example it is possible to select the optimum formulations and processes with a reasonable confidence. Building in QbD to the development process minimizes answers to regulatory review questions and hence, first cycle approval. It can reduce the time for preparing common technical documents (CTD) and also reduce overall product and process development costs. Finally, it will allow for continuing improvements throughout the product life-cycle. The application of QbD minimizes the risks of failing bioequivalence studies, scale-up, validation, and stability studies. It is required to spend considerable time during the product and process characterization phase compared to the execution of the trials. The key to making QbD and QbR implementation a success is the appropriate product and process characterization based on sound scientific principles together with risk assessment. The other requirements for successful implementation of the approach are a strong commitment by top management, appropriate planning, and focused project management.

DISCLOSURE AND CONFLICTS OF INTEREST

The author reports no declarations of interest.

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Table 13 Risk assessment and mitigating risks by control strategy

MATERIAL/PROCESS	CMA/CPPS	IMPACT ON PROCESS/CQAS	RISK LEVEL	RANGES USED FOR BIO/STABILITY BATCH	PROPOSED OPERATING RANGE (Min – Max)	CONTROL STRATEGY
INPUT MATERIALS						
Drug Substance	Polymorphic From	Mfg. Process, Dissolution		Parameter used for bio or stability study batch	Ranges based on the successful experimental trials and bio batch	Specification limits
	Particle size (µm)	BU, DU, hardness, dissolution				
	Impurity (oxidative)	Stability				
	Water content	Mfg. process, dissolution, degradation, microbial growth				
	Particle size	BU, DU				
Major Excipients	Peroxide	Stability				
	Metal Ions	Stability				
Primary Packaging Materials	WVTR/OVTR	Assay, dissolution, degradation				
UNIT OPERATIONS						
Screening	Screen size	BU, DU		Parameter used for bio or stability study batch	Ranges based on the successful experimental trials and bio batch	Acceptance or operating parameter: Fixed or ranges with target
Compaction	CF, RG, RS	Compression, dissolution				
Final Blending	Blend time, blender rpm	Appearance, BU, DU, dissolution				
Compression	Compression speed	Sticking, picking, hardness, dissolution				
	Core tablet hardness	Dissolution				
Delayed Release Coating	Coating dispersion mixing time	Dissolution				
	Coating dispersion holding time	Micro growth				
	Air flow rate					
	Gun distance					
	Pan Speed					
	Spray Rate					
	Atomizing and Pattern Air Pressure					
	Exhaust Air Temp	Film Integrity and dissolution				
	Inlet Air Humidity					
	% of polymer applied on per sq. cm of tablet					
	Coating weight gain					

Table 14 Prior knowledge justification

ELEMENTS	EXAMPLE PRODUCT	PROPOSED PRODUCT	COMMENT
DRUG SUBSTANCE			
Chemical Name	A	C	NA
Polymorphism	Do not exist	Do not exist	Similar
Chiral Center	None	None	Similar
BCS Class/Solubility	Class I, Soluble at pH 1.2 to 7.5	Class I, Soluble at pH 1.2 to 7.5	Similar
pKa	6.0	7.0	Similar
Partition Coefficient	Log P: 0.5 at 25˚C, pH: 7.0	Log P: 0.6 at 25˚C, pH: 6.8	Similar
Particle Size	D50:40-60µm D90: NMT 90µm	D50: NMT50µm D90: NMT80 µm	Comparable
Water Content	LT 2.0%	LT2.5%	Comparable
FORMULATION			
Drug Content	15 %$^{w}/_{w}$	20 %$^{w}/_{w}$	Comparable
Binder Content	12% $^{w}/_{w}$	10% $^{w}/_{w}$	Comparable
Disintegrant			
Mechanism	Wicking (Porosity and capillary action)	Wicking (Porosity and capillary action)	Same
Content	5% $^{w}/_{w}$	4% $^{w}/_{w}$	
Major Diluent and Binder Ratio	3:2	2:1	Comparable
Glidant	0.5% $^{w}/_{w}$	0.8% $^{w}/_{w}$	Comparable
Lubricant	2.0%	1.8%	Comparable
MANUFACTURING			
Batch Size	300 kg	280 kg	Within ± 10%
Process	Dry Granulation	Dry Granulation	Same
Pre-blending time	15 minutes	12 minutes	Comparable
Final blending time	5 minutes	5 minutes	Same
In-process criteria			
Tablet shape	Modified Caplet	Caplet	Similar
Tablet weight	220 mg	200 mg	Comparable
Tablet hardness	10 – 18 kp	8 – 16 kp	Similar

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