AAPS Introductions in the Pharmaceutical Sciences

Ajay Pazhayattil · Naheed Sayeed-Desta
Emilija Fredro-Kumbaradzi
Marzena Ingram · Jordan Collins

Solid Oral Dose Process Validation, Volume Two

Lifecycle Approach Application

aaps®

Springer

AAPS Introductions in the Pharmaceutical Sciences

Series Editor

Robin M. Zavod
Midwestern University
Downers Grove, IL, USA

Springer and the American Association of Pharmaceutical Scientists (AAPS) have partnered again to produce a second series that juxtaposes the *AAPS Advances in the Pharmaceutical Sciences* series. It is a set of introductory volumes that lay out the foundations of the different established pockets and emerging subfields of the pharmaceutical sciences. Springer and the AAPS aim to publish scholarly science focused on general topics in the pharma and biotech industries, and should be of interest to students, scientists, and industry professionals.

More information about this series at http://www.springer.com/series/15769

Ajay Pazhayattil • Naheed Sayeed-Desta
Emilija Fredro-Kumbaradzi • Marzena Ingram
Jordan Collins

Solid Oral Dose Process Validation, Volume Two

Lifecycle Approach Application

aaps®

Springer

Ajay Pazhayattil
Independent Management Consultant
Welland, ON, Canada

Emilija Fredro-Kumbaradzi
Apotex Inc.
Toronto, ON, Canada

Jordan Collins
Privacy Analytics
An IQVIA Company
Toronto, ON, Canada

Naheed Sayeed-Desta
Sanofi Pasteur
Toronto, ON, Canada

Marzena Ingram
Eurofins Alphora
Richmond Hill, ON, Canada

ISSN 2522-834X ISSN 2522-8358 (electronic)
AAPS Introductions in the Pharmaceutical Sciences
ISBN 978-3-030-27483-2 ISBN 978-3-030-27484-9 (eBook)
https://doi.org/10.1007/978-3-030-27484-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Pharmaceutical solid oral dosage form Process Validation methodology has evolved since the introduction of the first FDA guidance in 1987. The current thinking on Process Validation reflects FDA's pharmaceutical cGMP for the twenty-first-century risk-based approach. Since the introduction of the science and risk-based lifecycle approach to Process Validation in 2011, there have been multiple strategies proposed to support the concepts discussed. *Solid dosage products remain the mainstay of the overall drug market and among the new molecular entities. Furthermore, generic products make up the majority of the prescription market share totaling approximately 91 percent of the prescriptions filled. The drive to develop introductions book series on "solid dose Process Validation" emanated from this fact. The two part series will address the basic concepts of Process Validation with a focus on high-volume generic solid dose manufacturing processes. The insights discussed in the books are directly associated to the regulatory guidance's and can be practically applied in development/manufacturing settings. The subject matter has been researched and substantiated with scientific evidences. The authors have carefully considered the approaches to ensure that they are practically applicable in generic solid dose manufacturing. We hope that the reader gain a comprehensive understanding on solid dose manufacturing Process Validation while enjoying the carefully selected contents. Thank you for choosing introductions book series on solid dose Process Validation for your learning needs!*

Welland, ON, Canada — Ajay Pazhayattil
Toronto, ON, Canada — Naheed Sayeed-Desta
Toronto, ON, Canada — Emilija Fredro-Kumbaradzi
Richmond Hill, ON, Canada — Marzena Ingram
Toronto, ON, Canada — Jordan Collins

Acknowledgments

The authors would like to thank Dr. Robin Zavod, PhD, editor in chief, *Currents in Pharmacy Teaching and Learning*, and professor, Pharmaceutical Sciences, Midwestern University Chicago College of Pharmacy, 555 31st Street, Downers Grove, IL 60515, for her encouragement in bringing the textbook on solid oral dose Process Validation. The Process Validation concepts have undergone significant changes in the past decade. We would also like to express our gratitude to all past and present colleagues at Apotex Inc. who have inspired us in collaborating and completing a comprehensive work.

Photo courtesy of AvacaPharma (US Office: AvacaPharma Inc., 1750 NW Maynard Rd., Suite #100, Cary, NC 27513, USA).

Contents

About the Authors

Ajay Pazhayattil is an industrial pharmacist successful in conceiving, implementing, and promoting novel methodologies in pharmaceutical quality assurance, regulatory affairs, and technical and manufacturing operations based on sound scientific principles. His industry experience extends through solid dose, liquids, and parenteral dosage forms. He has been in leadership roles with Eurofins Scientific, Apotex, Pharmetics, ANI Pharmaceuticals, Vita Health, Patheon, Emcure Pharmaceuticals, and Accord Healthcare. He has implemented a comprehensive lifecycle management system supporting ICH Q8 to Q12 for global sites. He holds an MPharm in Medicinal Chemistry and completed his doctoral program in business. He has authored multiple pharmaceutical journal articles.

Naheed Sayeed-Desta has extensive experience in formulation, technology transfer, and validation, providing strategic directions on lifecycle management of small molecules. She is the lead author of several journal articles and is an active contributor in industry organizations. She earned her BSc degree in Biology from Western University and her MBA in Management from California Southern University. She currently holds the position of deputy director of Validation Services at Sanofi Pasteur in Toronto, Ontario, providing leadership in the biopharmaceutical quality sector.

Emilija Fredro-Kumbaradzi is manager of Biowaivers & Biocorrelation team within the Formulation Development Department at Apotex Inc., Toronto, who is responsible for the biopharmaceutical aspects of drug product. She has extensive experience in the development of generic formulations for immediate and modified release products intended for various markets. Prior to Apotex, she has held a position of professor of Pharmaceutical Technology at the Faculty of Pharmacy, University of Skopje, Macedonia. She has received her BSc degree in Pharmacy from the University of Skopje; MSc degree from the University of Belgrade, Serbia; and PhD in Pharmaceutical Sciences from the University of Skopje, Macedonia. Her current research interests include solid dosage forms of low-soluble drugs and various approaches and technologies in drug formulation to remediate solubility and stability issues, selection of bio-indicative dissolution, and in silico modeling.

Marzena Ingram is a pharmaceutical industry professional with extensive quality assurance and technical operations experience in solid dose and active pharmaceutical ingredients manufacturing operations. She holds senior management position at Eurofins Alphora Research Inc. Prior to Eurofins, she was senior manager of Continued Process Verification at Apotex Inc. She developed a specialized Continued Process Verification team and spearheaded the implementation of a product lifecycle program to meet the global regulatory requirements. She has also introduced and published statistically driven product assessment processes and has led the implementation of a comprehensive Process Validation lifecycle management software solution.

Jordan Collins is Senior Solutions architect at Privacy Analytics, an IQVIA company responsible for leading client engagements assessing the risk of reidentification of individuals and supplying guidance on anonymization for data sets shared for secondary purposes. He also currently provides statistical consulting services, primarily to healthcare researchers and pharmaceutical companies. He has extensive experience in performing statistical analyses across a wide variety of industries. Prior to Privacy Analytics, he held the position of manager of Statistical Support at Apotex Inc. He received his BSc (Honors) degree in Mathematics from Mount Allison University, MSc degree in Mathematics from McMaster University, MA degree in Applied Statistics from York University, and PhD in Philosophy from the University of Auckland, New Zealand. His current research interests include the application of Bayesian statistics to industrial decision-making and the development of machine learning techniques for use in process optimization.

Chapter 1
Stage 1A: Quality by Design Product Development

Abstract A quality by design (QbD)-based process design as per ICH Q8 is applied for development of solid dose products. The QbD principle ensures that the quality profile of the drug product is consistently met and there is no significant variability observed during commercial manufacturing. The chapter will discuss product development (Stage 1A) of an immediate release tablet dosage form for oral administration. The focus will be on the specifics of developing a generic drug product candidate where the predefined innovator target product profile attributes can be used as reference. When the development process identifies interaction between the factors, further experiments should be conducted to understanding the interactions well such that a risk-based data-driven approach to product development is utilized. A product development report (PRD) is a part of the regulatory submission dossier for review and approval. The report describes in a systematic manner the stages of the product development.

Keywords Quality by design · Design space · Design of experiments · Risk assessment · Control strategy

Quality cannot be tested into products; quality can only be built into products [1]. Development of the robust product with desired quality attributes that are consistently met requires a systematic approach in product development. General knowledge and experience with dosage forms, manufacturing processes, drug substance, and excipient characteristics are used only as a starting point in designing the set of experiments for a specific product under development. This set of experiments aids in gaining knowledge and understanding for the specific product, both material- and process-related attributes. At the experimental stage, selected critical elements of the materials (the drug substance and proposed excipients) along with manufacturing process parameters at each processing step are varied systematically in predefined design to confirm its impact on the product performance, i.e., on product critical quality attributes (Quality Target Product Profile, QTPP). Ultimately, the outcome of the study serves to propose a proper control strategy over critical material attributes (CMA) and critical process parameters (CPP) that

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9_1

will ensure the quality profile of the drug product is consistently met and there is no significant batch to batch variability.

Full implementation of QbD (Fig. 1.1) is a win-win-win situation [2]:

- Manufacturers – better understanding of product/process, more efficient process, reduced regulatory burden
- Regulators – providing regulatory flexibility without sacrificing quality
- Patients – increased assurance of product quality

During the QbD development, factors that impact quality of the product need to be identified, the level of risk to be assigned, and accordingly studies to be done to understand the extent of the impact of all the parameters. In a case where interaction between the factors may happen, the experiments should be directed toward understanding the interactions as well.

Factors that impact the quality are:

- Formulation – drug substance and excipients
- Manufacturing process – selected steps and critical process parameters for each step
- Packaging configuration – packaging components

To illustrate the thinking process behind scientifically based product development and steps of the quality by design approach, an example of product development of an immediate release solid oral dosage form has been selected and discussed, with interpretation of the risk-based approach in sequence of development.

The example of product development is a tablet dosage form for oral administration with immediate drug release profile. Example will represent a development process of a generic drug. In this scenario, some of the target product profile attributes are predefined by the same attributes of the innovator's product, which is used as a reference. Namely, the generic product should be developed such as to demonstrate similar pharmacokinetic (PK) profile, i.e., efficacy, and similar safety while administered as the same dosage form as an innovator using the same route of administration. However, to achieve this similarity, it does not mean that generic product must be a "copy" of the innovator's product. Formulators can select alternate inactive ingredients and manufacturing processes to manufacture the generic product, as long as their product demonstrates efficacy and safety comparable to the reference product. In fact, often enough there are intellectual property constraints for use of certain ingredients, certain ranges of particle size for active or intermediates (e.g., granulation), and/or manufacturing approaches which were utilized by the innovator. Obviously, patented claims are coming from the knowledge

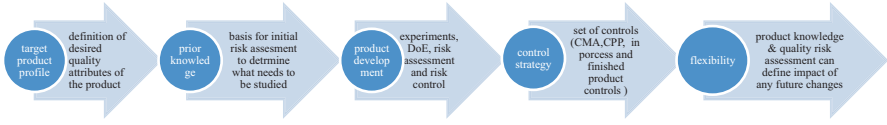


Fig. 1.1 Overview

gained during the development of the innovator's product on most critical material attributes, processes, or process parameters that would yield in desirable product profile. Therefore, to design the generic version of the drug product using alternate formulation approaches requires creativity, scientific knowledge, and innovation. Often enough, scientifically based alternate solution in achieving desired product performance, developed by the generic company during the formulation development process, is innovative and original by itself, so it becomes subject to intellectual property protection per se.

The essential steps in QbD drug development process are shown in the diagram below [Fig. 1.2, also Fig. 3.2. from Volume 1, The basics].

Product Development Report (PDR)

PDR is a part of the submission dossier for regulatory approval. It describes in systematic manner the stages of the development. Typical sections of the development report which outline the steps of quality by design approach of a generic product are:

1. Analysis of the Reference Drug Product
2. Quality Target Profile
3. Components of the Drug Product
   - Drug Substance
   - Excipients
4. Drug Product
   - Formulation Risk Assessment
   - Formulation Development Studies
5. Manufacturing Process Development
   - Identification of Critical Process Parameters
   - Manufacture of Stability Batches
6. Control Strategy

The QbD development steps will be discussed in above order.

Analysis of the Reference Drug Product

The first step in development of a generic product is thorough understanding of the Reference Listed Drug (RLD) product. It encompasses PK aspects, physicochemical characteristics, formulation details, and in vitro drug release behavior. All these characteristics are to be evaluated in close correlation to the drug substance

Fig. 1.2 QbD process

properties that are critical to in vivo performance. This will help understand what are the critical attributes of the reference formulation that define the in vivo behavior, i.e., drug bioavailability. Complexity of the development will be mainly driven by the properties of the drug substance – solubility and permeability. Drug substances with high solubility in terms of Biopharmaceutics Classification System (BCS) would be easier to develop as an immediate release dosage form as composition and process are unlikely to significantly affect the drug release. On the other hand, low soluble drug substances increase the complexity as it is important to understand whether and by how much the solubility of the poorly soluble drug substance was altered by the formulation approach utilized by the innovator. Hence, deep analysis on the available information on reference product with regard to the active ingredient (e.g., polymorph, particle size) along with the excipients and/or manufacturing process that may alter the solubility is essential. Only with proper understanding of the reference product, the right targets will be set, and success of the development of the generic product would be warrantied.

Pharmacokinetic (PK) characteristics of the reference product are described in the product monograph. Analysis of the pharmacokinetic parameters reveals the extent and rate of drug absorption upon oral administration, the effect of food on absorption, as well as details on distribution, metabolism, and elimination from the body.

Formulation-qualitative composition of the innovator's product is listed in the product monograph. It gives an idea on whether any alteration to the solubility of the drug substance may have been made (applicable to low soluble compounds). Knowledge of the functions of excipients is essential for this judgment. It may also give an indication of the manufacturing process utilized, as some of the ingredients are suitable for specific processing. In addition to literature search, further analysis may be performed on reference product to get further details on the manufacturing process, if deemed critical.

Physicochemical characteristics of the innovator's product are determined as a reference and do not need to be identical for the generic product. However, there are certain regulatory limitations specific to certain markets that need to be met. For example, FDA provides limitation on size of the generic product relative to the brand (Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, Guidance for Industry, FDA, 2015) [3]: generics can be equal or smaller, but if bigger, it provides limitation as when and by how much bigger they could be. For certain markets, similar appearance may bring marketing advantage for the generic product, and hence the product should be designed with similar appearance as the reference product. Also, the disintegration time of the tablet may be an important information for a formulator as it may correlate to the desired dissolution profile of the reference product.

Example of summary of information on reference product composition and physical characteristics is shown (Tables 1.1 and 1.2).

Drug release behavior of the reference product is one of the most important characteristics that need to be evaluated in conjunction with the pharmacokinetic characteristics and drug substance solubility. Drug solubility is being assessed in

Table 1.1 Components of the RLD product

Function
Active
Disintegrant
Diluent
Lubricant
Binder
Binder
Solubilizer

Table 1.2 Physicochemical characterization of the RLD product

Brand name	
Company, country	
Strength (mg)	
Batch number and expiry date for chemical testing	
Diameter (inches)	
Appearance	
Score line	
Tablet coating	
Average weight (mg)	
Thickness (inches)	
Hardness (kp)	
Disintegration (min:ss)	
Assay (%)	
Content uniformity	Mean (n = 10)
	AV
	% RSD
	Minimum
	Maximum
Dissolution mean (%)	At "X" minutes
Related compounds (%)	RC1 RC2 RC3, etc. Unknown

accordance to the BCS system. More discussion on BCS system and the meaning of the BCS classification will be provided below under the section of drug substance. Dissolution will give clear indication of what is the expected release of the drug substance from the product in the gastrointestinal tract. It is typically evaluated in various dissolution media mimicking the physiological pH conditions across the gastrointestinal tract. Graph below represents the drug release across the pH range (example product). Note if the solubility of the drug substance is low, the dissolution media may contain surfactant and no release would be achieved in the absence of surfactant.

As shown in the graph (Fig. 1.3), the dissolution is overall pH independent, albeit somewhat faster in pH 4.5.

It is worth noting that besides the standard dissolution across the physiological pH range, some additional dissolution conditions may be selected and utilized during the product development. Those additional conditions should be chosen such as to be more bio-indicative and discriminatory toward the formulation and process variables which would facilitate the selection of the best formulation candidate for the bioequivalence study against the reference product. To better mimic the conditions in the gastrointestinal tract, biorelevant dissolution media [4] have been developed for in vitro use. These media mimic the content of physiological fluids in the absence or presence of food, i.e., under fasted and fed conditions. They are also called biomimetic media (Table 1.3).

Biomimetic media are suitable for evaluation of the low solubility drugs, as the simulated content of the gastrointestinal tract includes surface active components, which will facilitate the dissolution rate and extent of poorly soluble drug substances. Nevertheless, interpretation of the dissolution data is still very critical part. It should always be kept in mind that in vitro dissolution test can only simulate the dissolution of the active in physiological fluids but not the absorption that takes

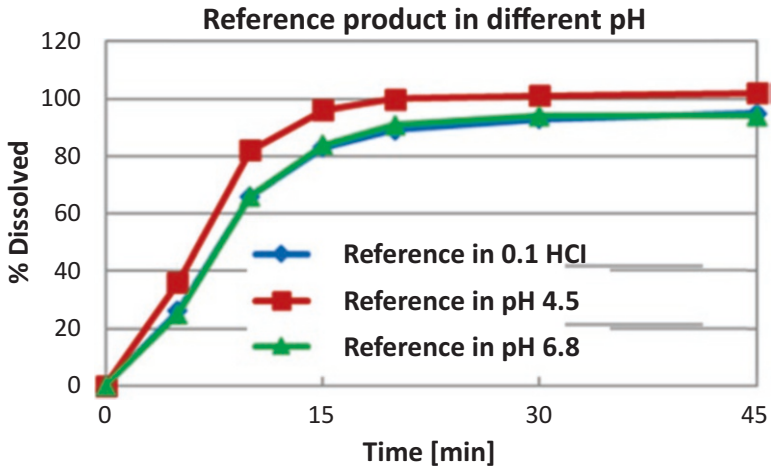


Fig. 1.3 Drug release from the reference product in different pH media

Table 1.3 Biorelevant (biomimetic) dissolution media

GIT segment	Fasted conditions	Fed conditions
Stomach	Fasted state simulated gastric fluid (FaSSGF)	Fed state simulated gastric fluid (FeSSGF)
Upper small intestine	Fasted state simulated intestinal fluid (FaSSIF)	Fed state simulated intestinal fluid (FeSSIF)
Colon	Fasted state simulated colonic fluid (FaSSCoF)	Fed state simulated colonic fluid (FeSSCoF)

place in vivo simultaneously with dissolution. The absorption in vivo will lead to depletion of the dissolved portion of the drug, thus enabling the additional drug amount from the dosage form to dissolve and further get absorbed. This is very critical for poorly soluble drug compounds as the in vitro dissolution result may not give an indication of the actual availability in vivo. Hence, the effect of drug permeability and in vivo absorption should be taken into consideration and adequately estimated.

Consequently, a holistic approach is required in understanding the reference product, i.e., understanding the target product profile before the generic product development begins. This requires data generation, information compilation, and, most importantly, proper analysis and interpretation. Most critical attributes that control innovator's product performance should be clearly identified as a prerequisite for successful development of generic product. In other words, identifying what is most critical and selecting the tests that would be able to properly measure impact of most critical factors is key to success – development of the generic product with comparable efficacy and safety as the innovator's product. More discussion on critical drug substance properties, excipient properties, and process is provided in sections below.

Selection of the Quality Target Product Profile (QTPP)

The QTPP represents "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" [5] (ICH Q8 (R2). The QTPP is essential for the development of the generic product with QbD approach as it represents a boundary for the design of the product. The attributes listed in the QTPP will ensure efficacy and safety profile equivalent to the reference product which is a prerequisite for the approval of a generic product. Summary of the QTPP for our example of the immediate release product is shown below (Table 1.4).

All the quality attributes that could be influenced by the formulation and manufacturing process variables are evaluated as a part of the development studies and discussed in detail. Determination is made as to whether or not they are critical to product quality, i.e., represent critical quality attributes (CQA). Examples of critical and noncritical quality attributes for an immediate release tablet are summarized below (Table 1.5).

The attributes that are found to be critical as they may be potentially impacted by the material attributes and process parameters will be closely monitored during the product development. Those are assay, degradation products/impurities, content uniformity, and dissolution. As an outcome of the development studies, the appropriate controls will be established for both materials (active and excipients) and process parameters to ensure robust product performance.

Table 1.4 Quality Target Product Profile (QTPP) for an example of immediate release tablets

QTPP element	QTPP target	Rationale
Dosage form	Tablet	Pharmaceutical equivalence requirement: Ssame dosage form
Dosage design	Immediate release tablet	Immediate release design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: Ssame route of administration
Dosage strength	Same as RLD	Pharmaceutical equivalence requirement: Ssame strength
Pharmacokinetics	Fasting and fed study. 90% confidence interval of the PK parameters should fall within bioequivalence limits	Bioequivalence requirement
Stability	At least 24 months shelf life at room temperature	Needed for commercialization
Drug product quality attributes	Physical attributes	Meeting the compendia or other applicable (quality) standards
	Identification	
	Assay	
	Content uniformity	
	Degradation products	
	Dissolution	
Container closure system	HDPE bottles/blisters	Based on commercial requirement

Components of the Drug Product

Components of the drug product are drug substance and inactive ingredients. In broader interpretation, container closure system (bottle, blister etc.) is part of the product (Fig. 1.4).

Drug Substance

Drug substance is in the center of product development. It is the drug substance properties that will dictate the approach in the development. Solubility, permeability, stability, polymorphic form, and form stability lay in the foundation of the product development pyramid. Drug substance properties can be classified as physical, chemical, and biological. The most relevant properties of the drug substance are considered along with their potential impact (Table 1.6).

Physicochemical and biological properties, for example, Compound A, are presented below.

Table 1.5 Critical and noncritical quality attributes of an example immediate release tablets

Drug product quality attributes		Target	Is this CQA?	Justification
Physical attributes	Appearance (color and shape)	To match RLD	Yes	Color and shape are not critical for immediate release product
	Size	Similar or smaller than RLD		Patient compliance
	Friability	NMT 0.8%		Formulation and compression parameters impact friability
	Hardness	To be defined		Formulation and compression parameters impact hardness
	Scoring configuration and divisibility	Unscored tablet	No	RLD is not scored
Identification		Positive for API	No	Formulation and process parameters unlikely to have any impact on identity
Assay		90–110% of the label claim	Yes	Material attributes and manufacturing process parameters impact the assay of the tablets
Content uniformity		Conforms to USP/EP uniformity of dosage units	Yes	Material attributes and manufacturing process parameters impact the uniformity
Degradation products		Meets ICH requirement	Yes	Material attributes and manufacturing process parameters impact degradation products
Drug release		Similar to RLD	Yes	Formulation, manufacturing process parameters, and material attributes impact drug release
Microbial limits		Meets relevant pharmacopoeia criteria	No	Formulation and process unlikely to have any impact

Drug Substance Physical Properties

Drug substance solubility: solubility of the example drug substance was found to be very low across the physiological pH range (Table 1.7).

Additional solubility determinations were performed in varying concentrations of surfactant, i.e., sodium dodecyl sulfate (SDS) (Fig. 1.5).

According to BCS, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–7.5. The highest dose/solubility of the example drug substance is less than 250 ml; therefore, it is a low soluble drug in terms of BCS.

Fig. 1.4 Container closure systems- bottles

Particle size: Since the drug substance is a low soluble drug, the particle size for this active ingredient is considered a critical quality attribute for dissolution and bioavailability. Hence, based upon the product development, appropriate particle size ranges are determined, and accordingly, three-tiered particle size control for the active ingredient is to be employed of the routine testing.

Drug Substance Chemical Properties

Stability of the drug substance is typically studied in solution and in the solid state.

Solution stability: Solution stability on drug substance is investigated under harsh stress conditions comprising acidic, basic, oxidative, thermal (water, high temperature), and UV/Vis light stress. Knowing the structure and possible hydrolytic, oxidative, or any other transformation, results for degradation products are being correlated to the related compounds that are likely to be formed as products of chemical transformation. Accordingly, specifications for routine control of the degradation product are established for both known (with determined) and also unknown degradation products that may have been detected.

Solid state stability: Solid state stability is investigated by exposing the drug substance and drug product to stress conditions comprising thermal, heat/humidity, and UV/Vis light stress.

Polymorphism and polymorphic stability: Polymorphic form selected for development and tendency for conversion during the manufacturing process as well as during the stability is typically discussed. The impact of polymorph change (if any)

Table 1.6 Drug substance properties

Physical properties	*Impact*
Salt and polymorph	Can affect solubility and stability
Melting point	Determines consistency at room temperature and potential for change during processing
Solubility – aqueous solubility across the pH range	Important to understand its dissolution state and availability for absorption in different segments of the Gastrointestinal tract
Appearance – particle shape, particle size, and distribution	Can affect solubility rate
Density	Critical to processability at different unit operations
Flow properties	Critical for processability, in particular when the drug load in the dosage form is high. If processability is poor, it will need to be altered through the manufacturing process
Hygroscopicity	Determines precautions during the manufacturing process and defines the packaging configuration
Others	
Chemical properties	*Impact*
Chemical stability in solid state	Crystalline and amorphous have different stability. It will define if significant stability issues (degradation) should be expected during the product shelf life. Appropriate measures to suppress the degradation would be selected accordingly
Chemical stability in solution	Drug substance in solution represent worst case scenario for chemical reactivity and aids in understanding the degradation pathways as a function of pH. Understanding specifics of pH sensitivity will aid in designing the stable drug product by applying a control over the pH of the microenvironment in the drug product that is favorable to maintaining stable drug substance
Oxidative stability	Oxidative stress on the drug substance will reveal the potential for oxidative degradation. Selection of the ingredients will be narrowed to those which do not have oxidative properties. Protection from oxygen from the air may be needed during the manufacturing process or in packaging. Alternatively, addition of an antioxidant to stabilize the product toward oxidation may be needed
Photosensitivity	Sensitivity to light is important to understand the potential contribution of the exposure to light on degradation
pKa	To understand the dissociation of the functional groups at different pH and the impact on solubility
Others	
Biological properties	*Impact*
Partition coefficient	Defines affinity of the drug substance toward hydrophilic or lipophilic media. Determined as *log* ratio of the amount found in octanol vs. water, it can indicate the absorption ability of the active which is driven by the balance between the hydrophilicity and lipophilicity of the compound

(continued)

Table 1.6 (continued)

Membrane permeability	Indicates absorption affinity in vivo. Could be determined in vitro (e.g., Caco-2 cell layer) or in vivo in animals (intestinal perfusion). Human PK studies, where mass balance or absolute bioavailability is determined, can be used as an indication of GIT permeability
Biopharmaceutics Classification System (BCS) Class	Solubility and permeability in terms of BCS: BCS 1. High solubility and high permeability BCS 2. Low solubility and high permeability BCS 3. High solubility and low permeability BCS 4. Low solubility and low permeability Solubility is classified based on single dose solubility in 250 ml of media across the pH range (high <250 ml, low >250 ml). Low soluble drugs are more challenging as the rate of the dissolution is critical to achieve bioavailability. The dissolution rate can be significantly impacted by formulation. High permeability is defined based on extent of absorption (more than 85–90% of administered dose)
Pharmacokinetic properties	They represent overall impact of drug substance physical, chemical, and biological properties in in vivo environment. Absorption, distribution, metabolism, and elimination are heavily driven by drug substance properties

Table 1.7 pH solubility at 37 °C

Solvent	Solubility (μg/mL)	Solubility in terms of BCS classification
0.1 N HCl	0.3	Low (>250 ml)
pH 2.5 buffer	0.3	Low (>250 ml)
pH 4.5 buffer	0.3	Low (>250 ml)
pH 6.8 buffer	0.3	Low (>250 ml)
pH 7.5 buffer	0.3	Low (>250 ml)

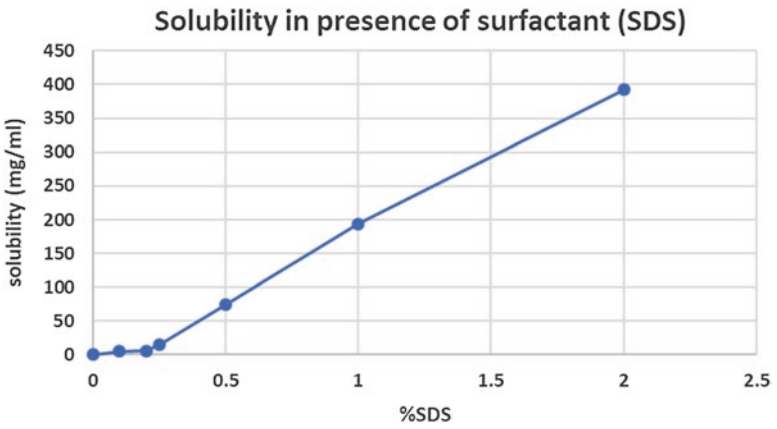


Fig. 1.5 Solubility in presence of surfactant (SDS)

needs to be adequately justified. Accordingly, if required, an appropriated control over polymorph in the drug product needs to be proposed.

Drug Substance Biological Properties

Based on solubility and permeability, the example drug substance is categorized and BCS 2 (low soluble, highly permeable) in accordance to BCS.

Risk Assessment of Potential Impact of API Attributes on Drug Product CQAs

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary.

The relative risk that each drug substance attribute presents was ranked as high, medium, or low (Fig. 1.6, Table 1.8). Those attributes that could have a high impact on the drug product CQAs warranted further investigation, whereas those attributes that had low impact on the drug product CQAs required no further investigation.

Relative risk ranking:

Low risk: No further investigation is needed.
Medium risk: Further investigation may be needed.
High risk: Further investigation is needed.
N/A: Not applicable.

Excipients

The excipients in the composition are selected based upon the excipients used in the innovator's product and excipient compatibility studies.

Excipient Compatibility Study

Compatibility studies of the excipients with the drug substance were studied in binary mixtures in solid state. Mixtures were exposed to different conditions, and generation of degradation product was monitored.

The forced degradation, photosensitivity studies along with the stability study data accumulated to date provide additional insurance of compatibility of the active ingredient with the formulated excipients.

DS / CMA / DP CQA	Particle size	Chemical Stability	Polymorphism	Impurities	Residual Solvents
Assay	Low	Low	N/A	Low	Low
Content Uniformity	High	Low	N/A	Low	Low
Impurities	Low	Low	N/A	Low	Low
Disintegration time	Low	Low	N/A	Low	Low
Dissolution	High	Low	N/A	Low	Low

Fig. 1.6 Potential impact of drug substance attributes on drug product attributes

Table 1.8 Risk assessment justification for drug substance

Drug substance attributes	Justification
Particle size	The drug substance is practically insoluble in water. It is classified as Class 2 drug according to the BCS; hence the drug substance particle size in the drug product is considered critical and would have major impact on dissolution. Moreover, if the content of the drug substance is low in the formulation, the particle size of active substance is also considered critical to affect the content uniformity of the finished product
Chemical stability	Drug substance is stable
Polymorphism	Polymorphic form adequately controlled by drug substance manufacturer. Potential conversion is not a concern
Impurities	Impurities adequately controlled by drug substance manufacturer
Residual solvents	Residual solvents adequately controlled by drug substance manufacturer

Inactive Ingredient Database: Limits

Levels of selected ingredients are compared to the maximum levels published in the Inactive Ingredient Database (FDA), and all fall below the maximum levels listed for the selected dosage form and route of administration. Hence there is no need for additional justification and/or toxicology study in support of the higher levels.

Drug Product

Formulation Development

Formulation development section describes the studies to arrive to the formulation that have desired product performance and is sufficiently robust for commercial manufacture. It begins with formulation risk assessment.

Formulation Risk Assessment

An initial formulation risk assessment is conducted to identify variables that could affect the CQAs of the example of immediate release tablets. The cause and effect technique can be used for risk assessment. Prior information of drug substance attributes and knowledge of developing an immediate release dosage form and unit operations such as wet granulation, drying, blending, and compression were utilized to quantify risk (Fig. 1.7). Quantitative risk priority numbers were mapped onto three categories (high, medium, and low) (Fig. 1.8).

Risk evaluation is performed on the selected excipients. Apart from API-excipient compatibility studies relevant to the core tablet excipients, the following risks were identified (Table 1.9).

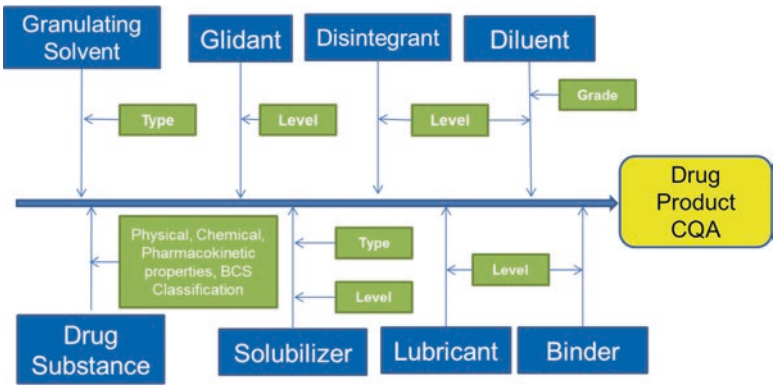


Fig. 1.7 Formulation variables that can affect the CQA

Formulation Composition Material Attributes	Drug Product CQAs			
	Assay	Impurities	Content Uniformity	Dissolution
Active Particle Size	Low	Low	High	High
Granulating Solvent Type	Low	High	Low	Low
Disintegrant Level	Low	Low	Low	Medium
Solubilizer Level/Type	Low	Low	Low	High
Binder Level	Low	Low	Low	High
Diluent Level/Grade	Low	Low	Medium	Medium
Lubricant Level	Low	Low	Low	Medium
Glidant Level	Low	Low	Low	Medium

Relative Risk Ranking:

Low Risk	No further investigation is needed
Medium Risk	Further investigation may be needed
High Risk	Further investigation is needed

Fig. 1.8 Initial formulation risk assessment

Formulation Development Study: Selection of Formulation Approach

Various formulation approaches are typically considered for formulation development. They are selected taking into consideration solubility of active. For a low soluble drug substance, possible approaches are:

- Organic solvent granulation whereas the active is dissolved
- Aqueous/hydroorganic granulation approach whereas active is in the powder bed
- Hot-melt granulation with a melting ingredient
- Dry granulation with micronized drug substance

Table 1.9 Risk assessment justification

Formulation attributes	Justification
API particle size	Critical to the dissolution profile and content uniformity
Granulating solvent type	It can potentially impact impurity profile
Disintegrant level	It can potentially impact disintegration and dissolution
Solubilizer level/ type	It can potentially impact dissolution profile
Binder level	It can potentially impact disintegration and dissolution
Diluent level/grade	It can potentially impact processability and blend homogeneity. It can impact disintegration and dissolution
Lubricant level	It can potentially impact processability and dissolution
Glidant level	It can potentially impact processability and dissolution

Typically, small-scale trials are executed with various approaches. Hot-melt granulation can cause impurity issues and may not improve the dissolution sufficiently. Dry granulation may not result in desired dissolution profile if the particle size is not the only controlling mechanism for release rate. The organic and aqueous-based granulations may offer additional advantages, such as solubilization of the low soluble drug substance.

The organic solvent granulation is a process where the active is dissolved in suitable organic solvent. This approach is designed to reduce particle size of active by dissolving it during the manufacturing. Reduced particle size of active and presence of surface active agent could be appropriate for a formulation of a low soluble drug.

For an organic solvent granulation approach, various organic solvents should be considered taking into account solubility and stability of the drug substance in each over the period of time and under different temperature that would correspond to the use of that solvent in the granulation process. Based on the drug substance stability in solution, an optimal solvent is selected. Trials are designed and conducted based on this approach. However, dissolution profile of the trial composition under discriminatory conditions selected for early development stage was found lower than the reference product. This is a concern for achieving bioequivalence. Reduction of particle size of the drug substance along with presence of surfactant was apparently not sufficient to achieve similar drug release to the innovator's product. It can be hypothesized that solubilization process is deemed critical. Hence, another approach whereby composition contains solubilizing agent and is manufactured using aqueous (hydroalcoholic)-based granulation process is evaluated in further development trials. This approach was found adequate resulting in dissolution profile similar to the reference. The profiles of the trials manufactured using solvent granulation and aqueous-based granulation approach are shown in the graph below (Fig. 1.9).

Consequently, aqueous-based granulation approach is selected for further development trials.

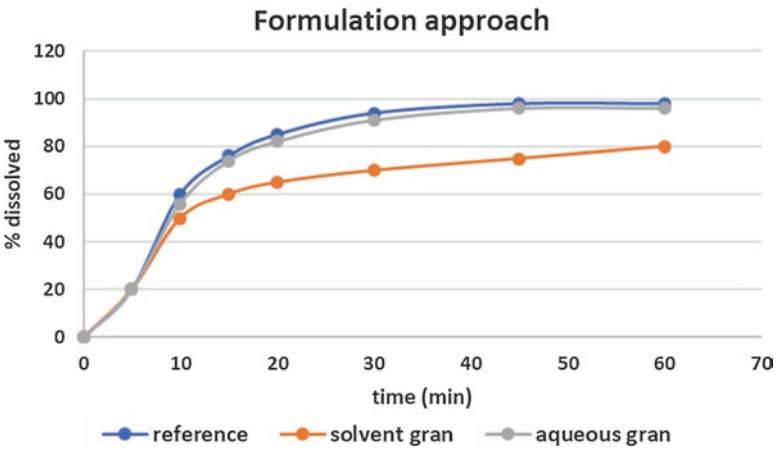


Fig. 1.9 Dissolution of trials with different formulation approach

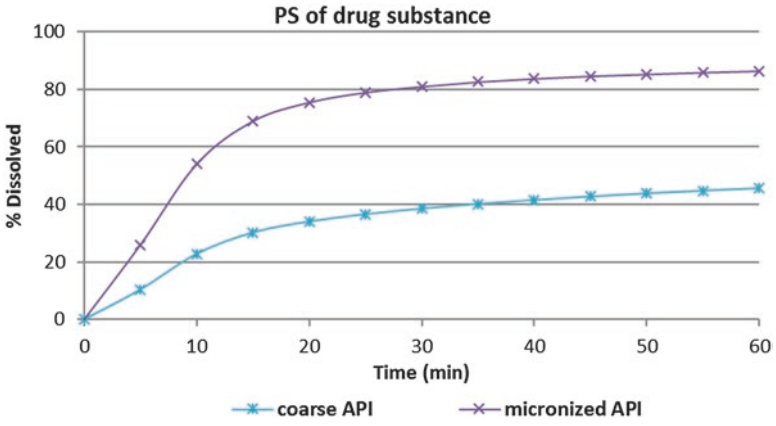


Fig. 1.10 Effect on particle size of drug substance on dissolution

Formulation Development Study: Optimization of Composition Variables for Aqueous-Based Granulation Approach

Effect of API particle size (Fig. 1.10): Considering the drug substance is a low soluble compound and aqueous granulation will not reduce the particle size since the drug substance will not dissolve in the aqueous-based solvent, the particle size is critical for dissolution and bioavailability. In order to decide on appropriate API particle size for aqueous granulation approach, trials using active of different particle size are to be conducted and subjected to dissolution. Based on the outcome, particle size of the API will be defined. If dissolution is incomplete, clearly reduction of particle size (e.g., micronization) is required.

Effect of binder: Effect of the binder in the composition is optimized by conducting trials with different levels and measuring the effect on tablet physical properties and dissolution.

Effect of solubilizer: Solubilizer type used in innovator product was adopted. The level of the selected solubilizer was optimized through evaluation of the dissolution as an attribute most responsive to the level change.

Effect of disintegrant: Type of disintegrant was selected based on innovator's product. Level was optimized in series of trials.

Effect of diluent: Diluents, in general, are less likely to have an impact on dissolution; however they can have impact on processability. Nevertheless, when the amount in the formulation is high and the drug substance is poorly soluble, selection of the type is critical for both – processability and dissolution. The type of disintegrant is to be selected considering the compatibility studies. The grade is also studied to select the more suitable one for the poorly soluble drug substance and the selected aqueous-based granulation manufacturing process. Based on processability and dissolution, final grade selection is made.

Formulation Development Study: Process Evaluation at Intermediate Scale

Based upon the formulation studies executed at small scale, composition and manufacturing process are selected. This formulation is to be taken to process evaluation stage, whereby the trials are executed at intermediate scale, to see if reproducible results can be obtained. At this initial process evaluation stage, some critical process parameters can be preliminary evaluated. For example, formation of degradation products which may be related to the duration of the process may be measured as a function of processing time. This is important to know prior to commencing the full process optimization. At this stage, additional changes to the process and/or composition are typically made to improve processability or product performance.

Once satisfactory performance is obtained at each processing stage as well as on the finished product, an additional dissolution testing is conducted on selected composition in various pH to evaluate dissolution similarity to the reference product across the pH range to confirm suitability of the formulation and process. Dissolution was found comparable to the reference across the different dissolution conditions, suggesting it would likely be proven to be bioequivalent to the innovator's product.

Conclusion of Formulation Development

Consequently, based on the formulation development studies, the composition and process are tentatively finalized. They are confirmed to be able to produce tablets with desirable, target quality attributes, and as such, the product is ready to move to the process optimization stage. Acceptable ranges for the high-risk attributes are established and included in the control strategy. Based on the results of the formulation development studies, the formulation risk assessment is revised (Fig. 1.11).

Formulation Composition Material Attributes	Drug Product CQAs			
	Assay	Impurities	Content Uniformity	Dissolution
Active Particle Size	Low	Low	Critical, Range Fixed	Critical, Range Fixed
Granulating Solvent Type	Low	Critical, Fixed	Low	Low
Disintegrant Level	Low	Low	Low	Not Critical within Design space. Addressed by trials
Solubilizer Level/Type	Low	Low	Low	Not Critical within Design space. Addressed by trials
Binder Level	Low	Low	Low	Not Critical within Design space. Addressed by trials
Diluent Level/Grade	Low	Low	Not Critical within Design space. Addressed by trials	Critical, Fixed
Lubricant Level	Low	Low	Low	Critical, Fixed
Glidant Level	Low	Low	Low	Critical, Fixed

Fig. 1.11 Results of formulation development on identified risk (revised risk assessment)

Manufacturing Process Development

The formulation and manufacturing process, confirmed to be viable during the process evaluation stage, are further taken into process optimization stage. Each of the processing steps is critically evaluated for potential impact of their critical process parameters using the equipment that operates on same principles as the one to be used for manufacture of submission batches and for the commercial scale manufacturing. Manufacturing steps are evaluated to understand their potential impact on the quality attributes of the finished product. For each stage, the identified critical process parameters are studied over a range of settings, and samples of intermediate and finished product were analyzed for critical quality attributes. Based on the analysis, the optimal operating ranges are recommended for future manufacture. Where applicable, acceptance criteria for in-process testing of key intermediates are also proposed and applied in the manufacture of stability batches, including the batches submitted for bioequivalence testing. A risk analysis, in accordance with ICH Q9, is used to establish which variables and unit operations are likely to have the greatest impact on product quality (Fig. 1.12).

The following processes are studied to address the parameters of high risk:

- Wet granulation – DOE to optimize the process parameters
- Blending – blend time analysis to select optimal blending parameters
- Compression – compression optimization study to optimize compression parameters and in-process controls

The optimization of these stages is discussed in further detail in the sections below.

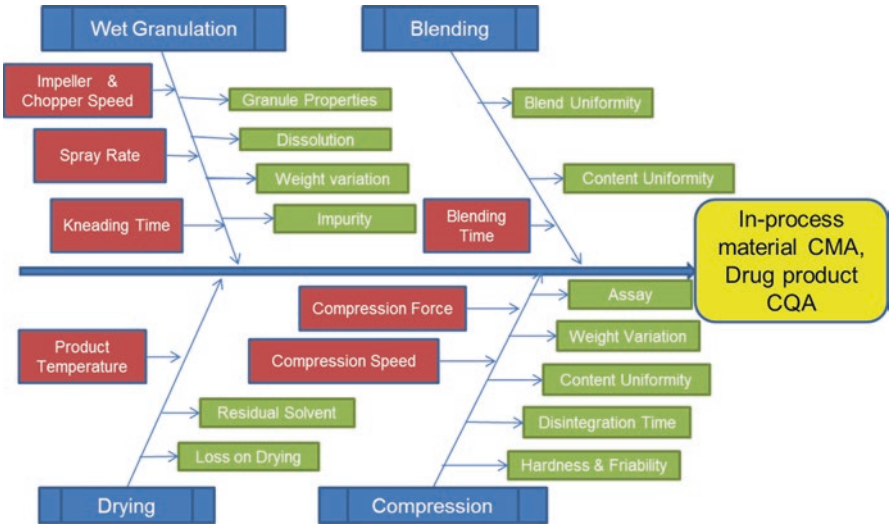


Fig. 1.12 Variables

Identification of Critical Process Parameters

Process parameters are identified as critical when a realistic change can result in failure to meet the QTPP. Process parameters are not critical when there is no trend to failure and there is no evidence of significant interactions within the proven acceptable range (PAR).

Trials are carried out to establish appropriate control strategies to minimize the effects of variability in material attributes and process parameters on CQAs. A summary of the impact analysis and the trials is illustrated below (Fig. 1.13).

Unit Operation / CMA, CQA	WET GRANULATION			DRYING	BLENDING	COMPRESSION	
	Mixing (Impeller/ Chopper) Speed	Spray Rate	Kneading Time	Product Temperature	Time	Compression Force	Compression Speed
Granulation particle Size Distribution	Medium	Medium	Medium	N/A	Low	N/A	N/A
Bulk Density	Medium	Low	Medium	N/A	Low	N/A	N/A
Residual Solvent	Low	Low	Low	High	N/A	N/A	N/A
Loss on Drying	Low	Low	Low	High	N/A	N/A	N/A
Blend Uniformity	Medium	Low	Medium	N/A	High	N/A	N/A
Weight Variation	Medium	Low	Low	N/A	Low	Low	High
Disintegration	Low	Low	Low	N/A	Low	High	Low
Hardness	N/A	N/A	N/A	N/A	Low	High	High
Friability	N/A	N/A	N/A	N/A	Low	High	High
Impurities	Low	Low	Medium	High	Low	Low	Low
Assay	Medium	Low	Low	N/A	Low	Low	Medium
Content Uniformity	Medium	Low	Medium	N/A	High	Low	High
Dissolution	Medium	Low	Medium	N/A	Low	High	Low

Relative risk ranking:

Low risk: no further investigation is needed.

Medium risk: Further investigation may be needed

High risk: further investigation is needed.

N/A: Not Applicable

Fig. 1.13 Summary of critical process parameters – risk assessment

Wet Granulation and Drying

Wet granulation process is used to distribute the solution with other ingredients and to provide homogenous mix that prevents segregation of the blend components. Due to shearing and kneading action of the impeller in a high shear granulator system (Fig. 1.14), wet mixing and drying can be done relatively quickly and efficiently. Drying of the wet material may require drying in fluid bed dryer (Fig. 1.15) as more efficient drying system, depending on the solvent boiling temperature. During the wet granulation process in high shear granulator, homogeneity of mix, particle size distribution, and bulk density are mainly affected by the impeller/chopper speed, solution addition rate, and kneading time. Thus, for wet granulation mixing study impeller/chopper speeds, flow rate and kneading time are considered to be critical process parameters of the finished dosage unit.

DOE study for wet granulation and drying process (Fig. 1.15): In order to propose ranges for abovementioned critical process parameters, a DOE can be applied (Table 1.10). Utilization of 2^{3-1} fractional factorial DOE to evaluate the influence of critical process parameters, i.e., impeller/chopper speed, solution flow rate, and kneading time on the physical and analytical performance parameters of finished dosage units and their effect on desired product profile, is typically applied.

The physical and chemical attributes of granules for all the DoE batches are summarized below:

(a) Loss of drying (LOD) – in process
(b) Residual solvent (organic volatile impurity, OVI)
(c) Water content

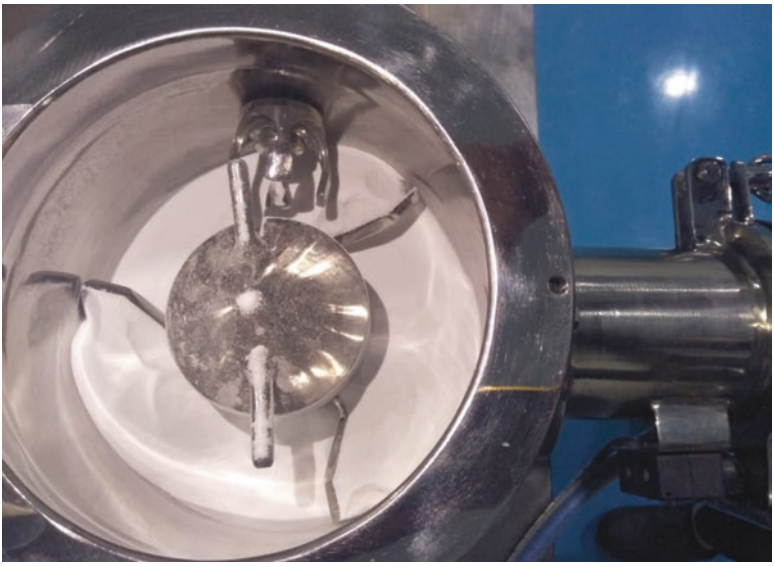


Fig. 1.14 High shear rapid mixer granulator (top view)

Fig. 1.15 Fluid bed dryer (Side view)

Table 1.10 Batch flow for 2^{3-1} fractional factorial design

Factors		**Coded values**		
		−1	**0**	**+1**
		Actual values		
A: Spray rate (g/min)		(Low)	(Target)	(High)
B: Impeller/chopper speed (rpm)		(Low)/(low)	(Target)/(target)	(High)/(high)
C: Kneading time		(Low)	(Target)	(High)
WTG	**Parameters for granulation**			
	Premix	**Liquid addition**		**Wet mixing**
	Impeller/chopper speeds (rpm)	**Impeller/chopper speeds (rpm)**	**Flow rate (g/min)**	**Kneading time (min)**
Trial 1	(Low)/off	(Low)/(low)	(High)	(Low)
Trial 2	(Low)/off	(Low)/(low)	(Low)	(High)
Trial 3	(High)/off	(High)/(high)	(High)	(High)
Trial 4	(High)/off	(High)/(high)	(Low)	(Low)
Trial 5	(Target)/off	(Target)/(target)	(Target)	(Target)

(d) Degradation products
(e) Granule particle size distribution
(f) Bulk and tapped density
(g) Blend uniformity

In-process loss on drying for all optimization batches was found to be consistent (Fig. 1.16). As wet granulation involves evaporation of the hydroorganic solvent after the granulation step, samples are collected throughout the drying stage to monitor the level of residual solvents and thus evaluate the efficacy of the drying process. The OVI and water contents from all optimization batches are evaluated in connection to the processing parameters (impeller/chopper speeds, spray rate, and kneading time). Results were well within the acceptable levels. As heat is used for drying, degradation products are also monitored throughout the drying process to evaluate the effect of heat on degradation. Based on impurity results, OVI and %water, an optimal drying time and in-process LOD limit are finalized. Considering the in-process LOD results, OVI, and RC results, appropriate controls for the drying step are recommended for commercial batch manufacture. Following the completion of the drying process, the dried material is milled through selected screen and then blended for particle size uniformity. Samples are removed after blending and evaluated for sieve profile and bulk density. Similar physical properties (particle size and density) and satisfactory blend uniformity results depict that all the DoE batches had comparable quality attributes.

Fig. 1.16 FBD parameters

Summary of DoE: Influence of CPP on CQA of Granulation

A statistical model incorporating interactive terms can be used to evaluate the effect of the independent variables on the dependent variables. An example of impact of granulation parameters on granule attributes is shown in the figure below (Fig. 1.17).

As shown in above charts, processing parameters impeller/chopper speed, flow rate, and kneading time within the studied range do not significantly impact granulation properties (particle size, bulk density, % water, and residual solvent). Since performing wet granulation at different settings can affect the quality attributes of the granulation, this can also affect the quality attributes of the finished dosage form. After defining the parameter ranges that ensured the granulation could be successfully manufactured, granulations from the DOE study are used to compress into tablets and evaluated against proposed acceptance criteria obtained during optimization of the compression stage. Particularly, granulations manufactured at extremes of wet granulation settings can result in tablets which display differences in physical attributes such as hardness and appearance, and analytical attributes such as dissolution can be affected.

The physical and chemical attributes of tablets for all the DoE batches are summarized below:

(h) Hardness
(i) Thickness
(j) Tablet weight (average weight and RSD)
(k) Friability
(l) Visual defects
(m) Assay dissolution
(n) Content uniformity

Summary of DoE: Influence of CPP on CQA of Tablets (Fig. 1.18)

As shown in the above charts, granulation processing parameters impeller/chopper speed, flow rate, and kneading time within the studied range do not significantly impact the tableting properties (hardness, thickness, and friability) as well as analytical results (assay and dissolution).

Granulation parameters of impeller/chopper speed, spray rate, and kneading time within the studied ranges resulted in granules with similar physical and chemical properties. The physical and chemical properties of the blend and finished dosage form produced from the granules were within acceptance criteria. Consequently, based on the acceptable physical parameters and critical product attributes of in-process and finished dosage form, the operating ranges for granulation parameters are proposed for manufacture of submission (exhibit) batches high shear granulator.

Blend time analysis: Homogeneity of the blend prior to dosing into tablets is critical prerequisite for achieving uniformity of the finished dosage form. Blend

% retained on Screen #1 (coarse)

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Impeller/Chopper Speed	-0.065	0.064846	-1.00		0.4992
Spray Rate	0.035	0.064846	0.54		0.6849
Kneading Time	0.025	0.064846	0.39		0.7657

% retained on Screen #2 (intermediate)

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	-1.83	1.815687	-1.01		0.4975
Impeller/Chopper Speed	1.27	1.815687	0.70		0.6114
Kneading Time	-0.49	1.815687	-0.27		0.8322

% below Screen #2 (fine)

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	2.055	1.889477	1.09		0.4733
Impeller/Chopper Speed	-1.425	1.889477	-0.75		0.5886
Kneading Time	0.505	1.889477	0.27		0.8337

Bulk Density

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Impeller/Chopper Speed	0.0365	0.015205	2.40		0.2513
Kneading Time	0.0175	0.015205	1.15		0.4554
Spray Rate	0.008	0.015205	0.53		0.6917

Fig. 1.17 Granulation parameters

% Water

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	-0.05	0.290689	-0.17		0.8916
Impeller/Chopper Speed	0	0.290689	0.00		1.0000
Kneading Time	0	0.290689	0.00		1.0000

Residual Solvent

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Impeller/Chopper Speed	-12.25	7.490828	-1.64		0.3494
Kneading Time	-3.75	7.490828	-0.50		0.7045
Spray Rate	0.25	7.490828	0.03		0.9788

Fig. 1.17 (continued)

homogeneity is ensured by blending process. The initial blending of the excipients and final blending immediately prior to dosing were identified as critical. All blending stages are performed in in-bin blenders of similar design operating under fixed rotation speed. Prior knowledge and experience with bin blending in bins of different size typically serve to support that the blending times are transferable between the bin sizes. Total number of rotations defines the blending process. Since the rotation speed is fixed, blending time would directly impact the homogeneity and hence it is considered critical for this stage. Blend time analysis is performed by evaluating the blend uniformity after different blending times, i.e., total number of bin revolutions. Blend uniformity at each blending time is measured by collecting samples from different locations in the bin and analyzing for blend assay. Based upon the results of the analysis, suitable blend times for each stage of manufacture will be proposed. Blend uniformity was measured at predetermined time points for the initial blend (5, 10, 15 min) of granulation with excipients (except for lubricant and glidant) and the final blend (5 min) with lubricant and glidant prior to dosing. Based on the results of these blend studies, the initial and final blend times are selected and recommended as adequate for submission batch manufacture.

Tablet compression: Compression process encompasses formation of the solid compact, and equipment settings can impact physical and chemical attributes of the produced tablets. Based on the risk assessment, two main parameters of the compression process were deemed of high risk – compression force and compression

Hardness

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Impeller/Chopper Speed	-0.4	0.424853	-0.94		0.5192
Spray Rate	-0.2	0.424853	-0.47		0.7199
Kneading Time	-0.15	0.424853	-0.35		0.7839

Thickness

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	0.000425	0.000548	0.78		0.5800
Kneading Time	-0.000325	0.000548	-0.59		0.6591
Impeller/Chopper Speed	0.000275	0.000548	0.50		0.7038

Friability

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Impeller/Chopper Speed	0.175	0.078262	2.24		0.2677
Spray Rate	0.075	0.078262	0.96		0.5135
Kneading Time	0.075	0.078262	0.96		0.5135

Assay

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	0.0375	0.124102	0.30		0.8132
Kneading Time	0.0375	0.124102	0.30		0.8132
Impeller/Chopper Speed	0.0125	0.124102	0.10		0.9361

Dissolution Study – Q time point

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	t Ratio	Prob>|t|
Spray Rate	2	0.447214	4.47		0.1400
Impeller/Chopper Speed	1	0.447214	2.24		0.2677
Kneading Time	0	0.447214	0.00		1.0000

Fig. 1.18 Influence of CPP on CQA of Tablets

speed. Compression force is high-risk parameter for tablet hardness, friability, disintegration time, and dissolution, while compression speed is critical to tablet weight and weight variability, hardness, friability, and content uniformity and medium risk to assay (through weight variability). The compression speed range is optimized for a specific tablet press, as the press design and number of stations will affect the time required for powder fill into die cavities and also the compression dwell time, i.e., time of exposure of powder to force applied by the upper and lower punch. These parameters are press specific, though inferences can be made between similar presses. Compression force clearly impacts mechanical strength of the tablet and consequently the friability and disintegration time. Acceptance criteria for tablet hardness and thickness were established during a compression optimization study. During this study, tablet samples are collected over a range of compression forces, in order to establish the extreme of minimum and maximum tablet hardness while still maintaining other relevant physical attributes within acceptable limits (acceptable friability, no visual defects on tablets, etc.). These tablets were also tested for analytical attributes such as dissolution, content uniformity, and assay to see if tablets made at extremes still meet these quality attributes. Also, considering the tablet weight can fluctuate within the defined weight ranges during the compression run, samples of "low" weight and "high" weight are intentionally produced and tested for all physical and chemical attributes. Thus, it is ensured that during the compression run, process will continuously produce tablets with acceptable quality. As a result of these studies, optimized ranges for compression speed and acceptance criteria for hardness and thickness are established based on the extremes of the observed values. Note that the press speed is parameter linked to the machine model and size, and as such it will need to be re-established should the press be changed. The established acceptance criteria for the tablets would remain same regardless of the press used, as they are attributes of the drug product and not the equipment.

Relationship between the compression force and hardness and the effect on dissolution as most critical response quality attribute is established (Figs. 1.19 and 1.20).

Linear correlation between force and tablet hardness was found. However, the increase of force/hardness had no impact on % active released at Q time point. Based on the optimization studies, the appropriate controls and operating ranges for critical manufacturing stages were established and proposed for manufacture of the stability batches. The adequacy of the proposed parameters will be verified during the submission manufacturing stage, where samples will be withdrawn and analyzed for each of the manufacturing stages and tested against the proposed acceptance criteria.

Manufacture of Submission Batches

Based upon the formulation, process, and acceptance criteria established during formulation and manufacturing process development studies, stability/submission exhibit batches were manufactured. Process parameters for critical manufacturing

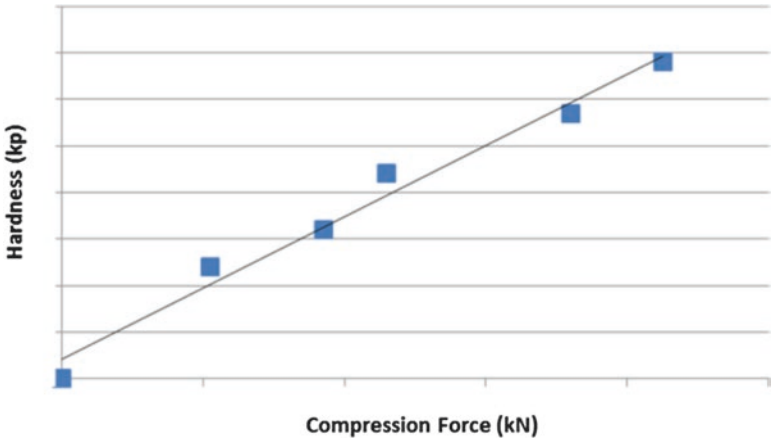


Fig. 1.19 Effect of compression force on hardness of tablets at target speed and target weight of tablets

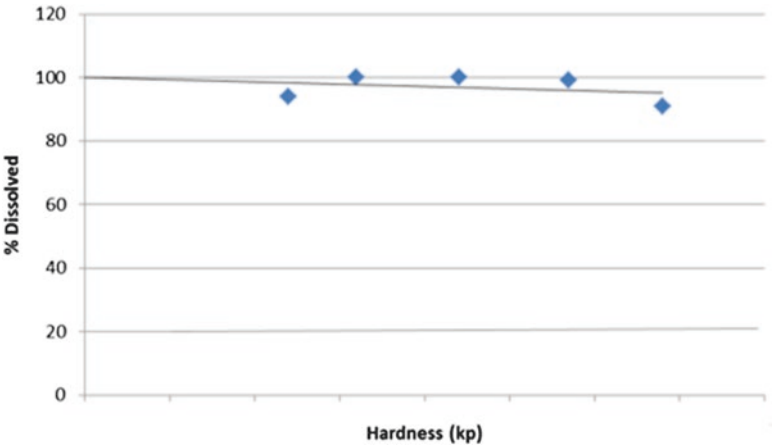


Fig. 1.20 Effect of hardness on dissolution of tablets at target speed and target weight of tablets

steps as well as the in-process controls for the drug product were those derived in optimization studies.

Results of Critical Stages of Manufacture

Data summarizing all in-process parameters, in-process controls, and finished product test results for the exhibit submission batches are outlined for each manufacturing stage. The results are to be reported and discussed. Below table (Table 1.11) illustrates the main manufacturing stages with corresponding process parameters and in-process controls for the example product.

Table 1.11 Manufacturing stages, process parameter, and in-process product controls

Manufacturing stage	Process (equipment) parameters	In-process product controls
Granulation and drying	Solution temperature Impeller speed Chopper speed Product temperature Mixing time Drying temperature Inlet temperature Drying time	In-process loss of drying (LOD) Residual solvent (organic) Residual solvent (water) Degradation products Sieve profile
Blending	Mixing time	Blend uniformity
Compression/tableting	Press speed	Tablet appearance Tablet weight (average weight and weight variability) Tablet hardness Tablet thickness Friability Disintegration time Dosage uniformity (stratified sampling[a]) Dissolution Assay Degradation products Finished product Cof A parameters (remaining)

[a]Stratified sampling

Stratified sampling represents an approach where tablet samples are being collected throughout the compression run, in predetermined intervals, typically every 5%, which results in 20 samples. This sampling is designed to ensure consistent process performance and identify any tendency for segregation which may result in shift of the values up or down as well as increased variability in assay from unit to unit. Acceptance criteria are outlined in ASTM [6]. Typical graphical representation of dosage uniformity results throughout the compression run is provided below (Fig. 1.21).

Control Strategy

Existing process understanding and prior knowledge of the scale-up process have assisted in defining scale-up plans for the example product along with appropriate controls to ensure consistent process performance and product quality. The controls include:

- Control of starting material attributes, in terms of critical quality attributes
- Controls on unit operations (critical process parameters)

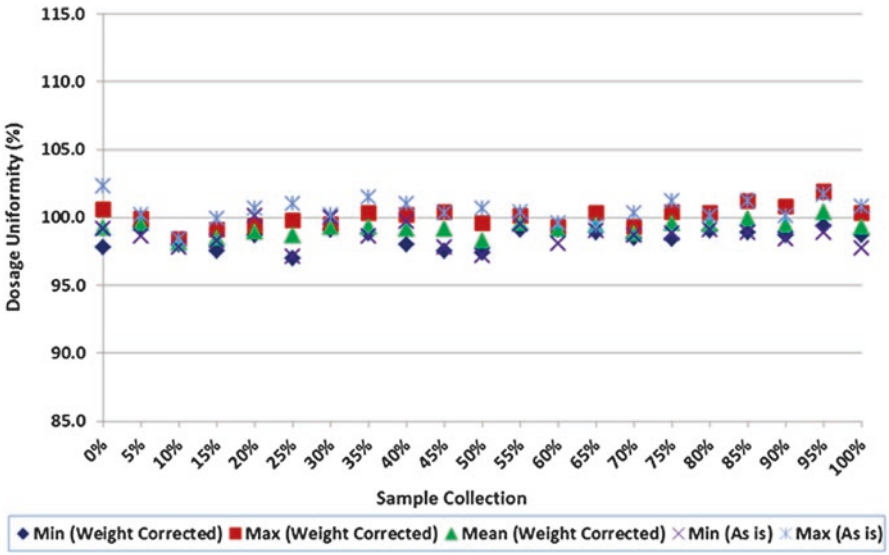


Fig. 1.21 Dosage uniformity results throughout the compression run

- Testing of critical quality attributes of in-process materials
- Specifications on critical quality attributes of the finished product

Risk assessment is updated based upon evaluation of the optimization data (Fig. 1.22).

Control strategy for wet granulation: Impeller/chopper speed, spray rate, and wet mixing (kneading) time were optimized, and ranges were defined to achieve the desired granulation.

Control strategy for blending: The control strategy for blending step is based on the impact of blending time on the CQA of the tablets. Based on our experimental trials, it was determined to mix the blend for specified time to achieve acceptable blend uniformity as well as content uniformity.

Control strategy for tablet compression: The control strategy for compression is to maintain the tablet attributes of hardness and tablet weight within the required ranges. Control of compression force is required for the acceptable hardness, weight variation, and friability of tablets, and dissolution profile is also impacted by compression force. Control on compression machine speed is also important to achieve specified weight variation and content uniformity to the tablets.

Unit Operation / CMA, CQA	WET GRANULATION			DRYING	BLENDING	COMPRESSION	
	Mixing (Impeller/ Chopper) Speed	Spray Rate	Kneading Time	Product Temperature	Time	Compression Force	Compression Speed
Granulation particle Size Distribution	Critical, PAR Identified	Critical, PAR Identified	Critical, PAR Identified	N/A	Low	N/A	N/A
Bulk Density	Critical, PAR Identified	Low	Critical, PAR Identified	N/A	Low	N/A	N/A
Residual Solvent	Low	Low	Low	Critical, PAR Identified	N/A	N/A	N/A
Loss on Drying	Low	Low	Low	Critical, PAR Identified	N/A	N/A	N/A
Blend Uniformity	Critical, PAR Identified	Low	Critical, PAR Identified	N/A	Critical, Fixed	N/A	N/A
Weight Variation	Critical, PAR Identified	Low	Low	N/A	Low	Low	Critical, PAR Identified
Disintegration	Low	Low	Low	N/A	Low	Critical, PAR Identified	Low
Hardness	N/A	N/A	N/A	N/A	Low	Critical, PAR Identified	Critical, PAR Identified
Friability	N/A	N/A	N/A	N/A	Low	Critical, PAR Identified	Critical, PAR Identified
Impurities	Low	Low	Critical, PAR Identified	Critical, PAR Identified	Low	Low	Low
Assay	Critical, PAR Identified	Low	Low	N/A	Low	Low	Critical, PAR Identified
Content Uniformity	Critical, PAR Identified	Low	Critical, PAR Identified	N/A	Critical, Fixed	Low	Critical, PAR Identified
Dissolution	Critical, PAR Identified	Low	Critical, PAR Identified	N/A	Low	Critical, PAR Identified	Low

PAR: Proven Acceptable Range

Relative risk ranking: Low risk: no further investigation is needed; Medium risk: Further investigation may be needed: High risk: further investigation is needed.; N/A: Not Applicable

Fig. 1.22 Summary of critical process parameters – updated risk assessment

References

1. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. ICH Q8 (R2)–pharmaceutical development, quality guidelines. 2009. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf.
2. Nasr M. Pharmaceutical development ICH Q8/Q(8)R, workshop on implementation of ICH Q8/Q9/Q10. 2008. https://www.ich.org/fileadmin/Public_Web_Site/Training/GCG_-_Endorsed_Training_Events/APEC_LSIF_JCCT_workshop_Beijing__China_Dec_08/Day_1/Regulatory_perspective.pdf.
3. Size, shape, and other physical attributes of generic tablets and capsules, guidance for industry. FDA; 2015. https://www.fda.gov/media/87344/download.
4. Jantratid E, Dressman J. Bio relevant dissolution media simulating the proximal human gastrointestinal tract: an update. Dissolut Technol. 2009;16:21.
5. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014;16(4):771–83.
6. ASTM E2709, Standard practice for demonstrating capability to comply with an acceptance procedure. https://www.astm.org/Standards/E2709.htm.

Chapter 2
Stage 1B: Scale-Up and Technology Transfer

Abstract Based on the manufacturing process unit operation, commercial scale can be a linear relationship or may require scale-up where scale-up factors need to be considered. Early development or Stage 1A data is normally conducted at small scale and not representative of commercial scale manufacturing. Further development work is therefore required for the scale-up and transfer of manufacturing processes to fit commercial manufacturing settings. This phase is referred to as Stage 1B. Stage 1B involves appropriate scaling, scale-up/down of the solid dose manufacturing unit operations to adapt to the requisite manufacturing capability while meeting the established CPPs and CQAs. Product/process knowledge management and scientific knowledge of product development and manufacturing science and technology enables effective scale-up and transfer of developed solid dose formulations to a commercial scale manufacturing site. Extensive Stage 1B activities including DoE based studies to better understand the interactions results in a robust design space. Typically, scale-up from Stage 1A is required to meet the commercial demands of a product.

Keywords Scale-up · Technology transfer · Critical process parameter · Commercial scale · Manufacturing science

Process scale-up and technology transfer activities require a balance between maintaining drug product properties established in the development and increasing production during commercial manufacturing. Early development or Stage 1A data is normally conducted at small scale and not representative of commercial scale manufacturing. However, extensive Stage 1 knowledge results in a robust design space and efficient scale-up and or technology transfer. Typically, it requires scale-up from Stage 1A to meet the commercial demands of a product. In some instances, more recently with a shift in generic demands, there are requirements to scale down a process after submission of Stage 1A data.

Depending on the processing unit operation, scale-up can be a linear relationship or require engineering scale-up factors to be considered for operational parameters. Additional Stage 1 development work is therefore required for the scale-up and

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9_2

transfer of manufacturing processes to fit commercial manufacturing settings. This is sometimes referred to as Stage 1B. This stage involves appropriate scaling, scale-up/scale-down of the solid dose manufacturing unit operations to adapt to the requisite manufacturing capability while meeting the established CPPs and CQAs. Adequate statistical measures and extrapolations are required in this stage based on existing sets of data. A revised control strategy and process design is developed as a result while keeping the established formulation design intact. Additional DoEs may be conducted to better understand normal operating ranges, variability, interactions between process parameters, and the impact of scale-up on in-process processing controls such as hold times. Risk assessment tools can be utilized to evaluate pre and post scale-up/scale-down optimization studies. This step considers the risks associated with the transfer of the developed manufacturing process from formulation development to commercial manufacturing settings, including a thorough assessment of equipment, facility, system, and utility capabilities. Cross-site transfer and scale-up/scale-down projects undergo similar assessment through the lifecycle of the product. As the body of knowledge increases, the existing supporting data can be utilized to substantiate such changes prior to initiating Stage 2 activities. The present chapter will discuss a systematic technology transfer process for a solid dose immediate release drug product.

It's also important to be aware of regulatory considerations. Regulators expect manufacturers to take a methodical approach to scaling up or transferring a product from one facility to another or from a demonstration batch to commercial manufacturing. For example, products manufactured for the United States must follow the Food and Drug Administration (FDA) sanctioned Scale-up and Post-Approval Changes (SUPAC) guidance [1]. The entire scale-up process must be validated in line with SUPAC guidelines every time it grows by a factor of at least 10. This process requires making either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA), depending on the nature and requirements of a product. Different jurisdictions will have different guidelines, so pharma manufactures must make sure they have assessed theirs and are ready and able to comply before making scale-up changes.

The 2011 FDA Process Validation Guidance requires a science and risk-based approach. The EU guidance Annex 15 describes the principles of qualification applicable to the facilities, equipment, and utilities used for the manufacture of medicinal products. It is a GMP requirement that manufacturers control the critical aspects of their particular commercial solid dose unit operations through qualification and validation over the entire lifecycle of the product and process. The principles presented in ICH Q8, Q9, Q10, Q11, and Q12 [2] are used to support qualification activities and to ensure a high level of product quality. Design and qualification of facility, utilities, and equipment precedes technology transfer to commercial site, scale-up, and process performance qualification to assure that the equipment/systems are well designed and are capable of consistently manufacturing the product. To effectively understand the product and process, solid dose manufacturers should consider the impacts of facilities, equipment, processing parameters,

and supporting utilities. Previous credible experience with similar products and processes can be utilized to determine proven acceptable ranges during scale-up process design.

Solid dose unit batch operations are evaluated at scale wherein a sufficient quantity of material is used to demonstrate the capability of the commercial scale manufacturing process. A series of optimization batches are created to evaluate the critical stages in the process. Manufacturing steps are evaluated in order to determine the steps that most significantly impact the quality attributes of the finished product. At each critical process stage, parameters are explored over a range of settings, with appropriate sampling and testing, in order to determine settings for commercial manufacture. Proposed acceptance criteria for quality attributes and processing parameters should be verified for all manufacturing stages based on the demonstrated ability to meet the desired requirements. Some of the key scale-up studies such as blend time studies, compaction parameter studies, and compression specification range confirmation studies have been elaborated in the *Solid Oral Dose Process Validation- Volume 1 Basics* textbook Chap. 3 Stage 1 Process Design: Quality by Design. These studies help in determining the CPPs that influence the CQAs and establishing adequate control strategies at commercial scale prior to initiating PPQ studies. The design of experiments (DOEs) are conducted (Fig. 2.1), for example, using a fractional factorial design for the critical parameter ranges. Once the data from the additional DoEs confirms the efficacy of the proposed solution,

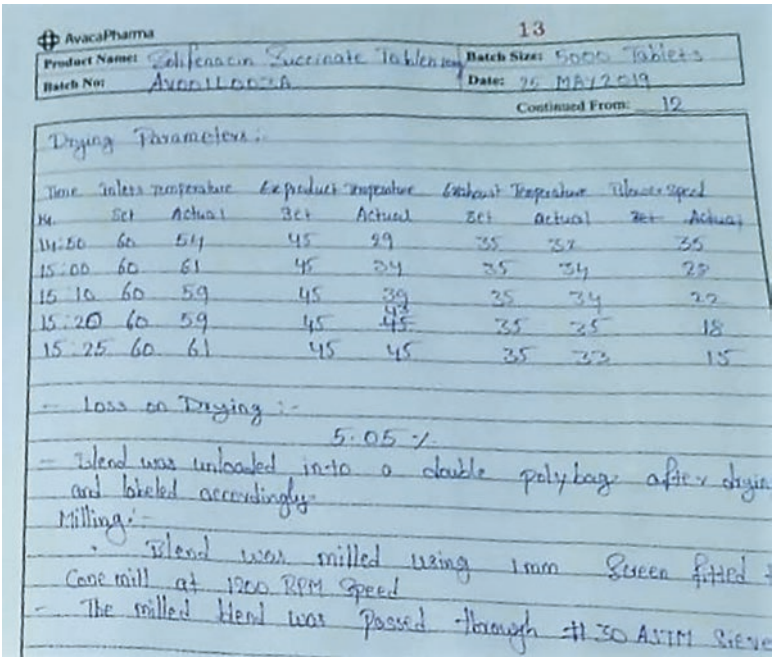


Fig. 2.1 Documenting DoE studies

demonstration batches with the proposed process is conducted. A scale-up risk assessment is subsequently performed to determine any residual scale-up risks prior to embarking on batches at full scale.

Data-Driven Objective Risk Scoring (DORS) Methodology

A data-driven objective risk scoring (DORS) methodology can be used pre scale-up and post scale-up demonstration batch for determining the scale-up risks. A collaborative decision making among the project owner and SMEs should be available from early development that will classify each of the identified material attributes and process parameters into the appropriate risk category. The next step is understanding the data available and risk scoring based on impact to CQAs (Figs. 2.2 and 2.3).

The risk ratio is then calculated from the following equation:

$$\text{Risk Ratio} = \frac{\text{Sum of Count of CMA / CPP factors}\left(\text{Critical / Not Evaluated with Set Point} + \text{Critical / Not Mitigated}\right)}{\text{Sum of Count of CMA / CPP factors}\left(\text{Critical / Mitigated} + \text{Critical / Not Evaluated with Set Point} + \text{Critical / Not Mitigated}\right)}$$

Risk ratio for the process is further classified into several risk levels (Table 2.1).

Based on the computed risk ratio, risk assessment charts can be constructed for the CQA with the MAs and/or PPs. The chart should provide an indication of the

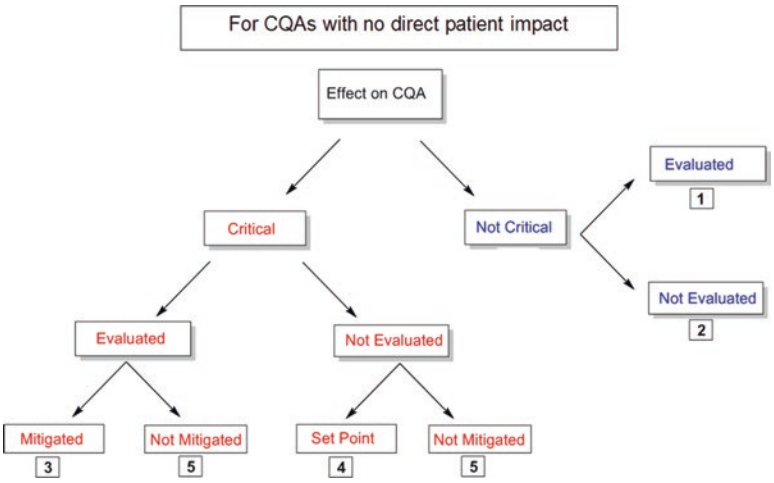


Fig. 2.2 CQAs with no direct patient impact

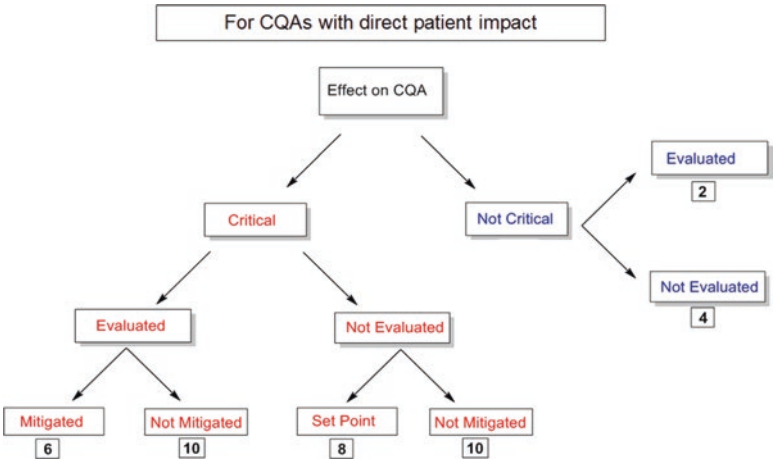


Fig. 2.3 CQAs with direct patient impact

Table 2.1 Risk ratio

Risk ratio	Risk
Less than 0.25	Low risk
0.25–0.75	Medium risk
Higher than 0.75	High risk

risk category for the MAs and/or PPs and ranking of the risk level/significance for each of the MAs and/or PPs. A typical risk assessment chart can be a heat map or a Pareto chart to summarize the findings and act as a visual aid (Fig. 2.4).

Based on the heat map and risk ratio for each stage, CMAs and CPPs can be selected for optimization of the process to minimize/eliminate the risk identified. Following optimization, the technical risk assessment [3] is repeated until the risk ratio is reduced to medium risk or low risk. With this information the next stage in the process is to conduct a demonstration batch. A demonstration or engineering batch is at commercial scale and normally executed in the GMP production facility intended for routine manufacturing. The protocols for demonstration batches are developed to delineate the sampling and testing plans associated with the full-scale batches. This should include sampling and testing requirements required for validation. Additional sampling and experimental evaluations can be incorporated during this study. The purpose of demonstration batches is, however, to determine the adequacy of the estimated unit operation process parameters developed based on the formulation development small-scale batches, DoE experimental studies, similar product/process knowledge, and literature.

A demonstration/technology transfer protocol should be flexible enough such that it allows for exploring the associated scale-up risks. The protocol should define the roles and responsibilities of parties involved, including the formulation development, technology transfer, commercial manufacturing, quality control, and

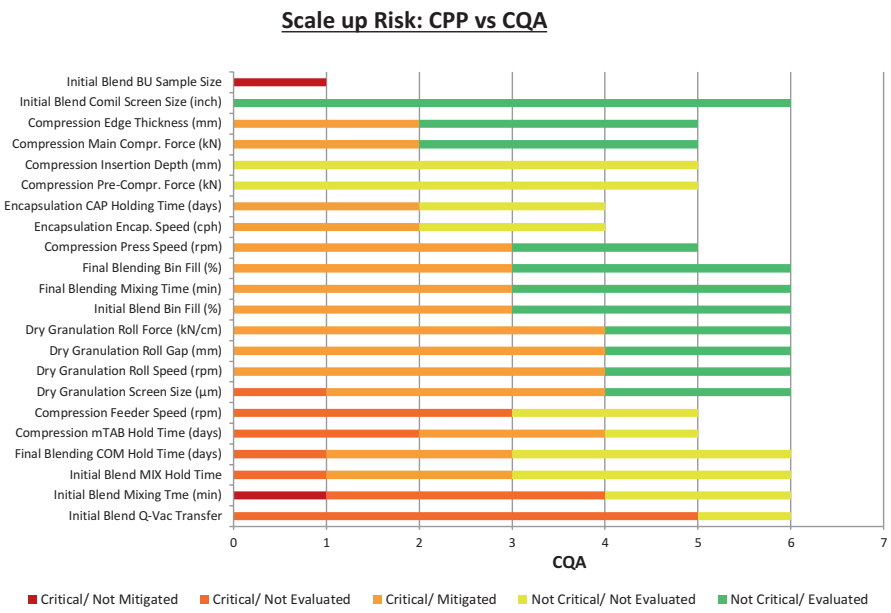


Fig. 2.4 Heat map

quality assurance groups at a minimum. With successful execution and reporting of the demonstration/engineering batches, the technology transfer (TT) hand-off expectations (between formulation development and commercial groups) are established at this stage. TT groups are involved in the PPQ batch execution to ensure the knowledge transfer was successful and also to ensure the execution is performed as expected. Transfers between companies demand extra care in planning and documentation. This requires a skilled and experience team that can manage the differences in equipment, culture, resources, and procedures. TT documentation includes a detailed description of the process, controls, scale-dependent and independent parameters, CPPs, facility requirements, analytical requirements, criteria for CQAs and in-process QAs, KPPs, and a risk analysis identifying potential challenging areas.

Process Capability and Quality Dashboard

From a documentation perspective, a process capability and quality dashboard (PCQd) may be utilized as a transfer criteria. The PCQd (Fig. 2.5) summarizes the statistical assessment and performance of the demonstration batch/es with predetermined criteria acceptable to both groups as a hand-off requirement. This ensures the desired commercial product robustness at this stage.

PCQd for a Solid Dose Immediate Release Product

	Process capability targets	Product performance
Compaction		
Sieve results	P_p >1	2.2
Compression		
IP hardness	P_{pk} >1	1.3
IP weight variation	P_{pk} >1	1.7
Press speed	All batches to be run at maximum validated speed	Meets
% yield	Meet alert limits as per SOP	Meets
Encapsulation		
Weights	P_{pk} >1	1.3
Speed	All batches to be run at maximum validated speed	Meets
% yield	Meet alert limits as per SOP	Meets
FP CQA		
FP disso	P_a >99.9%	Meets
FP assay	P_a >99.9%	Meets
FP CU	AV <10	Meets
Compliance		
# of process deviations	Zero	Meets

Fig. 2.5 An example PCQd

Process scale-up should be preceded by successful small-scale submissions. Any challenges observed for processing steps at small scale must be rectified or optimized prior to scale-up activities.

An example of a proposed standard commercial solid dose unit operations for full-scale demonstration is shown below (Fig. 2.6).

Using this simple workflow of a manufacturing process, each unit batch operation is evaluated. The main phases of tablet manufacturing are particle sizing, mixing, compression, and coating. Particle sizing includes milling, deagglomeration, and granulation processes that either reduce particle size or increase it. Some challenges faced during scale-up this stage are degradation and polymorphism, due to stress or heat generated during the milling and compaction processes. It is important to understand the powder properties, feed rates, and sequence of materials during this process. Bigger batch sizes lead to longer processing times and equipment running for longer periods that may heat up if proper controls are not in place. During dry granulation cooling rollers may be used to minimize heat generation and potential polymorphism of some heat-sensitive active pharmaceutical ingredients. Compaction CPP ranges can be verified at this stage during scale-up. Parameter ranges determined through DoE trials for roller speed, compaction force, and gap width can be verified during demonstration batches for the semicontinuous operation.

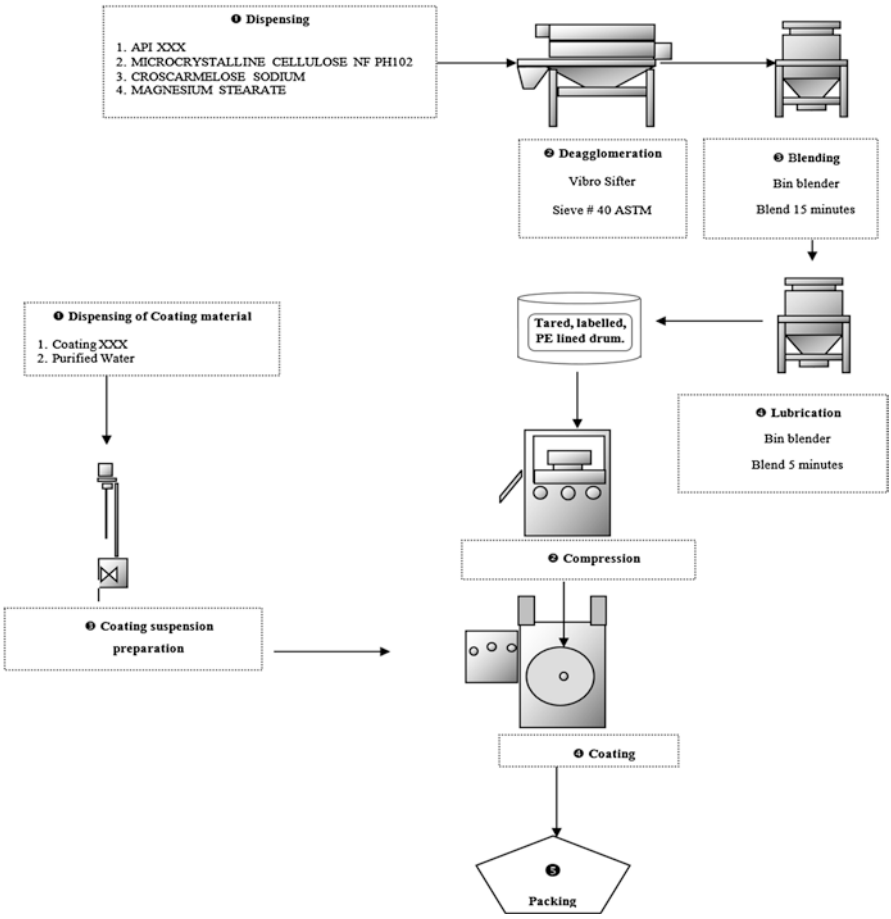


Fig. 2.6 Solid dose operations

Challenges in the mixing phase include powder transfer, blend handling and storage, and blend uniformity. Determining the mixing speed and time is easier if similar blender types are used in small-scale and large-scale facilities, for example, bin blenders versus V-blenders. The Froude number (insert reference) may be used to predict scale-up of tumbling blenders. Hold time studies are required for all stages of unit operations, particularly at the final blend stage that is most susceptible to quality impact to demonstrate the routine processing hold times have no impact to CQAs. Blend uniformity is one of the most challenging components and is discussed later in the chapter in more detail.

Tableting has a number of challenges that include powder flow, segregation, and tablet speeds for efficiency. Small-scale batches are normally hand scooped into the hopper or feeder of a single press. Therefore, powder flow properties are not fully understood. During scale-up, powder is gravity fed from a hopper to the press

through a plastic lay flat about a few feet in length. Good powder flow and uniform blends provide for less potential of segregation and higher tablet press speeds, thus resulting in higher outputs for single- or double-sided presses. There are many case studies and literature available on powder flow behaviors and patterns. Segregation at tableting can occur due to particle size, shape, density, moisture content, electrostatic properties, and surface area. The key is to identify potential sources of variability or issues and manage them. The same powder knowledge is applied to encapsulation process as well where powder is filled into capsule bodies. There are of course various other factors for encapsulation process depending on the type of machine used. Higher turret speeds, however, impact the dwell time which may impact the dissolution profile of the tablets. In order to maintain the same dwell time to achieve the required dissolution profile, the following equation can be used during scale-up:

$$\mathrm{dt} = \frac{\mathrm{Dhf}}{\mathrm{Dpc} \times \pi \times \mathrm{rpm}} (60)(1000)$$

where:

dt = dwell time (milliseconds)
Dhf = head flat diameter (millimeters)
Dpc = pitch circle diameter of turret (millimeters)
Rpm = revolutions per minute (turret speed)

The equation can be used to estimate turret speeds between different types of presses as well as for scale-up or technology transfer. Compression forces used during tableting are sometimes dependent on the compaction force used during dry granulation. Fibrous material such as microcrystalline cellulose loses its compressibility if high compaction forces are used and therefore cannot be compressed further during tableting. This requires studies in both compaction and tableting stages do understand the total force that can be applied to the granules during formation and compression into tablets (Fig. 2.7). This is crucial for tablet thickness, hardness, and dissolution profiles.

Coating process challenges are magnified if functional coating is used or multiple layers of coating is applied (Fig. 2.8). Each coating process needs to be robust to ensure minimal variation in coating thickness and uniform coating performance. Scale-up factors used for coating are normally linear for the proportion of tablet core bed and the rate of coating solution application. Spray rates, pan speed, gun distance, and bed temperatures are CPPs (Table 2.2) that need to be determined at larger scale through trial and error.

CQAs collected from each unit operations as per a standard scale-up protocol are compiled as shown below (Tables 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, Figs. 2.9, 2.10, and 2.11).

The blend uniformity for lubricated granules at 5 minutes ranges from 93.8% to 100.9%, mean blend uniformity data ranges from 96.1 to 97.2%, and the relative standard deviation ranges from 1.1% to 2.0%. From the results the variability

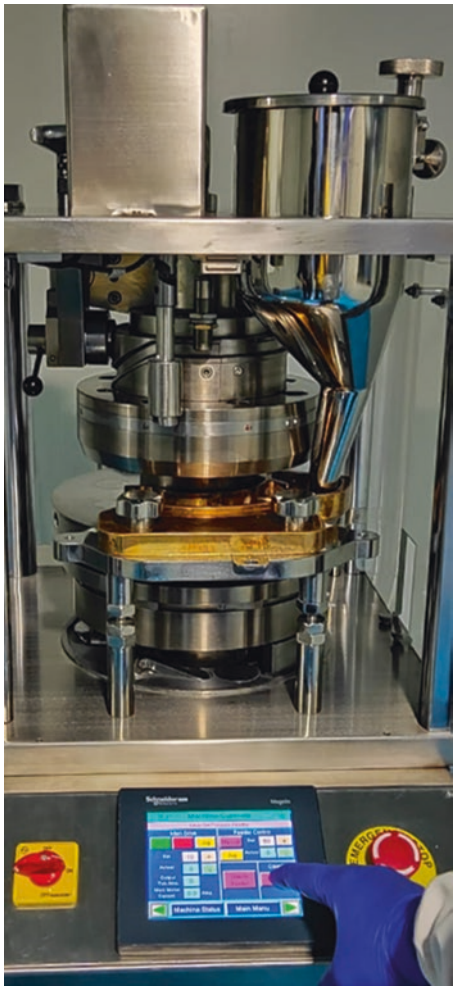


Fig. 2.7 Rotary tablet press setup

between the batches is minimal. The results from the demonstration blend batches confirm that the drug is uniformly distributed through the blend with the use of commercial scale blender.

All mean results were within the specified limit of 90–110% of the label claim at each time point/location. All the individual results were within the range of 75.0% to 125.0% of label claim. The % RSD for three batches was found to be ranging from 1.7% to 2.1%, which is less than 4.0% (acceptance criteria of readily pass classification). From the above data, it can be concluded that the drug substance is homogeneous in the lubricated blend during the compression.

The probability of meeting the USP <905> AV acceptance criteria, Pa (AV), was determined by comparing the tested content uniformity statistics of the batch with a theoretical construct. Pa was calculated using in-process CU results as well as FP CU results.

Fig. 2.8 Coating pan

Table 2.2 CPPs from each of the sample unit operation include as below

Operation	CPP
Particle sizing	Milling screen size Milling speed Impellor type Compaction roller speed, force
Mixing	Blending speed Blending time Lubrication over blend time and speed
Tableting	Compression speed
Coating	Solution spray rate Pan speed Product bed/exhaust temperature

CpK result is >1.33 for in-process content uniformity, indicating a well-controlled process, while Pa is >99.99%, thereby meeting USP <905> AV acceptance criteria.

For dissolution, the triplicate results of the batch were analyzed per USP guidelines. Acceptance criteria for dissolution testing following the rules in outlined in USP General Chapter <711> Dissolution (Table 2.9).

The probability of meeting the acceptance criteria (P_a) [4] for a future batch at a particular stage was determined by comparing the tested dissolution statistics of the pooled batches with a theoretical construct. The theoretical construct was developed using a Monte Carlo simulation of the USP acceptance criteria guidelines with defined batch averages and variability and based upon a normal distribution. Confidence limits are used to indicate how well the determined dissolution capability is known. The probability of meeting each particular stage acceptance criteria

Table 2.3 Lubrication

Sample no	Sampling locations	Acceptance criteria: 90.0%–110.0% B. No. ABCD Blender: 1
1	Top – Back left	96.6
2	Top – Back right	95.4
3	Top – Front right	96.0
4	Top – Front left	97.1
5	Top – Center	95.7
6	Middle – Central front	98.4
7	Middle – Central back	99.3
8	Middle – Central right	94.3
9	Middle – Central left	94.2
10	Bottom – Center bottom	93.8
Min		*93.8*
Max		*99.3*
Mean		*96.1*
% RSD		*1.9*

Table 2.4 Results

Test	Specifications	Observations Batch no: ABCD
Appearance	White to light brown powder	Conforms
Assay	95.0%–105.0%	96.4
Water content	Not more than 5.0%	3.6
Bulk density (g/ml)	For information only	0.450
Tapped density (g/ml)	For information only	0.655

and the associated lower 95% confidence limits were determined for each stage with the pooled analysis that incorporates the data from all batches. A statistical summary of a dissolution capability analysis for the PPQ batches is provided in the table below. These results indicate a well-controlled process.

Prob. of meeting USP <905> AV criteria at each stage

	L1	L2
Pa (USP<905> AV)	99.98%	>99.99%

Statistical evaluation for process capability for each CQA (IPCU, FPCU, dissolution) using CpK and Pa statistical analysis is always performed. The probability of meeting the USP <905> AV acceptance criteria, Pa (AV), for a future batch is determined by comparing the tested content uniformity statistics of the batch with a theoretical construct. Pa was calculated using in-process CU results as well as FP CU results. All results and analyses during the demonstration batch assessment indicate a well-controlled process that is capable of meeting the required specifications for content uniformity, dissolution, and assay during commercial manufacturing,

Table 2.5 Stratified content uniformity sampling results from compression

	Batch no.: EFGH Tablet press: 1			
#	Table 1	Table 2	Table 3	Mean (%)
Initial	104.8	102.8	102.1	103.2
After app. 18,000 tablets	101.7	100.8	102.1	101.5
After app. 36,000 tablets	102.3	101.6	100.8	101.6
After app. 54,000 tablets	101.1	102.1	101.7	101.6
After app. 72,000 tablets	103.2	101.5	102.1	102.3
After app. 90,000 tablets	103.3	100.2	100.9	101.5
After app. 108,000 tablets	99.8	99.9	101.8	100.5
After app. 126,000 tablets	102.7	101.1	99.1	101.0
After app. 144,000 tablets	99.7	99.5	98.7	99.3
Sudden stop	101.9	101.8	101.1	101.6
Start after stop	100.9	101.7	100.1	100.9
After app. 162,000 tablets	98.2	100.4	102.9	100.5
After app. 180,000 tablets	101.7	99.5	100.9	100.7
After app. 198,000 tablets	99.3	101.8	101.3	100.8
After app. 216,000 tablets	100.9	101.0	99.3	100.4
After app. 234,000 tablets	101.5	98.8	99.4	99.9
After app. 252,000 tablets	100.1	99.7	98.9	99.6
After app. 270,000 tablets	97.6	98.3	98.2	98.0
After app. 288,000 tablets	100.2	101.4	98.2	99.9
End	99.2	99.8	99.3	99.4
90% hopper level	94.1	99.4	101.9	98.5
50% hopper level	98.5	100.1	100.0	99.6
10% hopper level	100.2	100.2	96.4	98.9
Mean (%)	100.5			
Min (%)	94.1			
Max (%)	103.3			
RSD (%)	1.7			

signaling the adequacy of the manufacturing process to proceed with process performance qualification studies at the determined scale. Recommendations from the technology transfer report are then incorporated to the final master batch records. The report defines the overall control strategy for the process. It has to be noted that the demonstration batches are normally taken in a GMP environment to simulate and challenge as many potential variables as possible during the demonstration.

Grouped Area Variance Estimate (GAVE) Method

A novel approach such as the Grouped Area Variance Estimate (GAVE) [5] method can be also applied to confirm blend and content uniformity at scale. The statistically based sampling, testing, and assessment plan were developed due to the

Table 2.6 Results

Tests	Specifications	Observations Batch no.: EFGH
Appearance	White to light brown colored, round-shaped, biconvex tablets, with engraved "XYZ" on one side and "BBB" over "20" on the other side	Conforms
Dissolution	As per USP/EP Q = 80% Time: 15 min	Min: 98 Max: 100 Mean: 99 %RSD:1.0 Pass stage 1
Assay	90.0 to 110.0% (% of claim)	98.5
Water content	NMT 6.0%	3.4

withdrawal of the FDA draft guidance for industry – powder blends and finished dosage units-stratified in-process dosage unit sampling and assessment. The GAVE approach is designed to fit solid dose processes assuring high statistical confidence in both powder blend uniformity and dosage unit uniformity complying with ASTM standards. It is a best practice that the sampling and testing of powder blends and finished dosage units during manufacturing of PPQ batches mimic the sampling and testing plan applied during demonstration batches. GAVE blend sampling plan has five sample locations from the top area, four locations from the middle area, and three locations from the bottom area of the powder blend. Three locations from the bottom of the bin blender hopper section assure that there are a minimum of three samples from this area for a statistically valid analysis. Although traditionally 10 locations are deemed adequate to map tumbling type mixers, 12 locations are recommended based on the geometry of bin blenders. There are therefore sufficient samples to determine within- and between-location variability. This is accomplished by grouping of locations within an area.

Samples for dosage uniformity testing are taken throughout the semicontinuous dosing process. A stratified sampling plan is followed during a dosing operation. The first sample is taken at the start, and remaining samples are taken at equal intervals until the end of the process with sampling points at no more than 5% of the batch. This results in a total of 20 strata samples of dosages representing the entire dosing run. Stratified sampling increases confidence of the uniformity of the batch as sample locations target problematic areas prone to potential segregation. A risk-based sampling plan (Fig. 2.12) that includes additional sampling points at the beginning and the end of the run may be applied based on product/process knowledge. Random variation is expected throughout a population; therefore, CU results are expected to be a normal distribution with no special cause variation. A minimum of 7 units from each of the 20 locations are required to be sampled for testing. For statistical rigor, 20 sample locations are sufficient. Three random samples are tested from each of the 20 strata resulting in 60 units from each blend for Tier 1 testing and a total of 140 (20×7) units for Tier 2 dosage uniformity testing.

Table 2.7 Coating results from the finished product

Tests	Specifications	Observations B. No.: IJKL Coating pan: 1
Appearance	Orange colored, round shaped, biconvex, film-coated tablets, with engraved "XYZ" on one side and "BBB" over "20"on the other side	Conforms
Identification	UPLC retention time: Corresponds to standard	Conforms
Identification	UV spectrum: Corresponds to standard	Conforms
Identification	PXRD diffractogram conforms to that of exhibit A	Conforms
Hardness	For information only	8.2kp
Water content	NMT 6.0% w/w	3.3%
Dissolution	As per USP/EP Q = 80% Time: 15 min	Mean: 103% %RSD: 1.1% Min: 101% Max: 104% Pass stage 1
Uniformity of dosage units	As per USP/EP	Mean: 98.3% %RSD: 1.3% Min: 96.9% Max: 100.8% AV: 3.2 Pass stage 1
Degradation products	Unidentified impurity: NMT 0.20% each	Below reporting threshold
	Total impurities: NMT 0.3%	Below reporting threshold
Enantiomeric purity	ELE S-isomer: NMT 0.15%	Below reporting threshold
Assay	90.0 to 110.0% (% of claim)	97.5%
Residual solvent	Meets the USP <467> option 1 based on the cumulative calculation of the residual solvent levels in the ingredients used in the product	Complies

Variance component analysis (VCA) allows for the quantification of sources of variability across different levels of units from a sampling scheme. VCA analysis is conducted to determine the potential source of variability: either within-area or between-areas. High between-area variance could indicate poor mixing, resulting in nonuniformity within the blender and potential for segregation. High within-area variance could indicate sampling bias or analytical errors. In the sampling plan proposed, single testing per location is performed with multiple tests per area; hence VCA is possible. Adequate mixing is directly assessed since it is more likely that mixing issues will appear as a difference between top, middle, and bottom areas of the blender than between locations lying potentially in the same area. When between-areas variability is observed, it indicates uniformity issues related to process/product. The identified potential source of variation observed in blend batches

Table 2.8 Dissolution profiles for the demonstration batches

% Drug dissolved																
Time (min)	Tab −1	Tab −2	Tab −3	Tab −4	Tab −5	Tab −6	Tab −7	Tab −8	Tab −9	Tab −10	Tab −11	Tab −12	Mean	Mini mum	Maximum	% RSD
5	92	97	97	87	93	93	83	87	89	92	92	93	91	83	97	5
10	101	105	103	100	102	100	97	100	99	99	101	101	101	97	105	2
15	103	106	105	102	103	101	101	104	102	103	103	104	103	101	106	1
20	104	106	105	103	104	102	102	105	104	104	105	105	104	102	106	1
30	104	106	105	103	104	102	103	106	105	105	105	105	104	102	106	1

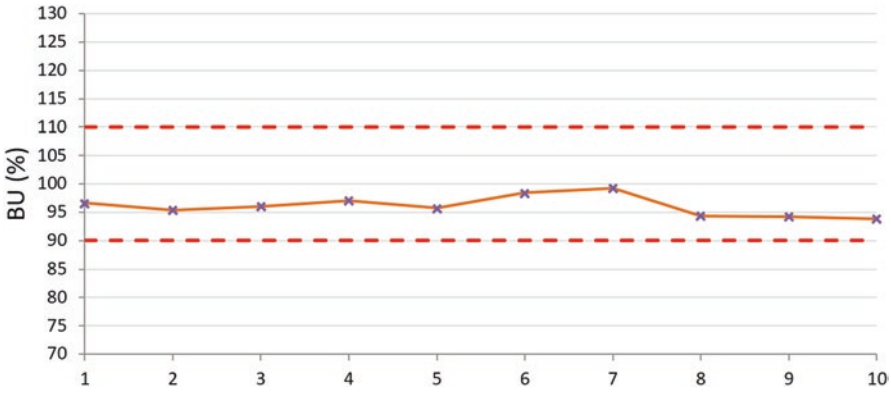


Fig. 2.9 Blend uniformity

Batch	C_{pk}	C_{pk} Lower 95%	C_{pk} Upper 95%
EFGH	**6.89**	5.29	8.48

Fig. 2.10 In-process (stratified) As-Is CU results

Batch	C_{pk}	C_{pk} Lower 95%	C_{pk} Upper 95%
EFGH	**5.67**	3.32	8.03

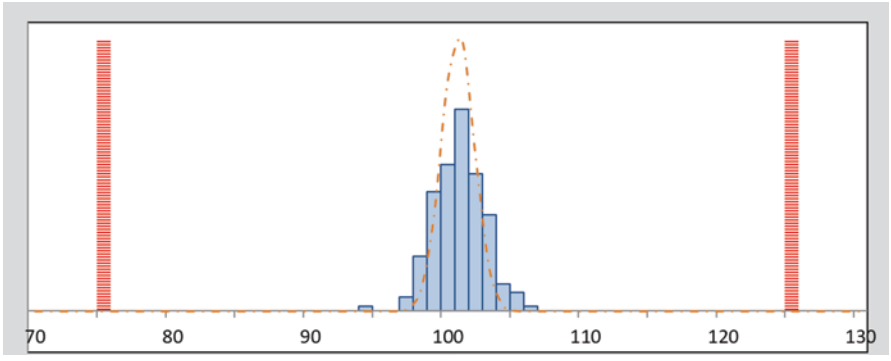


Fig. 2.11 Finished product As-Is CU results

Table 2.9 The USP rules for immediate release dosage forms indicate

Stage	# of units	Acceptance criteria
1	6	Each unit is not less than Q + 5%
2	6	Average of 12 units (S1 + S2) is ≥ Q No unit is less than Q-15%
3	12	Average of 24 units (S1 + S2 + S3) is ≥ Q Not more than two units are less than Q-15% No unit is less than Q-25%

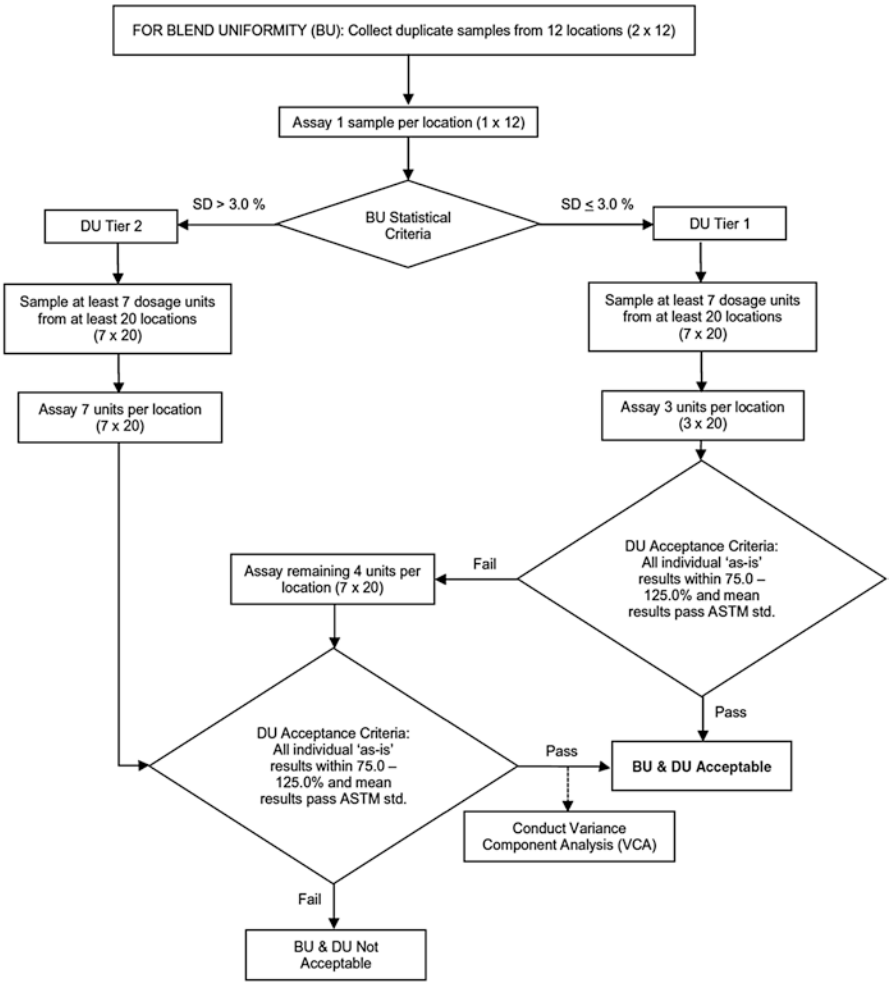


Fig. 2.12 Process flow diagram for assessment of blend and dosage uniformity for demonstration batch

may be further evaluated and preventative actions implemented, if required. For further assessment, additional data is required which can be gathered from heightened sampling and testing. The GAVE approach may be applied at small-scale development with batch sizes of powder blends in 2 cu. ft. or greater. For smaller scale a more suitable sampling analysis can be applied.

The introduction of new products or processes into an existing facility requires good product knowledge as multiple input variables can introduce complexities during commercial manufacturing. The technology transfer activities (R&D to commercial or between sites) follow the ASTM E2500 recommendations for a risk-based approach. Critical quality attributes (CQAs), critical process parameters (CPPs), process control strategy information, statistical assessment of generated data, and prior production experience on the product and/or similar products are all considered for product technology transfer and scale-up prior to initiating PPQ studies. Good knowledge management and scientific knowledge in product development and manufacturing science and technology groups enable effective transfer of developed solid dose formulations for commercial scale manufacturing. In the case of technology transfer to a CMO, both the sending and receiving parties need good communication of challenges, experiences, and controls required for a successful transfer of processing and commercialization.

References

1. SUPAC-IR: immediate-release solid oral dosage forms: Scale-up and post-approval changes: chemistry, manufacturing and controls, in vitro dissolution testing, and in vivo bioequivalence documentation, November 1995.
2. Q12: technical and regulatory considerations for pharmaceutical product lifecycle management.
3. ICH. International conference on harmonisation of technical requirements for the registration of pharmaceuticals for human use (ICH) guidance document: Q9: quality risk management. Geneva; 2005, ICH Expert Working Group. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf.
4. Alsmeyer D, Pazhayattil A, Chen S, Munaretto F, Hye M, Sanghvi P. Acceptance probability (pa) analysis for process validation lifecycle stages. AAPS PharmSciTech. 2016;17(2):516–22.
5. Sayeed-Desta N, Pazhayattil AB, Collins J, Doshi C. A science and risk-based pragmatic methodology for blend and content uniformity assessment. AAPS PharmSciTech. 2018;19(3):1483–92.

Chapter 3
Stage 2A and 2B: Batch Determination, Sampling, and Testing Plan

Abstract The qualification Stage 2 encompasses Stage 2A and Stage 2B. Stage 2A ensures that the equipment, utilities, facility, and system designs are adequately qualified. Stage 2B further ensures the qualification of process performance. Process performance qualification (PPQ) or Stage 2B confirms that the manufacturing process as designed is capable of reproducible commercial manufacturing. Heightened sampling and testing is recommended during Stage 2B while simulating standard commercial manufacturing conditions. PPQ activities are performed in line with lifecycle approach by incorporating quality risk management and statistically based assessments. Completion of Stage 2B studies is a major milestone for product commercialization. The final PPQ report hence is required to be thoroughly reviewed and approved by the responsible departments to ensure the adequacy of processes prior to moving to commercial manufacturing. As an outcome, the PPQ report may suggest change control requirements to further enhance the control strategy for the product per lifecycle requirements.

Keywords Process performance qualification · Stage 2 · Change control · Number of batches · Lifecycle

The primary goal of Stage 2 is to ensure that the process design developed at Stage 1 is assessed for its capability to ensure consistent product quality during commercial manufacturing. Stage 2 encompasses Stage 2A (qualification of equipment, utilities, facility, and system designs) and Stage 2B (process performance qualification). Completion of Stage 2 is imperative prior to commercial distribution of a drug product. Solid dose Stage 2B is primarily performed in such a way that it emulates the commercial manufacturing settings while collecting additional data to statistically justify the use of the manufacturing process for continued commercial manufacturing. Basic requirements of Stage 2A have been discussed in Chapter 4 of Vol. 1. Since guidance for commissioning and qualification (design qualification, installation qualification, operational qualification, and performance qualification) are extensively reviewed in ISPE baseline guidance, this chapter will focus on Stage 2B

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9_3

requirements. Process qualification is defined as confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing, as per US FDA guidance on Process Validation [1].

Estimating Number of Stage 2B (PPQ) Batches

Activities in Stage 2 PPQ should be based on well-grounded scientific justification, an appropriate level of product and process understanding, and adequate demonstration of process control. The 2011 FDA guidance states that the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. This indicates a need to understand both within and between batch variability. The estimation of the number of Stage 2B batches to be assessed should be therefore based on an analysis that accounts for the manufacturer's batch-to-batch variation. The best strategy is to determine the minimum number of batches for which a projected confidence interval of the product's critical quality attributes resides completely and readily within the desired specifications. That is, based on current information, the number of batches that, upon evaluation, should provide sufficient data so that a statistically confident conclusion of the product's critical quality attributes can be achieved should be examined. For a product quality attribute to be tested to comply with current specifications, its tested mean shall be as close as possible to the center of the specification, and its standard deviation shall be as minimal as possible under the assumption of normal distribution. Based on this assumption, we create a confidence interval of the product quality attribute measurement that is a combination of the confidence interval of the process mean and the confidence interval of the process standard deviation. Because each specific quality attribute is framed differently, often with distinct requirements, the form of the equations used to determine confidence intervals should be tailored per quality attribute. For example, USP dosage uniformity indicates computation of an acceptance value (AV) that must be less than 15 to meet the Stage 1 criteria. A confidence interval is then estimated for each number of potential PPQ batches based on previously collected product-specific data (i.e., the magnitude of the within or intra-batch statistics) and historical evidence of batch-to-batch variability for comparable products (i.e., between or inter-batch). Per this approach, the projected number of PPQ batches is determined [2] where the entire confidence interval resides within the specification limits. This is illustrated below (Fig. 3.1) for the dosage uniformity AV quality attribute.

The form of the equation is dependent on the specific quality attribute; comparable derivations can be accomplished for other attributes such as assay and dissolution. It should be noted that the number of PPQ batches estimation does not supplant the need to produce the PPQ batches or review the data generated from these batches.

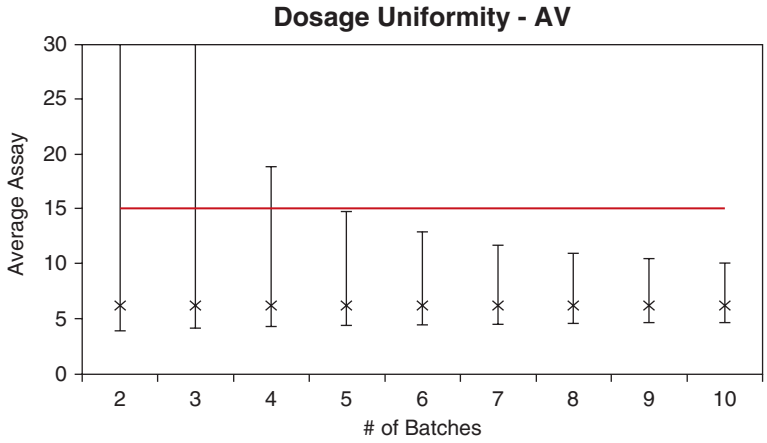
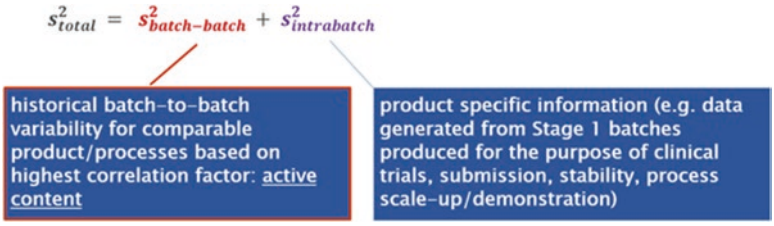


Fig. 3.1 Dosage uniformity

The total or overall variability of a process can be represented as a summation of individual component variation. This may be mathematically denoted as:

$$S^2_{\text{total}} = S^2_{\text{batch batch}} + S^2_{\text{intra batch}} + S^2_{\text{sampling}} + S^2_{\text{analytical}} + \ldots$$

The total variation is comprised of variation derived from batch-to-batch, intra-batch, sampling, and analytical variability sources. In general, Stage 1 process design provides an assessment of most variation sources with the notable exception of the batch-to-batch (between or inter-batch) variability. Thus, data from Stage 1 provides a reasonable measure of product intra-batch performance. However, it is impossible to assess the batch-to-batch variability until several batches of product are produced and analyzed. To approximate this component, it is reasonable to assert that a similar process/product will exhibit similar batch-to-batch characteristics. As such, tabulated evidence from historical records can provide a good estimate. Therefore, the number of Stage 2B PPQ batches required is the number of batches when the projected "best estimate" confidence interval of the product quality attribute measurements (which is a combination of the CI of the process mean and the CI of the process standard deviation) resides completely within the specification range.



A critical factor in the overall determination of the suggested number of PPQ batches is the batch-to-batch (or between batch) variability. Prior to the PPQ campaign, this factor for the particular product has yet to be determined. However, data of comparable campaigns provide a reasonable indication of the anticipated batch-to-batch variability. The magnitude of the batch-to-batch variability is potentially dependent on several different factors; one factor in particular is the API content or product label claim. To gain an understanding of batch-to-batch variability, historical dosage uniformity and dissolution data from historical batches and molecules has to be compiled. The batch-to-batch variability is then extracted from each campaign by separating the intra-batch variability from the overall total campaign variability. The distribution of each campaign batch-to batch standard deviation results in a typical distribution profile expected for a collection of standard deviation data. Summary data from the historical evidence are stored in reference tables and are used as a reasonable approximation of the batch-to-batch component of variation used in justifying the number of batches that should be evaluated during PPQ to provide a reasonable confidence that the evaluated process is robust. Once PPQ batches are manufactured and tested, it is prudent to compare the estimation of the batch-to-batch variation with the truly observed PPQ batch-to-batch variation. It has to be noted that both the product-specific information and historical batch-to-batch process information may vary significantly among different manufacturing facilities (due to personnel, operation, process, equipment, raw material, and other factors). The sources of variation for other types of manufacturing technologies will differ. In order to statistically justify how many validation batches should be produced, the company should gain an understanding of the variation they observe from the various processes based on their historical data. Several methodologies are available that discuss the challenge of justifying a statistical model for determining a sufficient number of batches.

Developing a Stage 2B Protocol

A major task while creating a lifecycle-based Stage 2B PPQ protocol is to develop a scientifically sound sampling and testing plan. Various strategies are applied based on the scenario of the solid dose drug product. This includes the dosage strengths, drug mechanism of action, release mechanism, absorption, manufacturing process steps, historical and Stage 1 data gathered, etc. This section will explain requirements for developing a solid dose Stage 2B prospective study protocol for a manufacturing process of a product with two strengths intended to be launched for multiple markets. Both strengths are manufactured from a common mix (e.g., mix 83.33% is the common mix). To establish batch size, batch data for each end of the limit – if it is a common mix – are required with dosage uniformity testing. Parameters, set points, and ranges that are not established during formulation development (FD) and during demonstration should be established during the Stage 2B study, which includes the following: dosing batch size, compression speed,

coating pan load range, and the coating operating guidelines (parameters – solution flow rate, pan speed, gun angle, arm angle, atomizing air pressure and pattern air pressure, etc.). In addition, the end of batch dosage uniformity verification and a stoppage sample may be performed to gather more data. Since a study is initiated for multiple markets, the testing methods and specifications have to be compared for each market. It is prudent to pursue the most stringent specifications and justify accordingly. In other cases the batches may need to be tested using the methods from the submitted specifications for both markets. If so, a market comparison assessment needs to be performed for the purpose. A minimum number of consecutive mix batches and three compression and film coating validation batches will have to be manufactured according to master manufacturing records to satisfy the Stage 2B requirements. The testing plan under the protocol is to evaluate whether the process consistently produces a product that meets predetermined specifications for chemical and physical properties.

The purpose and scope of the protocol should be followed by summary of master manufacturing records, summary of materials and their specifications, summary of equipment used and their qualification, calibration status, requirements for training, facility, utility, and environmental conditions. A prerequisite (Table 3.1) confirmation is required at the stage.

The manufacturing processes are to be executed according to master manufacturing records, SOPs, and TMs (technical manuals) and in compliance with cGMP. Sampling is to be conducted according to validation protocols and relevant SOPs, WIs (Work Instructions), and TMs. The departmental roles and responsibilities (Table 3.2) are to be clearly described in a protocol.

The manufacturing process flowchart (Fig. 3.2) per Stage 1 development outcomes is provided.

The sampling and testing will be performed as per the predefined heightened sampling and testing plan (Table 3.3) in the protocol. The additional data at critical processing stages is gathered in order to verify that each quality attribute is met. The sample size and plan should be determined with the help of statistical tools and a risk assessment. The operational parameters for the Stage 2B batches are clearly defined in the protocol as it is in the master manufacturing record. The protocol should require a summary of process operating ranges achieved during the Stage 2B studies in the report. The critical process parameters such as spray rate, liquid addition time, solvent used, impeller speeds, mixing time, etc. should be verified during the study. The qualified press speed ranges are verified during the PPQ run. The press speed along with the achieved hardness (Fig. 3.3), thickness, friability (Fig. 3.4), and compression force ranges is to be analyzed within the PPQ report. The US FDA guidance on Process Validation clearly states that the PPQ data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within the commercial manufacturing conditions; hence it is not ideal to generate worst case data during PPQ studies. The operating ranges are established based on studies performed during Stage 1.

The dissolution profiles of the PPQ batches are compared with the dissolution profile of the submission study batch using the f2 similarity factor (comparability criteria

Table 3.1 PPQ prerequisite checklist

#	Documentation/requirements	Yes/no
1	Enhanced design review (equipment/facility/utility/system)	✓
2	Pre-inspection delivery (equipment/utility/system)	✓
3	Factory acceptance test (equipment/utility/system)	✓
4	System impact assessment	✓
5	Commissioning report (equipment/facility/utility/system)	✓
6	Operating manual (equipment/utility/system)	✓
7	Installation qualification protocol/report (equipment/utility/system)	✓
8	Operational qualification protocol/report (equipment/utility/system)	✓
9	Performance qualification protocol/report (equipment/facility/utility/system)	✓
10	Preventive maintenance schedule (equipment/facility/utility/system)	✓
11	Calibration reports (equipment/utility/system)	✓
12	Validation master plan – Pprocess, method, equipment/facility/utility/system	✓
13	Product development report (CPP, NOR, CS)	✓
14	Technology transfer report	✓
15	Standard operating procedure (operation, cleaning, PM, calibration)	✓
16	Quality management system (change control)	✓
17	Continued process verification procedure (only for changes)	✓
18	Technical risk assessment report	✓
19	Personnel training records	✓

of 50–100). If the mean dissolution rate of both the PPQ batches and the comparative batch is greater than 85% at the 15-min time point, comparative dissolution using the f2 similarity factor will not be required, and the profiles can be considered comparable. Statistical evaluations, for example, dosage uniformity process capability (CpK/Pa) and dissolution process capability (Pa) analyses, are also performed on the executed PPQ batches. All the results are documented in the PPQ report. The certificate of analysis results of the active raw material(s) will be included in the PPQ report. Where possible and practical, different batches of raw material are to be used to manufacture the PPQ batches. All results must conform to the specifications as per the raw material specification. The process yields observed for the executed PPQ batches are documented within the PPQ report. However, a process yield limit is established only once adequate data has been compiled (a minimum evaluation of ten commercial batches). Deviations from the manufacturing processes or protocol procedures or failure to meet acceptance criteria shall be reviewed for their impact on the protocol

Table 3.2 Protocol execution responsibilities

Responsibility	PV	Production	PPQ Lab	QC Lab	Quality	TO	Quality	Stability Lab
Protocol generation	X							
Protocol review and approval	X	X				X	X	
Coordination of protocol execution including distribution of protocol for execution to production, validation lab, quality control lab, and quality in-process, as applicable	X							
Execute manufacturing processes according to MPDs, SOPs, and TMs (technical manuals) and in compliance with cGMP		X						
Execution of protocol		X						
Provide online assistance during protocol execution, as applicable					X	X		
Sample the manufacturing processes according to validation protocol and relevant SOPs, WIs (work instructions), and TMs		X						
Distribute samples to appropriate departments for testing	X	X			X			
Test samples per protocol and according to relevant compendial test methods or validated test methods in accordance with applicable cGMP, GLP, and GALP			X	X	X			
Compilation and analysis of data and test results	X							
Preparation of interim and/or final report	X							
Approval of the interim and/or final report	X	X				X	X	
Identify and place PPQ batches on stability as required								X

objective and the qualification of the manufacturing process. These deviations are referenced and discussed in the PPQ report with its impact to the process. Any revision to an approved PPQ protocol requires reapproval of all signatories.

A bin blender sampling plan as discussed in Chap. 2 (GAVE approach) [3] can be applied for the PPQ batches. Similar approaches can be applied for V-blender

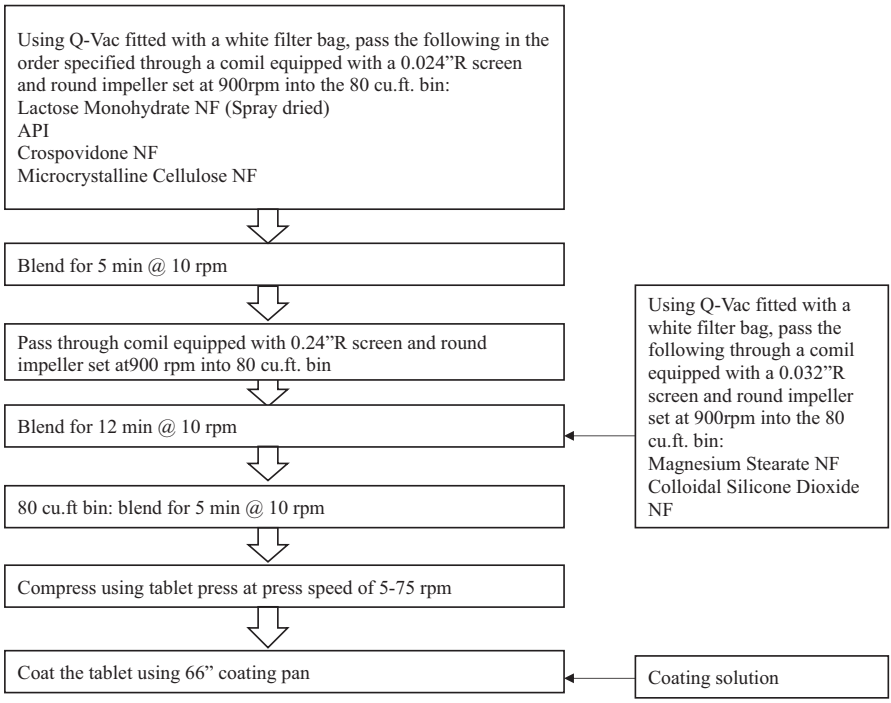


Fig. 3.2 Flowchart

sampling (Table 3.4, Fig. 3.5). The sampling is typically performed with adjustable sampling thief or die cavity thief. Each sample represents, by weight, approx. 2.5 dosage units, of the lowest strength. The first set of samples is to be assayed for label claim percent of active name. Other sample sizes can be used unless otherwise justified in the study protocol. As always, duplicate samples are removed for testing.

To verify press speed, each validation batch is compressed at the slowest speed for the first 30 min of run time. Upon confirmation of consistent performance and successful physical results at this speed, it is attempted to compress the remainder of the batch at the highest achievable speed. A visual AQL inspection using sampling plan for general AQL Inspection on top of each tote is performed during the compression run. Sampling intervals are calculated for a batch (Fig. 3.6). Recalculations must be performed throughout batch manufacture as required to ensure the defined number of samples is actually collected for testing.

Coating pan loads are normally established during Stage 1; if the same is not established, one pan must be coated at minimum pan load, one pan at maximum pan load, and the third pan load in between the minimum and maximum pan loads to establish the pan load during the PPQ study. Approximately 50 tablets are taken

Table 3.3 Example of PPQ additional testing requirements

Equipment	Operation	Parameters	Parameters to be verified	In-process testing	PPQ testing
Weigh scales	Weighing	Noncritical	N/A	None	Not required
Quadro Vacuum	Material loading	Noncritical	N/A	None	Not required
Russell Finex Sieve	Screening	# 6 mesh screen	# 6 mesh screen	None	Not required
80 cu. ft. Bin	Initial blend	5 min@ 10 rpm	5 min@ 10 rpm	None	Not required
Quadro Comil	Milling	0.024R round-round	0.024R round-round	None	Not required
Gerteis compactor	Compaction	Gap width, compaction force Roll speed	Screen size	Particle size distribution (sieve analysis) Bulk density Tapped density	Not required
80 cu. ft. bin	Final Blending	10 min @ 10 rpm	10 min @ 10 rpm	None	Blend uniformity Particle size distribution (sieve analysis) Bulk density Tapped density
Secondary containers	Unloading	Noncritical	N/A	None	Blend uniformity
Korsch tablet press	Compression	Press speed, pre-compression force, main compression force, cam size	Press speed, pre-compression force, main compression force	Hardness, thickness, weight, friability, disintegration, appearance	Dosage uniformity Dissolution
Coating solution train	Coating solution preparation	Noncritical	N/A	None	Not required
Coating pan (66″)	Film coating	Pan load range Pan speed Solution flow rate Gun angle, arm angle, atomizing air pressure, pattern air pressure	Pan load range Pan speed Solution flow rate Gun angle, arm angle, atomizing air pressure, pattern air pressure	Appearance, weight gain, average weight	AQL Dissolution

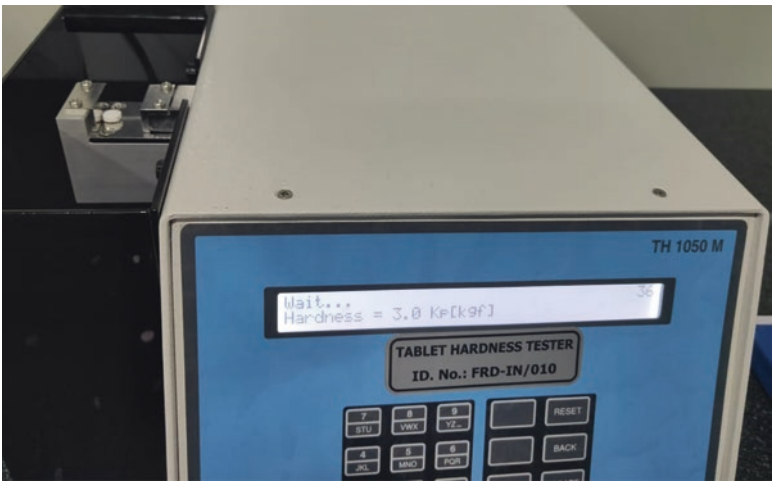
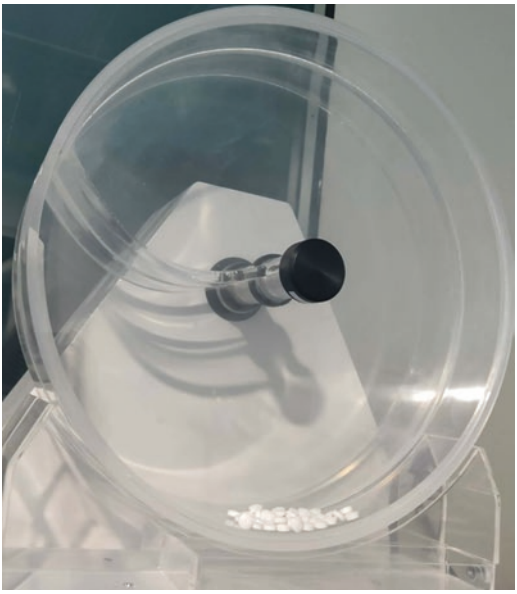


Fig. 3.3 Hardness tester

Fig. 3.4 Friability tester



from each coating pan at the end of the coating process. If one pan, test $N = 12$ for dissolution profile. If two pans, test $N = 6$ per pan for dissolution profile. If three or more pans, test $N = 6$ per pan for dissolution profile and $N = 12$ for dissolution profile on a composite sample. Provide a summary report including all data from the composite testing results.

Table 3.4 Example of V-blender sampling plan

Blend uniformity sampling plan			
V-blender location	Sampling location	# Samples	Visual verification (sample present in each bottle) initial and date
Trial 1	Random	1	N/A
Trial 2	Random	1	
Trial 3	Random	1	
1	Top of the blender – top left	2	Confirm that each of the 20 bottles contains a sample and the label on each bottle is completely filled out
2	Top of the blender – top center	2	
3	Top of the blender – top right	2	
4	Middle of the blender – central left	2	
5	Middle of the blender – central center	2	
6	Middle of the blender – central right	2	
7	Bottom of the blender – bottom left	2	
8	Bottom of the blender – bottom center back	2	
9	Bottom of the blender – bottom center front	2	
10	Bottom of the blender – bottom right	2	

Applying Matrix/Bracketing Approach

A risk-based Stage 2B PPQ matrix approach can be applied where appropriate. In a scenario where a common blend is used, with three bin batch sizes, proportional strengths of an uncoated tablet product, etc., a matrix approach (Table 3.5) may be applied in place of a traditional PPQ strategy. The sampling and testing requirements need to be applicable for the proposed changes such as new active ingredient, active ingredient process change, new product launch, etc.

The matrixing/bracketing approach needs to be developed based on a product risk assessment and statistical justification for the adequate number of sample points. The cons of matrixing include high risk of impacting all processes in the event of a failure, potential restrictions in verification studies during PPQ, minimal possibilities of bin batch splitting, etc. However the same result of establishing a data-driven evidence of consistent manufacturing process may be achieved through

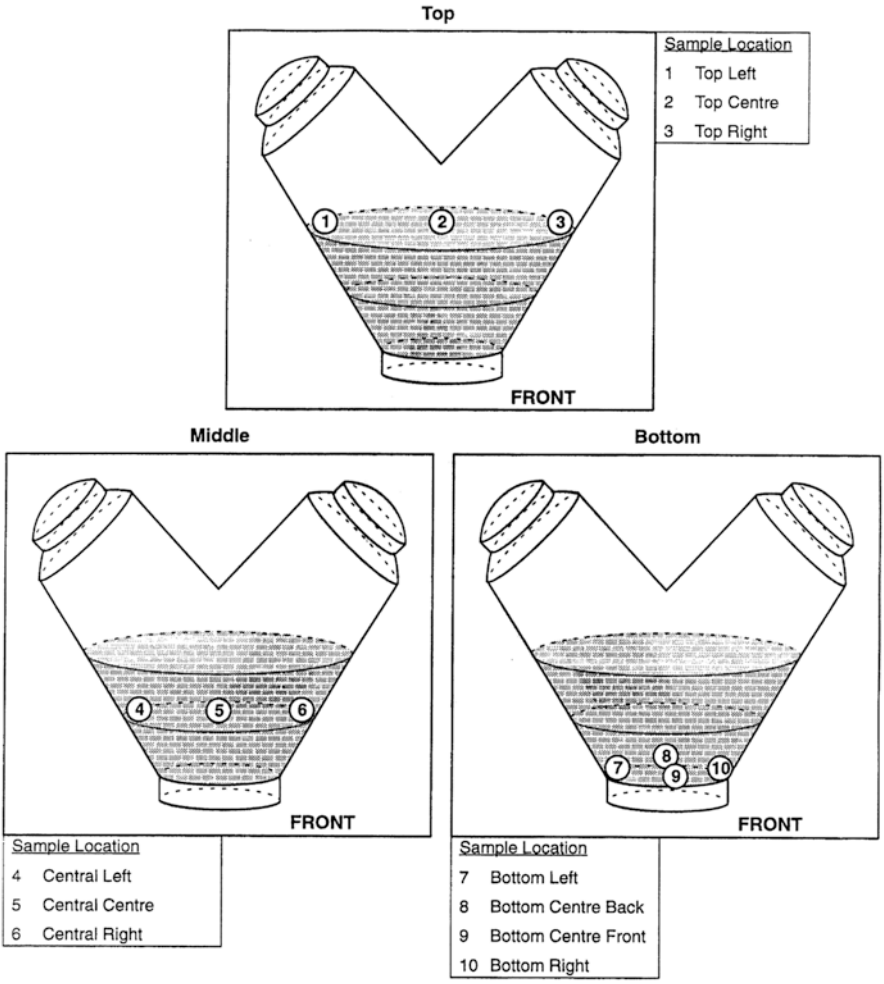


Fig. 3.5 V-blender sampling locations. Note: Front of mixer is where the discharge handle can be found

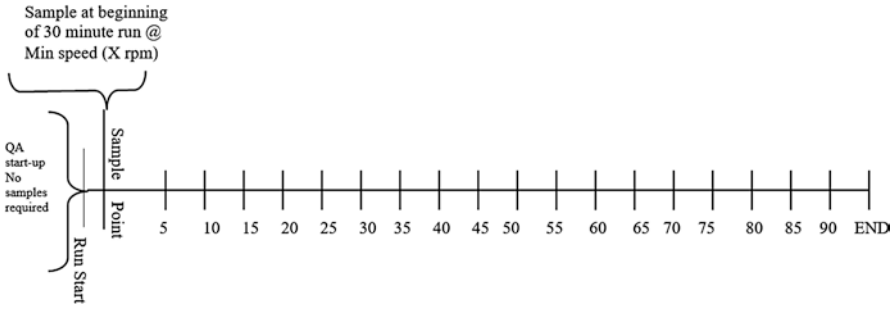


Fig. 3.6 Example of a traditional dosage unit sampling plan

Table 3.5 Example of a matrix PPQ approach

New API		
BU	CU	Disso
Typical traditional PV strategy		
Triplicate × BME × 10 location × 3 full blends × 3 bin × 3 strength = 2430	Triplicate × 20 location × 3 tab batches × 3 bin size × 3 strength = 1620	*N* = 12/batch × 3 tab batches × 3 strength × 3 bin sizes = 324
API (SDC)		
Triplicate × BME × 10 location × 3 full blends × 3 bin × 3 strength = 2430	Triplicate × 20 location × 3 tab batches × 3 bin size × 3 strength = 1620	*N* = 12/batch × 3 tab batches × 3 strength × 3 bin sizes = 324
Launch + site transfer + process changes + scale-up/scale-down		
Triplicate × BME × 10 location × 3 full blends × 3 bin × 3 strength = 2430	Triplicate × 20 location × 3 tab batches × 3 bin size × 3 strength = 1620	*N* = 12/batch × 3 tab batches × 3 strength × 3 bin sizes = 324
Fit for purpose risk-based matrix strategy		
10 location × 3 full blends = 30	Triplicate × 20 location × 3 tab batches s × 3 strength = 540	*N* = 12/ batch × 3 tab batches × 3 strength =108
API (SDC)		
10 location × 1 full blend = 10	Triplicate × 20 location × 1 tab batch × 1 strength =60	*N* = 12 × 1 batch =12
Launch + site transfer + process changes + scale-up/scale-down		
10 location × 3 batches × 3 bin sizes = 90	Triplicate × 20 location × 3 tab batches × 3 bin size × 3 strength = 1620	*N* = 12/batch × 3 tab batches × 3 strength × 3 bin sizes = 324

a matrix approach as well, thus reducing the number of test samples and time constraints to complete the PPQ study.

Elements of a Stage 2B PPQ Study Report

The objective of the PPQ report is to ascertain that the manufacturing process that had undergone adequate process design in Stage 1 meets the process performance qualification (PPQ) requirements, as defined in the Stage 2 PPQ protocol. It confirms that all physical and chemical test results from the PPQ batches have satisfied the acceptance criteria of the PPQ protocol and are comparable to the results of the biostudy/submission batches from Stage 1. Based on these results and the implementation of the change control requirements, if any, the organization can conclude that the manufacturing process for the product using specific active pharmaceutical ingredient has successfully completed Stage 2: process performance qualification for the various markets. The product will then continue to Stage 3: continued process verification program [4]. In the initial sections, the raw material and semi-finished batches used at each of the processing stages are summarized with their respective results such that the report displays the variability of material attributes,

Table 3.6 Blend physical test results for PPQ batches

Batch #	Bulk density (g/cc)	Tapped density (g/cc)	20 mesh (%)	40 mesh (%)	60 mesh (%)	80 mesh (%)	100 mesh (%)	Fines (%)
R7661	0.57–0.58	0.74–0.75	0	0	2	7–8	8	83
R7662	0.58–0.59	0.74–0.76	0	0	2–3	8	8	81–82
R7663	0.58	0.75–0.76	0	0	2	8	9	81–82

Table 3.7 Blend uniformity results for PPQ batches

US / Int. Acceptance criteria	Range: Mean – 10% to mean + 10%; RSD: NMT 5.0%		
Batch #	R7661	R7662	R7663
Acceptance criteria per batch	90.1–110.1	87.4–107.4	89.1–109.1
Average (%)	100.1	97.4	99.1
RSD (%)	2.0	3.6	2.1
Minimum (%)	96.2	90.9	96.6
Maximum (%)	102.9	104.6	103.3

Table 3.8 Compression speed challenge results

Batch #	Actual batch Qty. (kg)	Compression speed (rpm) 5–75 rpm	Approx. Run time (hrs)
R7651	986.4	5	0.5
		75	47.0
R7655	968.7	5	0.5
		75	47.0
R7658	985.6	5	0.5
		75	47.0

Table 3.9 Tablet press parameters

Fill cam (mm)	14	14	14	14
Pre- com force (kN)	2.4–3.2	2.6–2.9	2.5	3.8
Main- com force (kN)	8.1–14	8.3–11.8	9.0–13.3	8.1–12.0

equipment, setup, and processing parameters at all stages and followed by in-process and final CQA results (Tables 3.6, 3.7, 3.8, 3.9, 3.10, and 3.11).

Based on the above set of data, the established speed for the process will be 5–75 rpm (Table 3.8); the criteria in protocol required running 30 min at low speed and rest at max.

A graphical representation of the data per batch such as the one below is then provided (Fig. 3.7).

Statistical analysis on stratified dosage uniformity (DU) tests is performed to determine the process capability for all PPQ batches. Commonly accepted statistical guidelines indicate processes with Cpk >1.33 as "well controlled." The Cpk values (Table 3.12) for below PPQ batches show greater than 1.33 (using the 95.0% confidence limits).

Table 3.10 Compression test results summarized

In process test	Spec.	R7651	R7655	R7658
Weight of 10 units (g)	Target: 1.00 (0.97–1.03)	0.99–1.01	0.99–1.02	0.98–1.02
Weight variation (mg)	Target: 100 (92.5–107.5)	97.7–104.0	97.2–104.7	96.7–103.8
Hardness (kp)	Target: 4.5 (2–7)	2–7	2–7	2–7
Thickness (in)	Target: 0.125 (0.120–0.135)	0.120–0.126	0.120–0.129	0.120–0.127
Friability (%)	NMT 0.8% after 100 rev (4 min @25 rpm)	0.1–02	0.2	0.1–02
Disintegration (min)	NMT 15 min (without disc)	2:59–3:04	2:50–3:18	2:35–5:30

Table 3.11 Dosage uniformity results

	Dosage uniformity			
	Acceptance criteria			
Batch #	Range mean (90.0–110%, weight corrected)	Minimum (75.0% As Is)	Maximum (125.0% As Is)	RSD (NMT 6.0% weight corrected)
R7651	97.3–104.4	91.6–103.3	100.7–109.0	3.3
R7655	99.0–103.8	96.7–103.2	100.8–108.7	2.6
R7658	97.2–103.9	93.6–103.3	99.5–107.8	2.7

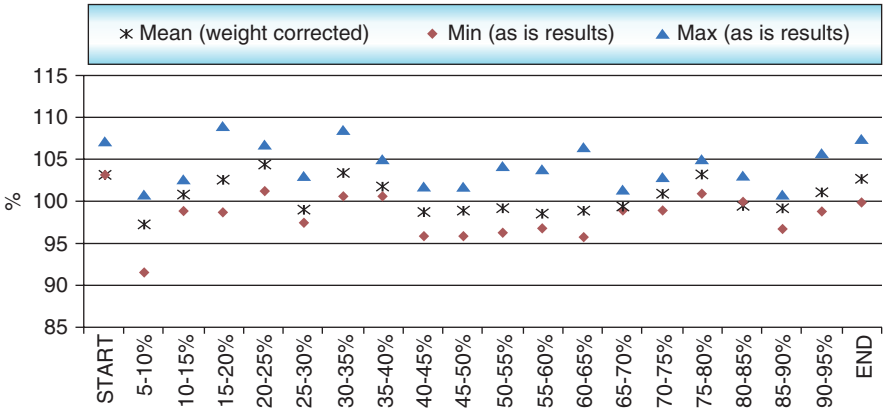


Fig. 3.7 Dosage uniformity

Table 3.12 Example of DU Cpk

	CpK		
Batch #	R7651	R7655	R7658
As Is	2.27	2.70	2.78
As is- pooled	2.56		
Weight corrected	1.64	2.77	1.87
Weight corrected- pooled	1.94		

Table 3.13 Coating process parameters

Film coating PP	Spec.	R7874		R7876		R7878	
		Pan 1	Pan 2	Pan 1	Pan 2	Pan 1	Pan 2
Pan load (kg)	464–491	464.0	491.0	491.0	491.0	491.0	
Pan speed (g/min)	2.0–6.0	2.0–6.0	2.0–6.0	2.0–6.0	2.0–6.0	2.0–6.0	2.0–6.0
Solution flow (g/min)	400–500	400–500	400–500	400–500	400–500	400–500	400–500
Spray gun distance (in)	8	8	8	8	8	8	8

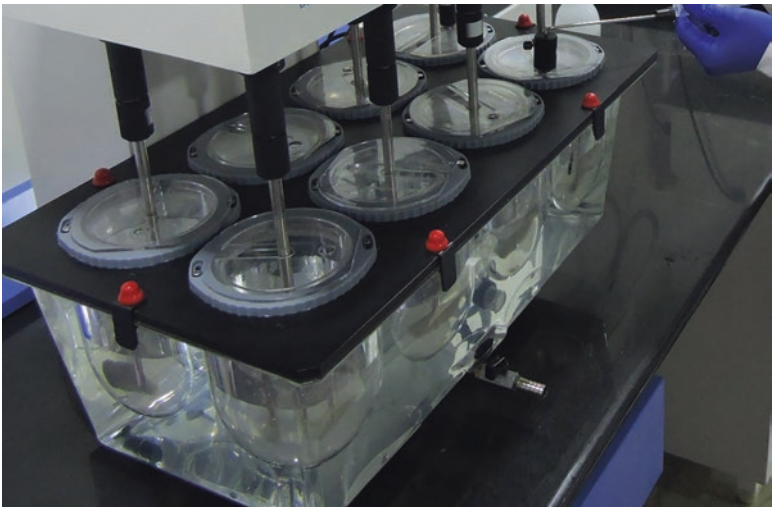


Fig. 3.8 Dissolution apparatus

Further the coating process parameters, as well as operating ranges, are tabulated as shown below (Table 3.13).

The AQL results pre and post coating process are also tabulated to ensure adequacy of coating. All PPQ batches have to meet the dissolution specifications (Fig. 3.8). The dissolution profiles of the composite samples for the three PPQ batches should be similar to the biostudy batch.

The data shown below depict that biostudy and PPQ batches dissolved ≥85% in 15 min (Fig. 3.9, Table 3.14).

Statistical evaluation for dissolution profiles (from composite) is then performed for the PPQ batches. As per the dissolution capability analysis, the probability of meeting the acceptance criteria (Pa) for future batches at a particular stage is determined by comparing the tested dissolution statistics of the pooled batches with a theoretical construct. The results indicate if the process is well controlled and can consistently meet the required specifications for dissolution, the target overall probability of meeting the dissolution specification should be >99.99%.

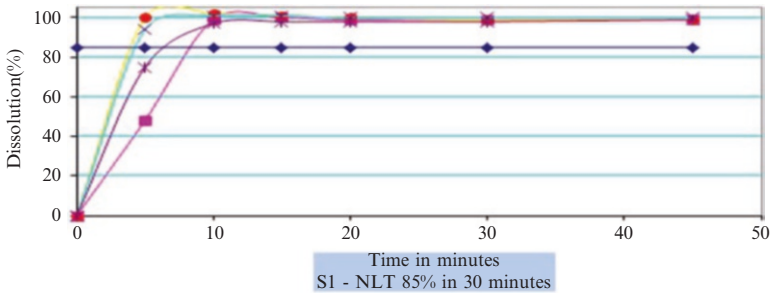


Fig. 3.9 Dissolution profile

Table 3.14 Single time point dissolution results per pan

Acceptance criteria: Range % dissolved per batch	NLT 85% (Q = 80%) dissolved in 30 min
R7874 Pan 1	94–103
R7874 Pan 2	98–103
R7876 Pan 1	95–105
R7876 Pan 2	93–102
R7878 Pan 1	95–101
R7878 Pan 2	98–107

The physical and chemical test results of the composite sample from each batch should meet the established finished product release criteria. All deviations, observations, and out-of-trend results should be discussed in the PPQ report to measure the impact on the product and process. As an outcome, the PPQ report may suggest change control requirements to further enhance the control strategy for the product per lifecycle requirements. Based on the physical and chemical test results from the PPQ batches that have satisfied the acceptance criteria of the PPQ protocol and comparable results to the biostudy batch, it can be concluded that the manufacturing process for the product has successfully completed Stage 2 process performance qualification. A certificate for successful completion of PPQ may be issued as required. The report would further require reference to the Stage 3A protocol in case of newly launched product/major changes or confirmation that the product can directly enter into Stage 3B monitoring program. The final PPQ report is a key milestone document in the Process Validation lifecycle and hence is required to be thoroughly reviewed and approved by the responsible departments to ensure the adequacy of processes prior to moving to commercial manufacturing.

References

1. FDA. Guidance for industry, process validation: general principles and practices, US Food and Drug Administration. 2011. http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf.
2. Pazhayattil A, Alsmeyer D, Chen S, Hye M, Ingram, M, Sanghvi P. Stage 2 Process performance qualification (PPQ): a scientific approach to determine the number of PPQ batches. AAPS PharmSciTech. 2015.
3. Sayeed-Desta N, Pazhayattil AB, Collins J, Doshi C. A science and risk-based pragmatic methodology for blend and content uniformity assessment.
4. Alsmeyer D, Pazhayattil AB. A case for continued process verification, Pharmaceutical Manufacturing.

Chapter 4
Stage 3A: Continued/Ongoing Process Verification

Abstract Stage 3A is the initial phase of the continued process verification stage. A defined number of batches undergo Stage 3A evaluation. It includes assessment of critical material attributes, critical process parameters, critical quality attributes, estimation of inherent process variability and PaCS index, process capability and quality dashboard (PCQd), and enhanced control strategy. Stage 3A assessment is a valuable resource for product development and future risk mitigation of similar products and processes. The discussed elements of Stage 3A address the industry and regulatory guidance requirements, to provide enough data supporting risk-based decisions on the product. Fit for purpose statistical tools are applied during the assessment. In-depth Stage 3A enhances the product control strategy. The report highlights any need for continuous improvement substantiated by statistically analyzed data. Stage 3A report is a repository of product/process knowledge and analyzes data from all three stages of Process Validation.

Keywords Continued process verification · Continuous improvement · Statistical analysis · Process capability · Control strategy

This chapter discusses the evaluation methodologies and statistical approaches for Process Validation lifecycle Stage 3A. The assessment methodologies can be applied to newly developed and launched molecules where a substantial amount of process and product knowledge has been gathered. Stage 3A encompasses determining the requisite number of Stage 3A batches, evaluation of critical material attributes, critical process parameters, critical quality attributes, estimation of inherent process variability and PaCS index, process capability and quality dashboard (PCQd), and enhanced control strategy. The US FDA Process Validation guidance encourages application of previous credible experience with similar products and processes. A complete Stage 3A assessment is therefore a valuable resource for product development and future risk mitigation of similar products and processes. The discussed elements of Stage 3A address the industry and regulatory guidance requirements, to provide enough data supporting risk-based decisions on the product.

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9_4

Stage 3A is the initial assessment post new product launch that utilizes a substantial body of data for statistical evaluation to gain deeper product understanding. A Stage 3A assessment utilizes data from all Process Validation stages. Stage 3A assessment is thus pivotal in understanding and managing product variability since the product control strategies are based on early estimates of process capability at the time of launch. The assessment of the predetermined number of batches therefore augments the initial process knowledge gained from quality by design (QbD)-based product development and verification (PPQ) stages. A Stage 3A protocol with the requirements defined is typically generated upon completion of the Process Validation lifecycle Stage 2B. The completion of a Stage 3A report demonstrates the organization's compliance with establishing an enhanced product control strategy and the attainment of a high level of product understanding and quality (Table 4.3).

Determining Number of Stage 3A Batches

US FDA Process Validation guidance recommends that the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. A novel approach was introduced by Pazhayattil et al. [1] to determine number of process performance qualification (Stage 2) batches. The approach uses previously collected product-specific information and historical batch-to-batch process information across multiple CQAs. Product-specific information includes data generated from Stage 1 batches produced for the purpose of clinical trials, submission or registration, stability, process scale-up/scale-down, and demonstration. This approach creates a confidence interval of the product quality attribute measurements that is a combination of the confidence interval of the process mean and the confidence interval of the process standard deviation. The projected numbers of PPQ batches are determined such that the entire simulated confidence interval resides within the specification limits. The same approach is applied to determine the number of Stage 3A batches, except that in place of intra-batch variability (S0) from Stage 1, the results from Stage 2 PPQ batches are utilized. For example, USP <905> dosage uniformity indicates computation of an acceptance value (AV) that must be less than 15 to meet the L1 criteria. Pre-existing batch data was used to determine the inter-batch variability (SB-B), and Stage 2 data was used to determine the intra-batch variability (S0). The upper confidence limit for the estimated number of Stage 3A batches is derived from:

$$S^{\mathrm{hi}}_{(N_{\mathrm{B}})} = \sqrt{\left\{ S_{\text{B-B}} * \sqrt{\frac{(N_{\mathrm{B}}-1)}{\chi^2_{\left(\frac{\alpha}{2},N_B-1\right)}}} \right\}^2 + \left\{ S_0 * \sqrt{\frac{(N_0-1)}{\chi^2_{\left(\frac{\alpha}{2},N_0-1\right)}}} \right\}^2}$$

Since each specific quality attribute is measured differently, with distinct requirements, the equations used to determine confidence intervals are formulated

per quality attribute. Where the number of batches determined from each quality attribute is not the same, a conservative approach of selecting the highest estimated number is recommended. An alternative approach could employ tolerance intervals in the sample size calculation where the number of batches required is determined such that, for instance, 95% of the data will be constrained to lie within specified bounds with 95% confidence.

Inherent Process Variability (IPV) and PaCS Index

A best estimate of process and method variability identifies the need for continuous improvement, enhances product and process understanding, and allows manufacturers to develop a better control strategy. Sources of variability can usually be attributed to the "six M's:" man, machine, material, measurement, method, and Mother Nature. By developing measures of the major sources of variability, a best estimate of the process' variability (manufacturing method) and analytical (measurement) method variability can be deduced. The first step in isolating the variability due to the manufacturing process from the variability due to the analytical method involves defining the response variable, or the critical quality attribute, and the source of data wherein the other sources of variability may be minimized. The Stage 3A batches, post-Stage 2 process performance qualification batches, are processed on the same model of qualified equipment (minimizing variability due to machine) by the same pool of trained operators, according to standard operating procedures (reducing any variability that might be created by man). Raw material used in the process must meet testing specifications and come from a common supplier (to minimize variability due to material), while environmental and facility controls and monitoring control the environmental variability (reducing the potential effects of Mother Nature). By minimizing these four sources of variability, the sources of manufacturing process and analytical method variability can be isolated.

Overall variability can be broken down to its main sources, as shown below:

$$S^2\text{Overall} = S^2\text{Process} + S^2\text{Analytical} + S^2\text{Other}$$

Given the controls on other sources of variability found in Stage 3A batches, S^2 Other can be assumed to be negligible. Any remaining variability can then be subsumed under the process and analytical sources to yield the partition of interest, namely:

$$S^2\text{Overall} = S^2\text{Process} + S^2\text{Analytical}$$

An estimate of the variability inherent to the process (IPV) and the variability due to the analytical method can then be attained by variance component analysis. Variance component analysis is a statistical tool that partitions overall variability

into individual components. The statistical model underlying this tool is the random-effects analysis of variance (ANOVA) model, which can be written as:

$$\text{yij} = m + \text{ai} + \text{eij} \,\text{where}\, i = 1,\ldots,r \,\text{and}\, j = 1,\ldots,n$$

where yij is the *j*th measurement in the *i*th group, *m* is the overall mean (an unknown constant), ai is the effect attributable to the *i*th batch, and eij is the residual error. It should be noted that, in this model, as opposed to a fixed-effects ANOVA model, ai is considered to be a random variable, where random conditions include different chemists, equipment, batches, and numbers of days. The random variables ai and eij are assumed to be independent, with mean zero and variance $\sigma^2 a$ and $\sigma^2 e$, respectively.

Inherent process variability (IPV) is a measure of batch-to-batch variability, while analytical (method) variability is a measure of the variability of material within the same batch. As such, estimates of $\sigma^2 a$ measure inherent process variability, while $\sigma^2 e$ measures analytical method variability. Other measures of interest can be obtained from the above model. For instance, the ratio of these two variance components provides a standardized measure of the variance of the population group means, while the intra-class correlation is a measure of the proportion of the total variance due to the process. Estimates for these values can be obtained from the ANOVA data provided (Table 4.1).

Other estimators are available, in particular for unbalanced data where a different number of measurements are taken per batch. The restricted maximum likelihood (REML) estimator is a viable alternative available in most statistical software packages. This model can be fit to situations in which the batch effect is considered random and each batch has n samples. For example, 20 batches might be considered to be a random sample from a larger pool of batches for a specific product. For each of these 20 batches, a random sample of 10 samples would be taken to measure finished product dosage uniformity. The variability in the mean finished product dosage uniformity between the batches, $\sigma^2 a$, would yield an estimate of the inherent process variability, while ρ_a would provide an estimate of the proportion of variability due to

Table 4.1 ANOVA

Source of variation	Degrees of freedom	Sum of squares	Mean square	Expected mean square
Between groups (Process)	$r-1$	$\text{SSA} = n\sum_{i=1}^{r}\left(\overline{y_{i.}} - \overline{y_{..}}\right)^2$	$\text{MSA} = \frac{\text{SSA}}{(k-1)}$	$n\sigma_a^2 + \sigma_e^2$
Within groups (Analytical)	$r(n-1)$	$\text{SSE} = \sum_{i=1}^{r}\sum_{j=1}^{n}\left(y_{ij} - \overline{y_{i.}}\right)^2$	$\text{MSE} = \frac{\text{SSE}}{k(n-1)}$	σ_e^2
Total	$rn-1$	$\text{SST} = \sum_{i=1}^{r}\sum_{j=1}^{n}\left(y_{ij} - \overline{y_{..}}\right)^2$		

the process. Confidence intervals can be constructed for these estimates and are available in common statistical software packages. The estimated IPV, as well as the ratio of total variance due to the process, can be used during Stage 3 batch monitoring to focus efforts on process improvement. As more information is gathered for a product, a rise in the IPV itself or a rise in the proportion of total variance due to the process (ρ_a) could indicate the need to investigate possible process improvements. On the other hand, a decrease in IPV or the decline in ρ_a would indicate that the process is improving. In order to obtain a picture of how well the process is performing overall for a specific product, a comparison with other products employing the same process can be made by generating a benchmark. The PaCS index [2] provides an indication of a current product's process performance in comparison to other similar products. To derive the PaCS index, a representative set of other products generated with the same process would be chosen. For each of these chosen products, the IPV would then be calculated as above. The PaCS index could then be calculated using the following equation:

$$\text{PaCS} = \text{IPV}_\text{P} \,/\, \text{IPV}_\text{B}$$

where IPV_B is the benchmark inherent process variability and IPV_P is the inherent process variability for the product under consideration. IPV_B is the median process variability of the selected products with processes similar to the current product.

A PaCS index greater than 1 indicates the process variability is high, while a PaCS less than 1 indicates that process variability is low compared to the benchmark. Therefore, a PaCS value that is less than 1 is preferred. Because the distribution of the PaCS index is not analytically derivable, confidence intervals can be estimated using Monte Carlo simulation. The PaCS index together with IPV values and the other derived statistics provide a platform upon which further decision-making can take place. For instance, high PaCS values would indicate that the process for a specific product is not performing as expected. Estimation of inherent process variability (IPVP) allows for determining a PaCS index for the product and helps in understanding the contribution to variability that comes from the manufacturing process and the analytical method used. In addition, PaCS is a metric developed in relation to the manufacturing process at a particular production site.

The index can be effectively used to determine continuous improvement projects at the site or for site transfer initiatives. PaCS provides with a tangible quantitative robustness figure for various supply chain decision-making scenarios. The index can be a component of periodic process performance review by senior management as recommended by ICH Q10 [3]. In addition, APV and the PaCS index may be used to decide such things as who should be primarily responsible for a specific continuous improvement project (i.e., whether process, analytical, or a combination). This is often a point of contention. It could also be used to determine which site has the best PaCS index with respect to a product. This factor will be considered when deciding for or against site product volume increases. In summary, the PaCS can provide valuable insight to decision-makers and help to drive continuous quality

Product	Average DU	$\widehat{S_a^2}$	$\widehat{S_e^2}$	$\widehat{S_y^2}$	$\hat{\rho}_a$	$\hat{\rho}_e$
Amlodipine 10 mg/ Atorvastatin 80 mg*	99.7 (98.7, 100.6)	1.61 (0.71, 5.60)	1.02 (0.77, 1.39)	2.63 (1.70, 6.63)	0.61 (0.39, 0.85)	0.39 (0.15, 0.61)
Cetrizine 10 mg	99.1 (98.3, 100.0)	0.80 (0.20, 4.28)	1.19 (3.43, 6.17)	2.00 (4.25, 9.11)	0.40 (0.04, 0.49)	0.60 (0.51, 0.96)
Citalopram 20 mg	100.5 (99.6, 101.4)	1.25 (0.46, 4.70)	2.33 (1.77, 3.19)	3.57 (2.65, 7.11)	0.35 (0.15, 0.67)	0.65 (033, 0.85)
Clopidogrel 75 mg	98.8 (97.9, 99.6)	0.96 (0.18, 4.30)	4.72 (3.60, 6.48)	5.68 (4.42, 9.38)	0.17 (0.03, 0.48)	0.83 (0.52, 0.97)
Famciclovir 500 mg	100.0 (99.2, 100.8)	0.58 (0.48, 4.18)	1.89 (0.98, 1.76)	2.37 (1.71, 5.50)	0.24 (0.26, 0.77)	0.76 (0.23, 0.74)
Gabapentin 800 mg	99.5 (99.1, 99.8)	0.18 (0.06, 0.73)	0.52 (0.39, 0.71)	0.70 (0.53, 1.28)	0.26 (0.09, 0.59)	0.74 (0.41, 0.91)
Imatinib 500 mg	99.2 (98.7, 99.6)	0.39 (0.15, 1.44)	0.63 (0.48, 0.87)	1.02 (0.75, 2.10)	0.38 (0.18, 0.70)	0.62 (0.30, 0.82)
Metformin 500 mg	101.2 (100.8, 101.7)	0.23 (0.00, 0.19)	1.84 (1.40, 2.52)	2.07 (1.62, 3.21)	0.11 (0.00, 0.40)	0.89 (0.60, 1.00)
Pentoxifylline 400 mg	98.2 (97.9, 98.5)	0.07 (0.00, 0.49)	1.11 (0.84, 1.52)	1.18 (0.92, 1.74)	0.06 (0.00, 0.31)	0.94 (0.69, 1.00)
Quetiapine 300 mg	98.9 (98.4, 99.3)	0.23 (0.03, 1.07)	1.35 (1.03, 1.85)	1.58 (1.23, 2.54)	0.14 (0.02, 0.45)	0.86 (0.55, 0.98)
Zopiclone 7.5 mg	99.5 (99.1, 100.0)	0.18 (0.00, 1.26)	2.89 (2.20, 3.96)	3.06 (2.40, 4.52)	0.06 (0.00, 0.31)	0.94 (0.69, 1.00)

Fig. 4.1 Example

improvement programs in biopharmaceutical and pharmaceutical development as well as manufacturing.

Given that IPV_P 0.09 and IPV_B of 0.39 [Fig. 4.1], the PaCS index is calculated as 0.09/0.39 = 0.23, indicating that the process variability for the FCT product is low compared to the benchmark. A product-specific PCQd is a critical component of Stage 3A assessment in projecting product robustness. The dashboard addresses the elements in the FDA's Guidance: Request for Quality Matrix, where the agency suggests optional metrics as evidence of manufacturing robustness and a commitment to quality. Data reported indicate low risk and may merit a reduction of site inspection frequency. Each processing stage can be evaluated against a predetermined process capability target to provide an overall product performance synopsis.

PCQd Process Capability Targets

A trained statistician is responsible for the selection of statistical tools employed in this assessment, i.e., evaluating process stability and capability. PCQd process capability targets may be set prior to Stage 3A initiation based on accepted process performance indices (e.g., P_p, P_{pk}) and stringent control limits. P_p formula considers the extent of variation given by standard deviation and an acceptable range allowed by specified limits despite the mean and hence is appropriate for in-process CQAs such as sieve analysis. For IP CQA the sample is intended to meet the specification requirement at predefined intervals through the manufacturing process. The P_{pk} estimate is able to diagnose decentralization problems aside from the process variation. As such, it is applicable to hardness and weight variation where meeting the target specification is the objective.

Probability of acceptance (P_a) is applicable for CQAs having stagewise acceptance criteria, such as dissolution, where traditional process capability measures are inadequate. Some of the benefits of implementing PCQd include (Table 4.2) enabling proactive risk mitigation activities, empowering management with product performance oversight, improving supply chain predictability and manufacturing reliability, encouraging implementation of emerging technology to reduce variability,

Table 4.2 PCQd performance dashboard

Unit operation/attribute	Capability target	Performance
Compaction		
Sieve results	$P_p > 1$	2.2
Compression		
IP hardness	$P_{pk} > 1$	1.3
IP weight variation	$P_{pk} > 1$	1.7
Tablet press speed	Max. verified	Meets
FP dissolution	$P_a > 99.9\%$	Meets
FP assay	$P_a > 99.9\%$	Meets
FP uniformity	AV < 10	Meets
PaCS uniformity	$\rho_{a\ \text{product}}/\rho_{a\ \text{benchmark}}$	Meets

and enabling regulators (e.g., US FDA) in developing a risk-based site inspection schedule. PCQd may also be utilized by organizations as a transfer criterion between product development and commercial operations responsible for the commercial lifecycle management of the product.

Process Performance and Product Quality Monitoring

ICH Q10 Pharmaceutical Quality System guidance states that process performance and product quality monitoring systems should provide tools for measurement and analysis of critical material attributes (CMAs), critical process parameters (CPPs), and critical quality attributes (CQAs) identified in the control strategy. An enhanced product control strategy is finalized based on quality by design (QbD) product development data, qualification results, and results from additional Stage 3A commercial batches. ICH Q8 (R2) Pharmaceutical Development requires control strategies for all critical attributes. A control strategy is designed to ensure that a product of required quality will be produced consistently. FDA recognizes the importance of utilizing post-launch learning that may be used to enhance product control strategy. CMAs for different lots of raw materials used in the manufacturing of Stage 3A batches may be assessed. Even though raw material lots meet vendor and in-house specification limits, it is important to ensure that trends observed in any of the identified CMAs are not adversely impacting finished product quality attributes such as dissolution, content uniformity, and assay. Additional process or specification controls may be required for drug product and/or drug substance manufacturing. CPPs evaluated at Stage 3A provide insight to any process drifts. Statistical process control charts may be used to for each CPP to evaluate the process parameter variability. Any observed trends may need appropriate actions to be taken. CPPs are defined in Stage 1 based on QbD-based product development. The extent of the CPPs' impact on CQAs is analyzed in case high variability is observed for CQAs,

Compaction-process parameter (Gerteis)	Critical	Early Stage 1	Post Stage 1			Post Stage 3A			Granule particle size distribution	
			Min	Max	Target	Min	Max	Target	Mesh	Specification
Force (KN/cm^2)	Yes	4–12	6	10	8	6	10	8	20	NLT 25
Roller gap (mm)	Yes	2.0–4.0	2.0	4.0	2.5	2.0	3.0	2.5	40 + 60	25–45
Roller speed (rpm)	Yes	2–12	5	10	8	6	10	8	80 + 100	25–45
Gran speed (rpm)	No								Fines	NMT 30

Fig. 4.2 Control strategy

e.g., parameters such as pre-compression force and main compression force on dissolution. Statistical models may be built to understand any new relationships that may surface in this further assessment and serve as a critical component in developing process understanding and control strategy.

In-process quality attributes at each of the manufacturing stages such as compaction, compression, and coating as well as finished product quality attributes such as assay, dissolution, and dosage uniformity are evaluated. A process is determined to be in a state of statistical control when it produces products that are stable and predictable over time, despite a certain amount of variability in the CQAs. Statistical process control charts are the most common tool in process monitoring. Process performance analysis (P_{pk}) and probability of acceptance analysis (P_a) are also used to provide quantifiable evaluations and predictions of the product performance. Analysis of results from Stage 3A batches can then be used to demonstrate the probability of future batches meeting CQA specification. A risk-based scientific assessment along with design of experiment (DoE) studies [4] allows a control strategy to be established in Stage 1, subsequently verified during Stage 2, and further enhanced during Stage 3A.

Defining a Stage 3B monitoring plan is part of the enhanced 3A control strategy [Fig. 4.2] for product lifecycle management. Further understanding of sources of variability and their impact on downstream processes, in-process materials, and drug product quality provide an opportunity to shift controls upstream and minimize the need for end product testing. Alternative approaches to meeting quality commitments (e.g., replacement of blend uniformity with stratified dosage uniformity or process analytical technologies such as NIR) are justified with the availability of additional data. The following types of assessments are typically conducted as part of Stage 3A review [Figs. 4.3, 4.4, and 4.5].

The Stage 3A summary enables the initiation of continuous improvement projects for further product enhancement and optimization (Table 4.3).

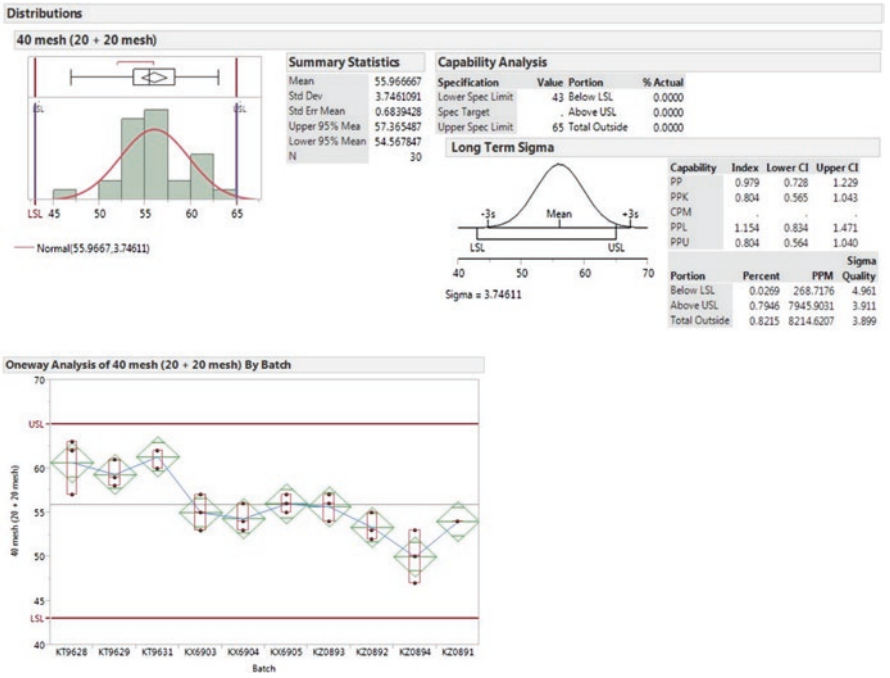


Fig. 4.3 Trending of sieve profile

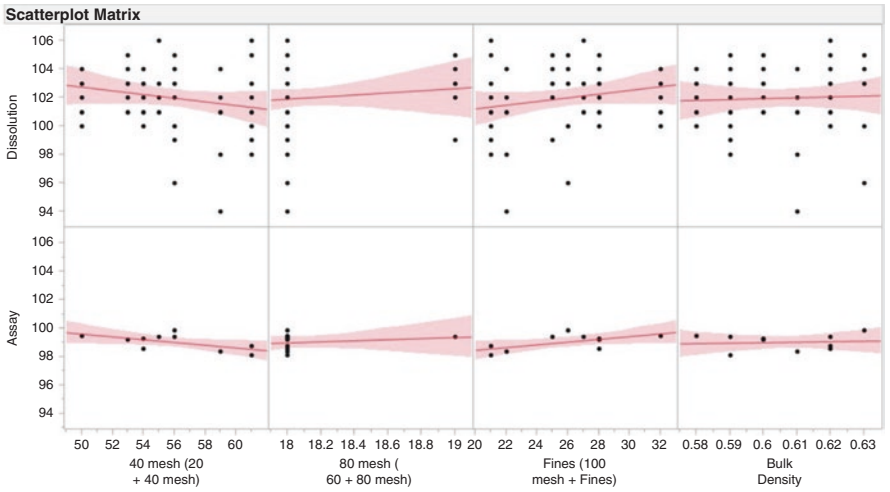


Fig. 4.4 Determining compaction and FP CQA correlation

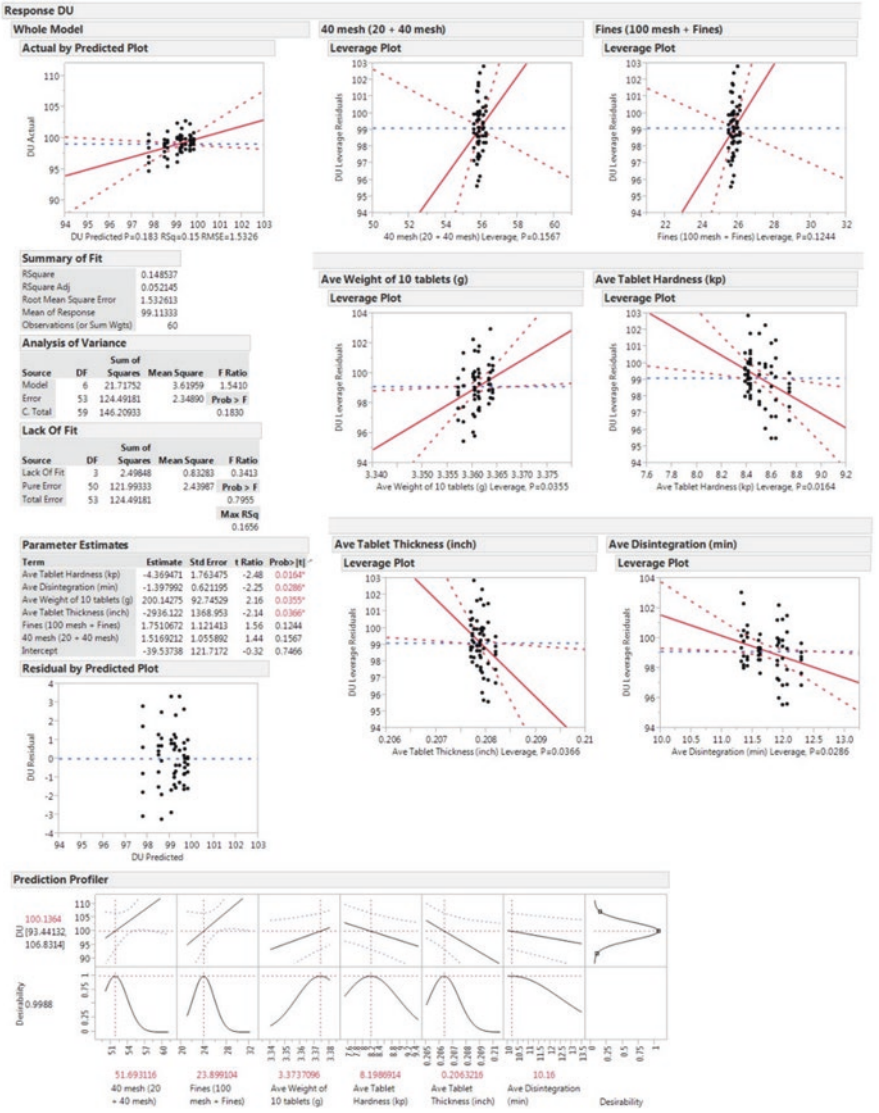


Fig. 4.5 Regression analysis for IP CQAs and DU

Table 4.3 Components of a Stage 3A protocol and report

Protocol	Report
Introduction and objective Current control strategy Determination of number of batches suggested for Stage 3A Assessment Assessment and statistical methods used: Inherent process variability (IPV), PaCS index Process capability and quality dashboard (PCQd) targets CMA, CPP, CQA evaluation	Executive summary Evaluation of critical material attributes, critical process parameters, critical quality attributes Estimation of inherent process variability (IPV) and PaCS index Process capability and quality dashboard (PCQd) Enhanced control strategy: CMA, CPP, CQA evaluation results Product quality review evaluation: failures, deviations, changes, complaint trends, adverse drug reactions, stability data CQAs identified for Stage 3B monitoring with targets Conclusions

References

1. Pazhayattil, A. Stage 2 Process performance qualification (PPQ): a scientific approach to determine the number of PPQ batches. AAPS PharmSciTech. 2015.
2. Collins J, Sayeed-Desta N, Pazhayattil A, Doshi C. A continuous improvement metric for pharmaceutical manufacturing. Pharm Technol.
3. ICH, Q10 Harmonized tripartite guideline, Pharmaceutical quality systems, (ICH, June 2008), ich.org, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf.
4. Politis SN, Colombo P, Colombo G, Rekkas MD. Design of experiments (DoE) in pharmaceutical development. Drug Dev Ind Pharm. 2017;43(6):889–901.

Chapter 5
Stage 3B: Continued/Ongoing Process Verification

Abstract Routine monitoring process parameters and quality attributes are required for detection of trends. The Stage 3B Continued/Ongoing Process Verification stage allows prevention of potential process failures. The product/process robustness monitoring is typically performed using electronic tools. Statistical process control (SPC) charts and automated notification of trends are key aspects of Stage 3B. Stage 3B process enables organizations to maintain an enhanced product control strategy. Stage 3B involved monitoring as well as decision-making based on a predetermined criteria. The observations and decisions are then adequately documented. The organization's product continuous improvement program is depended on an effective Stage 3B program. The assessment may result in tasks including continued close monitoring, enhancement of control strategy, or remediation project. Established statistical tools are employed as part of the ongoing assessment to guard against overreaction to individual events and prevent failure to detect unintended process variability. Stage 3B strategy for legacy and newly developed and launched product may differ.

Keywords Continued process verification · Ongoing process verification · Continuous improvement · Capability · Statistical process control · Out of statistical control

Stage 3B is routine continued process verification and trending of CPPs and IP and FP CQAs within established alert limits. An automated Stage 3B process enables organizations to maintain an enhanced product control strategy [1] (Fig. 5.1).

Statistical Process Control (SPC) Rules

The Stage 3B CPV program allows us to be compliant and avoid regulatory risks. The Stage 3B data inputs include Stage 1: Design of experiments (DoE), control strategy optimization, product/process remediation, and continuous improvement

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9_5

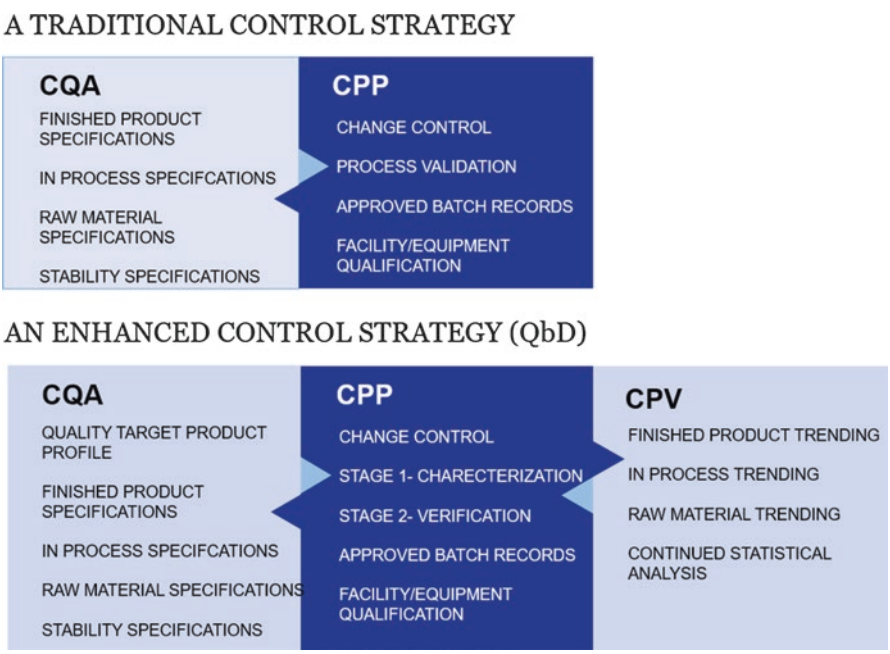


Fig. 5.1 Enhanced control strategy

as well as Stage 2: Determining number of Stage 2 batches, developing sampling testing plan, bracketing or matrixing approach, and process capability analysis. Stage 3B is for the routine continued process verification for commercial batches within established alert limits. Stage 3B ensures that during routine production the process remains in a state of control. A system or systems for detecting unplanned departures from the process as designed are essential to accomplish this goal. Collection and evaluation of process performance data will allow detection of process drift. The information collected should verify that the quality attributes are being appropriately controlled throughout the process. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements. Statistical process control (SPC) tools [2] primarily used in Stage 3B were initially developed by Walter Shewhart and gained popularity following W. Edwards Deming implementation in the automobile industry. SPC trend limits, coupled with control chart rules (e.g., Western Electric [3] or Nelson rules), alert to potential nonrandom events or deviations. There are a multitude of SPC charting rules that may be useful to identify potentially statistically anomalous events. These include (Table 5.1):

Triggering one of such rules indicates with reasonable statistical confidence that something may have changed within the process that may have an impact on the product robustness and control. Signals should trigger a response reaction based on the risk. Stage 3B CPV efforts can identify variability in the process and/or signal potential process improvements as a process is likely to encounter sources of variation. Statistical signals however need not be classified as deviations and investigated

Table 5.1 SPC rules

Rule	Description	Possible concern
Rule 1	One point more than three standard deviations from mean	Indicates a statistically anomalous event
Rule 2	Nine sequential points on the same side of the mean	Potential prolonged bias
Rule 3	Six sequential points continually decreasing or increasing	A potential trend
Rule 4	14 sequential points alternate (oscillate) in direction	Potential multiple underlying processes

Table 5.2 CPV complements APR

APQR Objectives	EU GMP Chapter 1	FDA 21 CFR 211.180	CPV
CQA Trending	Requirement	Requirement	✓
Determine need to change Specs/Process	Requirement	Requirement	✓
Stability Trend Review	Requirement	Requirement	✓
Monitoring/Revalidation	Requirement	Requirement	✓

immediately. A controlled manufacturing process is expected to see acceptable "process shift" signals, and not all signals are created equally. The reaction strategy should therefore depend on the influence on patient impact CQA's.

Continued Process Verification Complementing Annual Product Review

Stage 3B (CPV) covers many annual product quality review [4] components as listed below (Table 5.2):

CPV Approach to Legacy Products

Legacy products with sufficient data can be directly placed into Stage 3B CPV program. The 3-1-2 approach [5] is applicable in such cases. If trends are identified for critical quality attributes, the product moves directly into Stage 1 remediation followed by Stage 2 and eventually back to Process Validation Stage 3.

Establishing Control Limits

The chapter will review some of the Stage 3B trending attributes by using a product as an example. The first is to set statistical continued process verification trending limits (CTL). An example of the calculation used to determine the CQA CTL is presented below:

Finished product CQAs–CTL:

CTL for dosage uniformity: $\bar{X} \pm 3\,\sigma$

where:

Target mean, $\bar{X} = 100\%$
σ (SD) = 4 based on RSD = 4%
CTL for assay: $\bar{X} \pm 3\,\sigma$

where:

Target mean, $\bar{X} = 100\%$
σ (SD) = 0.94 for product has dosage strength less than 25 mg
σ (SD) = 0.80 for product has dosage strength between 25 mg and 100 mg
σ (SD) = 0.60 for product has dosage strength greater than 100 mg
σ (SD) provides a reasonable indication of the anticipated batch-to-batch variability. The magnitude of the batch-to-batch variability is potentially dependent on several factors; one factor in particular is the API content or product label claim. The assay is directly proportional to weight of the dosage unit which is again directly proportional to the active content or label claim as well.

For the finished product, there is typically only one assay sample (i.e., a composite of ten dosage units) analyzed per batch. Thus, the impact of intra-batch variation on assay is considered less significant in assessing the overall variation. And therefore, the variability in active content in dosage uniformity is considered the best estimate of the batch-to-batch variability in assay. As with content uniformity data, pre-existing batch data was used to determine the inter-batch variability. For this estimate, the average of all the content uniformity analyzed for each validation batch was used to determine the batch-to-batch standard deviation (SD). This was accomplished with the current analysis primarily because the content uniformity data was readily available and it was considered that the batch-to-batch variability for assay and average content uniformity would be comparable. Considering the fact that evidence from historical records can provide a good estimate, data from over 200 validation campaigns encompassing over 700 individual batches and approximately 100 distinct molecules was compiled to gain an understanding of batch-to-batch variability. Based on the product label claim, the expected batch-to-batch variability (SD) in active content (SD) was calculated as below which were used as the estimates of variability in assay (Table 5.3):

Table 5.3 Claim

Product label claim	σ (SD)
<25 mg	0.94
25 mg–100 mg	0.80
>100 mg	0.60

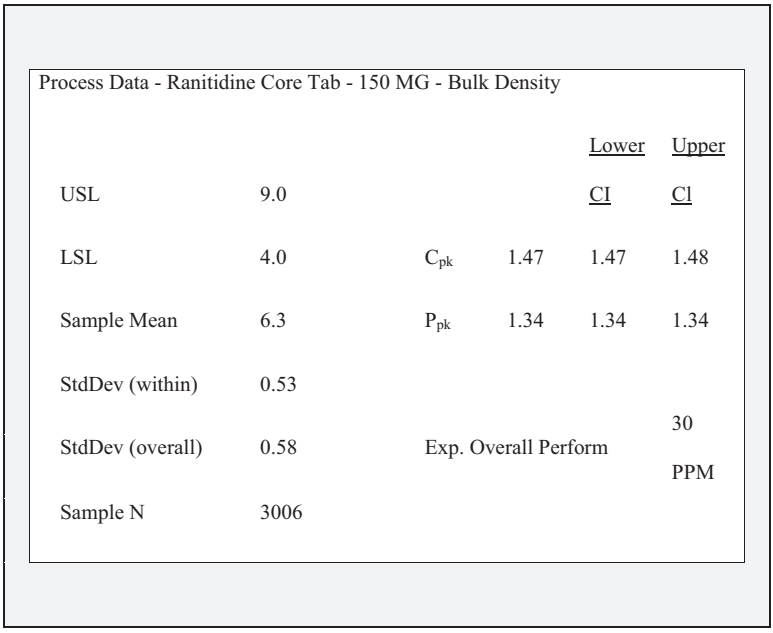


Fig. 5.2 Process capability and performance – Bulk density (Target: 0.6 g/cc, Range: 0.4–0.8 g/cc)

Dissolution Limit

No individual tablet has less than *Q*% dissolved at the specified time point indicated in the finished product C of A for immediate release dosage forms.

In-process product CQAs–CTL

CTL for weight variation of individual core tablet

LSL +10% of the target weight, USL-10% of the target weight

CTL for hardness of core tablet

LSL +10% of the target weight, USL-10% of the target weight

Below are examples of attributes that are trended for Stage 3B monitoring

Bulk density (Figs. 5.2, 5.3, and 5.4)

Critical process parameters: Compression (Figs. 5.5 and 5.6)

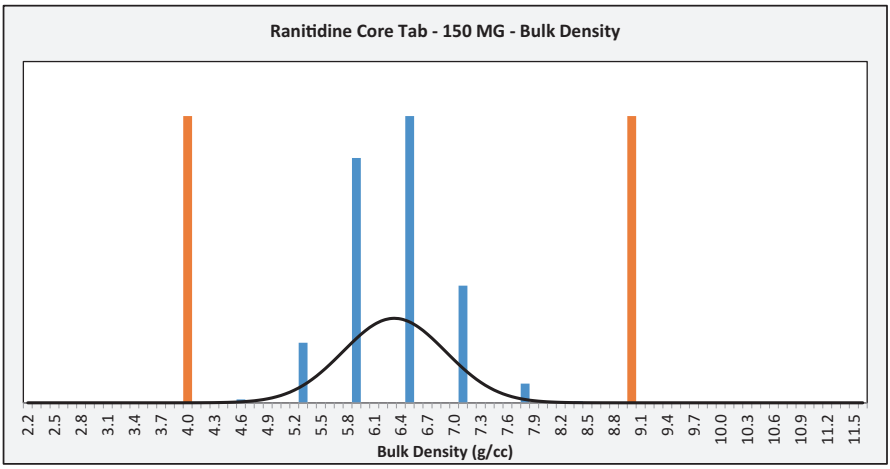


Fig. 5.3 Histogram – Bulk density (Target: 0.6 g/cc, Range: 0.4–0.8 g/cc)

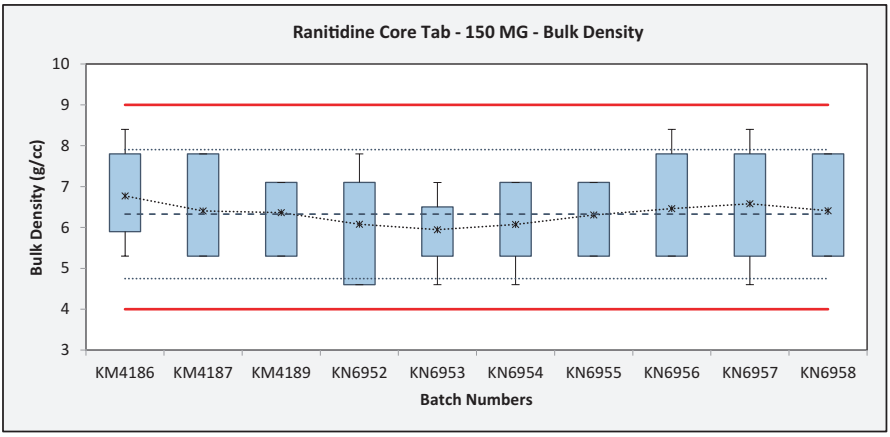


Fig. 5.4 Box plot – Bulk density (Target: 0.6 g/cc, Range: 0.4–0.8 g/cc)

Critical quality attributes: Compression (Figs. 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, and 5.17).

Critical process parameters: Film coating (Fig. 5.18)

Critical quality attributes: Film coating (Figs. 5.19, 5.20, 5.21, and 5.22).

Critical quality attributes: Finished product certificate of analysis (Figs. 5.23, 5.24, 5.25, 5.26, 5.27, and 5.28)

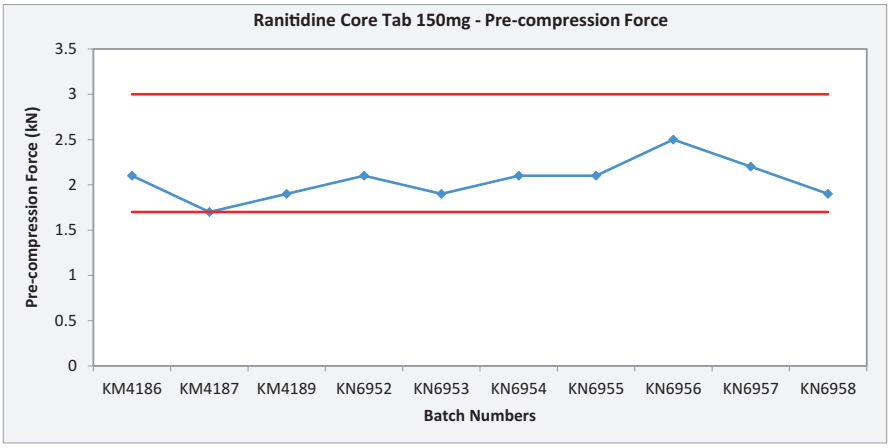


Fig. 5.5 Pre-compression force (Range: 1.7–3.0 kN)

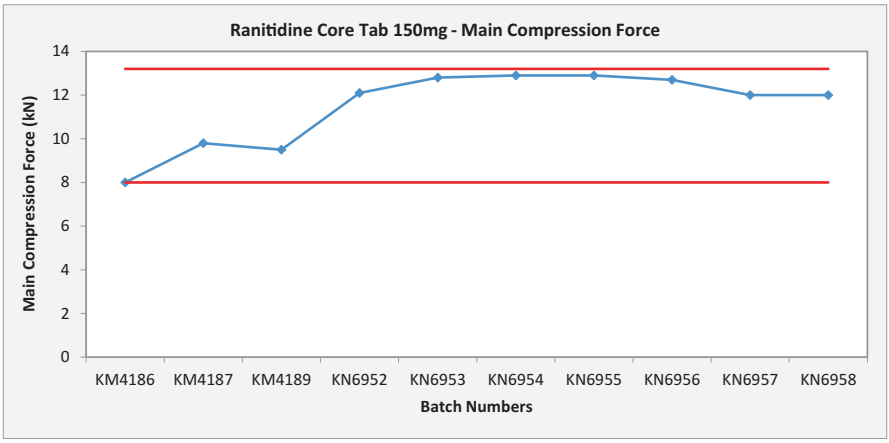


Fig. 5.6 Main compression force (Range: 8.0–13.3 kN)

A Stage 3B Process Flow Diagram

An automated Stage 3B process enables organizations to maintain and act on the SPC alerts. The below process steps may be adopted for effective implementation of a Stage 3B program (Fig. 5.29).

Process Data - Ranitidine Core Tab - 150 MG - Hardness

				Lower	Upper
USL	9.0			CI	CI
LSL	4.0	C_{pk}	1.47	1.47	1.48
Sample Mean	6.3	P_{pk}	1.34	1.34	1.34
StdDev (within)	0.53				
StdDev (overall)	0.58	Exp. Overall Perform			30 PPM
Sample N	3006				

Fig. 5.7 Process capability and performance – Hardness (Target 6.5 kP, Range: 4.0–9.0 kP)

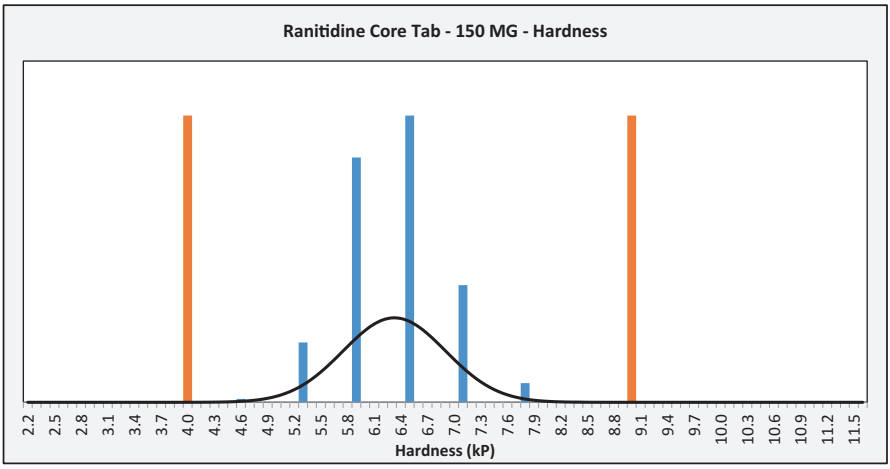


Fig. 5.8 Histogram – Hardness (Target 6.5 kP, Range: 4.0–9.0 kP)

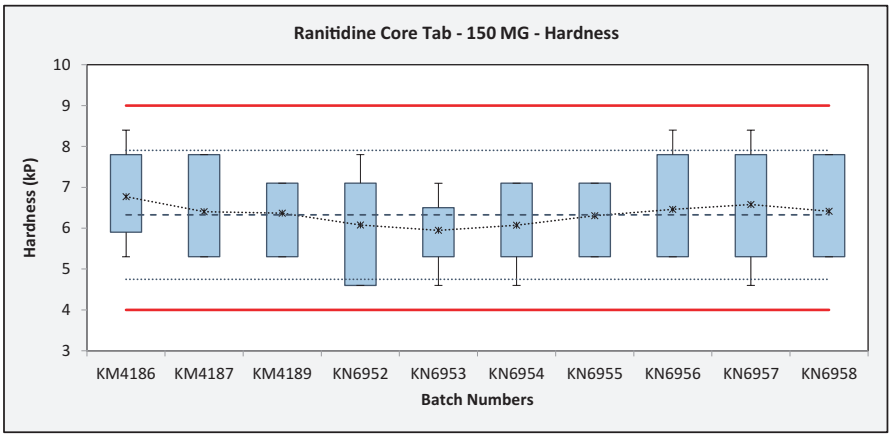


Fig. 5.9 Box plot – Hardness (Target 6.5 kP, Range: 4.0–9.0 kP)

Process Data - Ranitidine Core Tab - 150 MG - Thickness

				Lower	Upper
				CI	CI
USL	0.165				
LSL	0.145	C_{pk}	3.26	3.25	3.26
Sample Mean	0.155	P_{pk}	2.98	2.97	2.98
StdDev (within)	0.0010				
StdDev (overall)	0.0011	Exp. Overall Perform			<1 PPB
Sample N	3003				

Fig. 5.10 Process capability and performance – Thickness (Target 0.155 inch, Range: 0.145–0.165 inch)

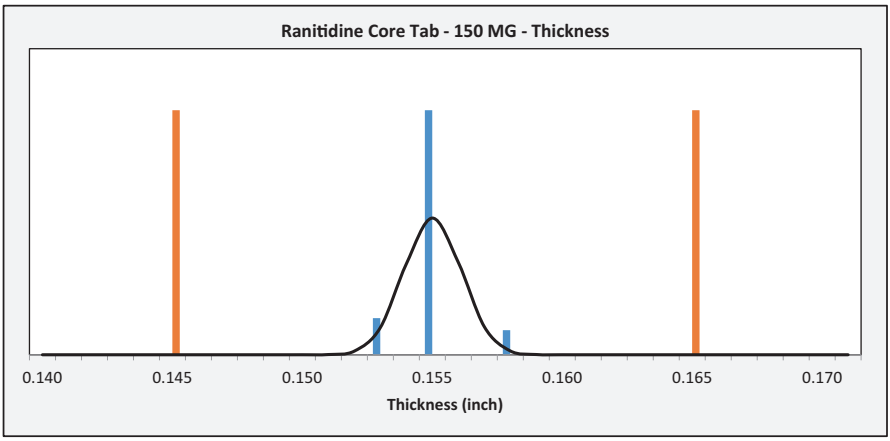


Fig. 5.11 Histogram – Thickness (Target 0.155 inch, Range: 0.145–0.165 inch)

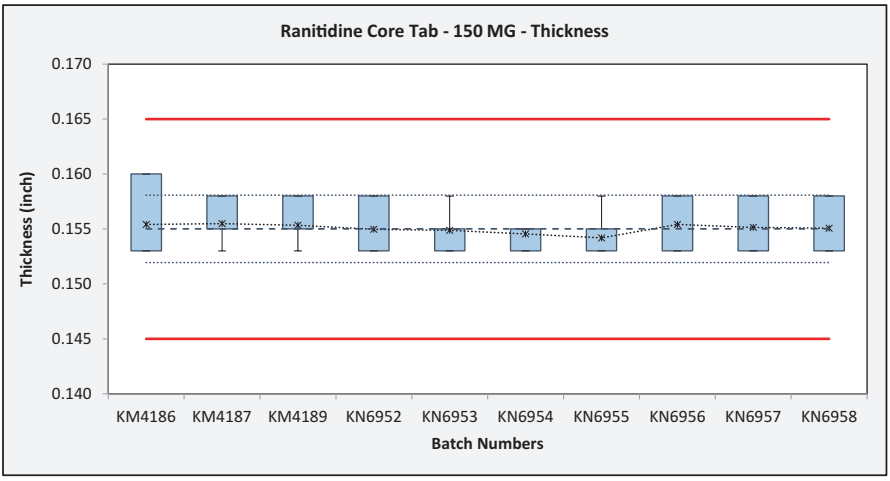


Fig. 5.12 Box plot – Thickness (Target 0.155 inch, Range: 0.145–0.165 inch)

Process Data - Ranitidine Core Tab - 150 MG - Weight of 10 Units

				Lower	Upper
USL	2.370			CI	CI
LSL	2.230	C_{pk}	2.15	2.14	2.17
Sample Mean	2.306	P_{pk}	1.59	1.58	1.60
StdDev (within)	0.0098				
		Exp. Overall Perform			1 PPM
StdDev (overall)	0.0133				
Sample N	613				

Fig. 5.13 Process capability and performance – Weight of 10 units (Target 2.30 g, Range: 2.23–2.37 g)

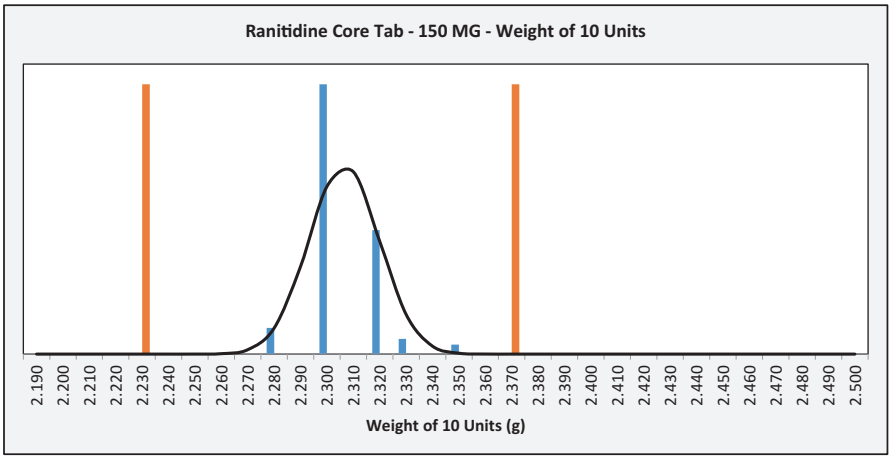


Fig. 5.14 Histogram – Weight of 10 units (Target 2.30 g, Range: 2.23–2.37 g)

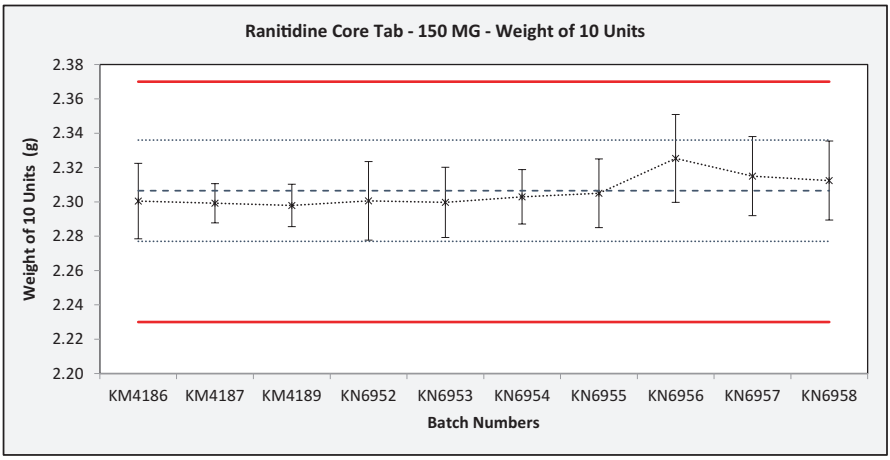


Fig. 5.15 Box plot – Weight of 10 units (Target 2.30 g, Range: 2.23–2.37 g)

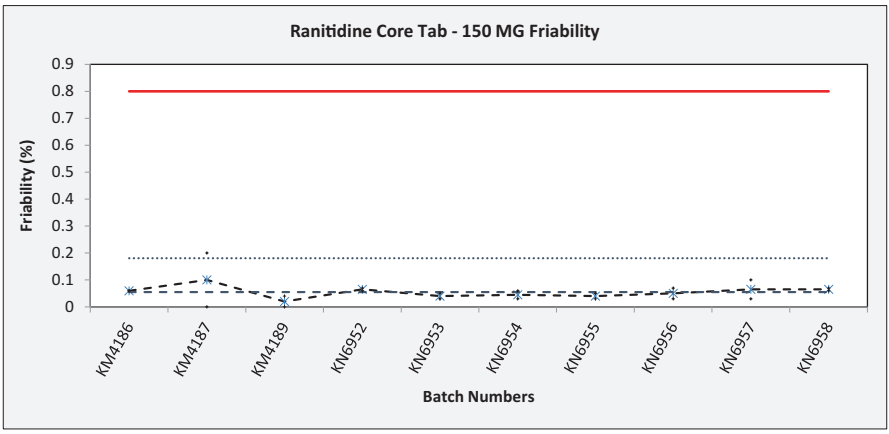


Fig. 5.16 SPC – Friability (NMT 0.8%, after 100 revolutions)

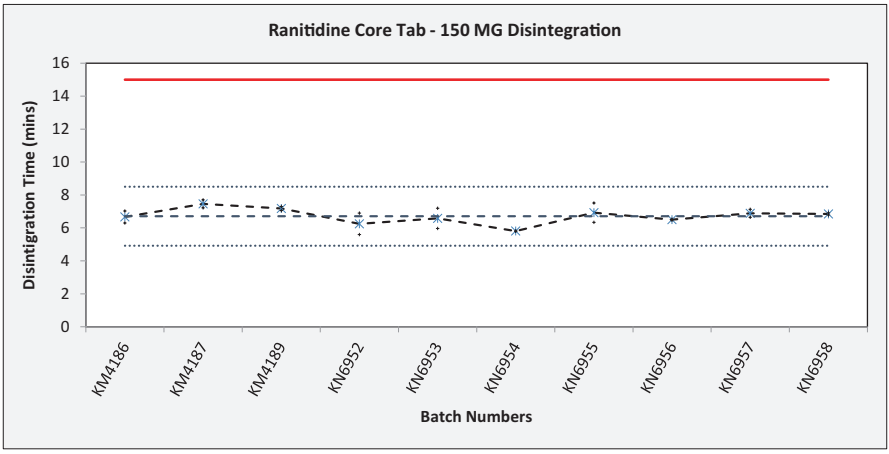


Fig. 5.17 SPC – Disintegration (NMT 15 min without disc)

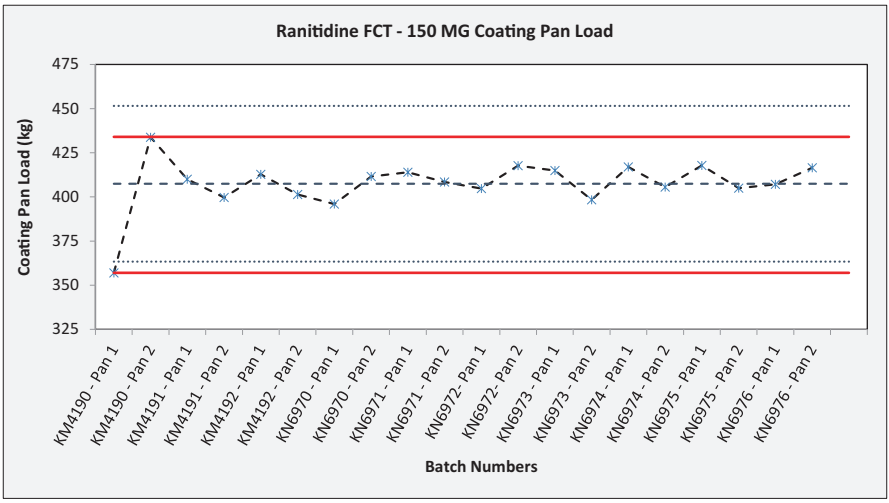


Fig. 5.18 SPC – Pan Load for 66″ pan (Range: 357–434 kg/pan)

Film Coating - Average Weight Gain

				Lower	Upper
USL	14			CI	CI
LSL	9	P_{pk}	1.43	0.93	1.93
Sample Mean	11.81				
StdDev (overall)	0.49				
		Exp. Overall Perform		10 PPM	
Sample N	20				

Fig. 5.19 Process capability and performance – Weight gain (Target: 11.6 mg, Range: 9.3–13.9 mg)

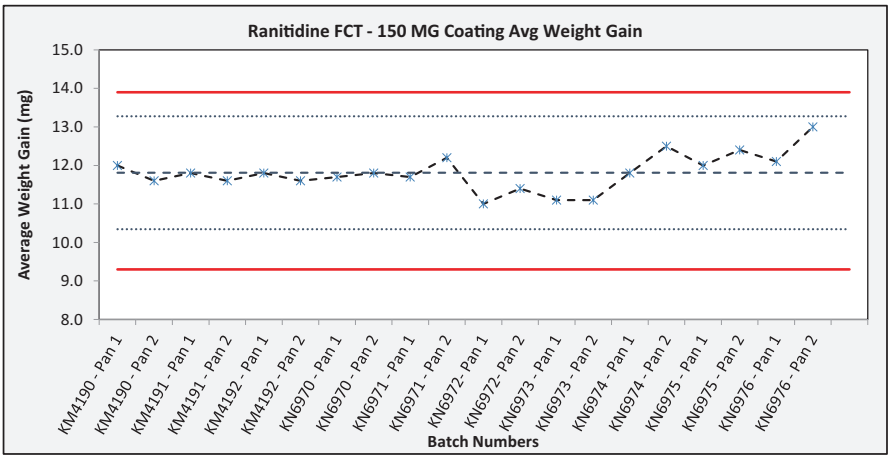


Fig. 5.20 SPC – Weight gain (Target: 11.6 mg, Range: 9.3–13.9 mg)

Film Coating - Average Weight

				Lower	Upper
USL	250			CI	Cl
LSL	232	P_{pk}	2.47	1.63	3.31
Sample Mean	241.0				
StdDev (overall)	1.21				
		Exp. Overall Perform		<1 PPB	
Sample N	20				

Fig. 5.21 Process capability and performance – Average weight (232–250 mg)

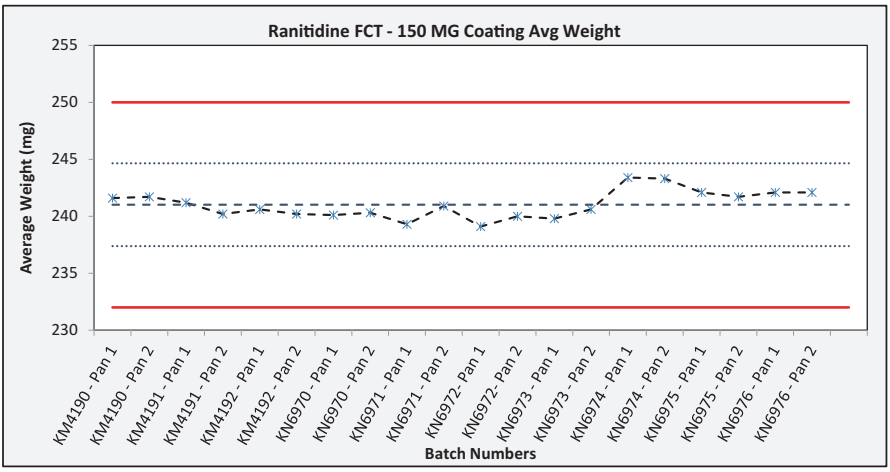


Fig. 5.22 SPC – Average weight (232–250 mg)

Certificate of Analysis - Dissolution

			Stagewise Acceptance Probabilities	
Q	80		P_a	lo 95%
Sample Mean	97.0	S1	99.66	97.57
StdDev (overall)	3.50	S2	>99.99%	>99.99%
Batches	10	S3	>99.99%	>99.99%

Fig. 5.23 Probability of acceptance – Dissolution

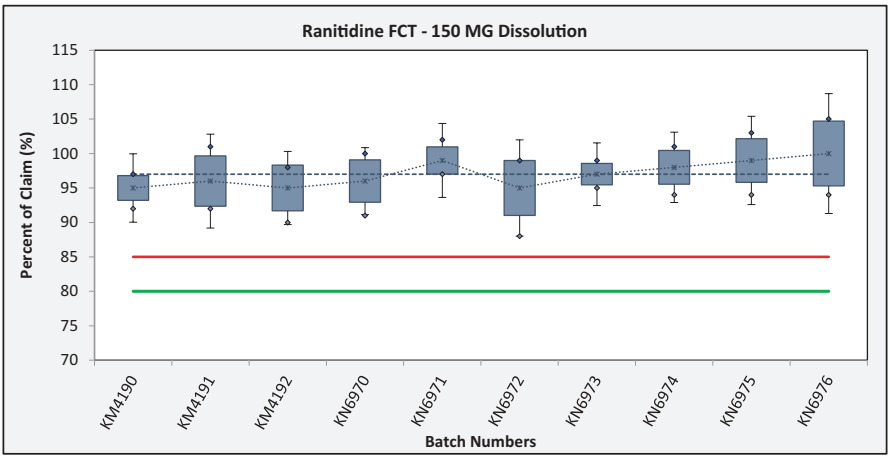


Fig. 5.24 Dissolution ($Q = 80\%$ in 45 min). Note: Green line represents Q and red line represents $Q + 5$.

Certificate of Analysis - Dosage Uniformity

				Lower	Upper
USL	125			CI	CI
LSL	75	P_{pk}	4.77	4.55	5.00
Sample Mean	100.0				
StdDev (overall)	1.74			<1 PPB	
		Exp.	Overall		
Sample N	100	Perform			

Fig. 5.25 Process capability and performance – Dosage uniformity

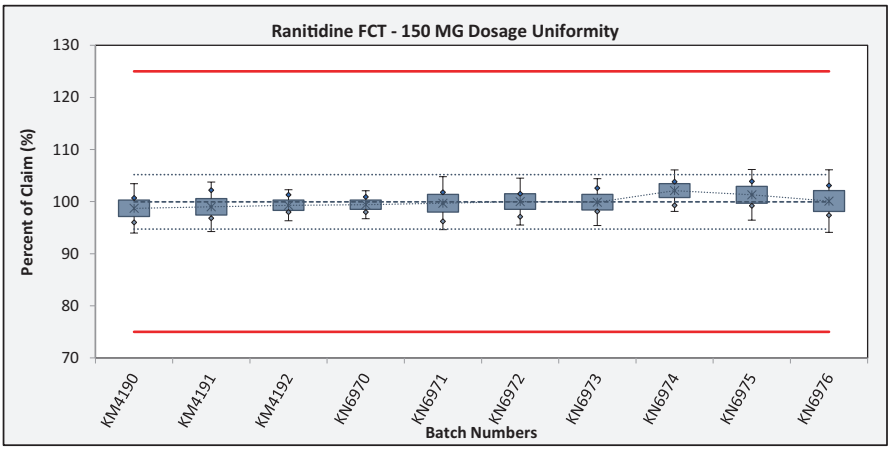


Fig. 5.26 Dosage uniformity (90–100%)

Certificate of Analysis - Assay (%)

				Lower	Upper
USL	105			CI	Cl
LSL	95	P_{pk}	1.57	0.78	2.37
Sample Mean	99.9				
StdDev (overall)	1.05	Exp. Perform	Overall	2 PPM	
Sample N	10				

Fig. 5.27 Process capability and performance – Assay (95–105%)

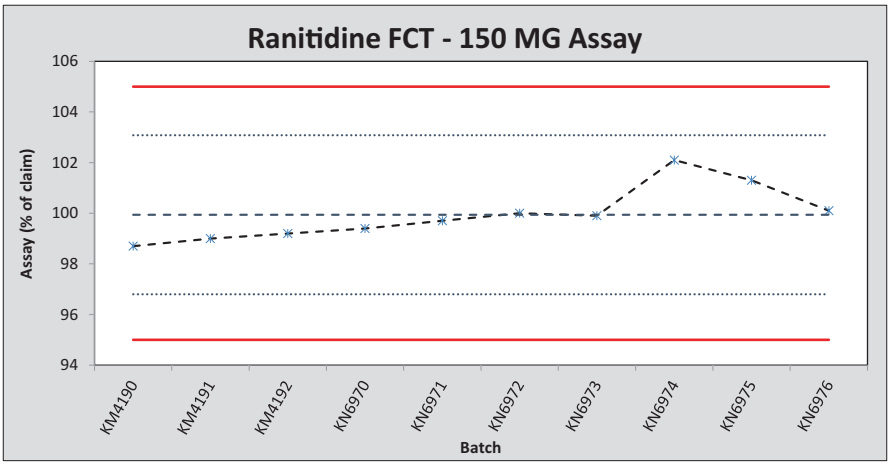


Fig. 5.28 Assay (95–105%)

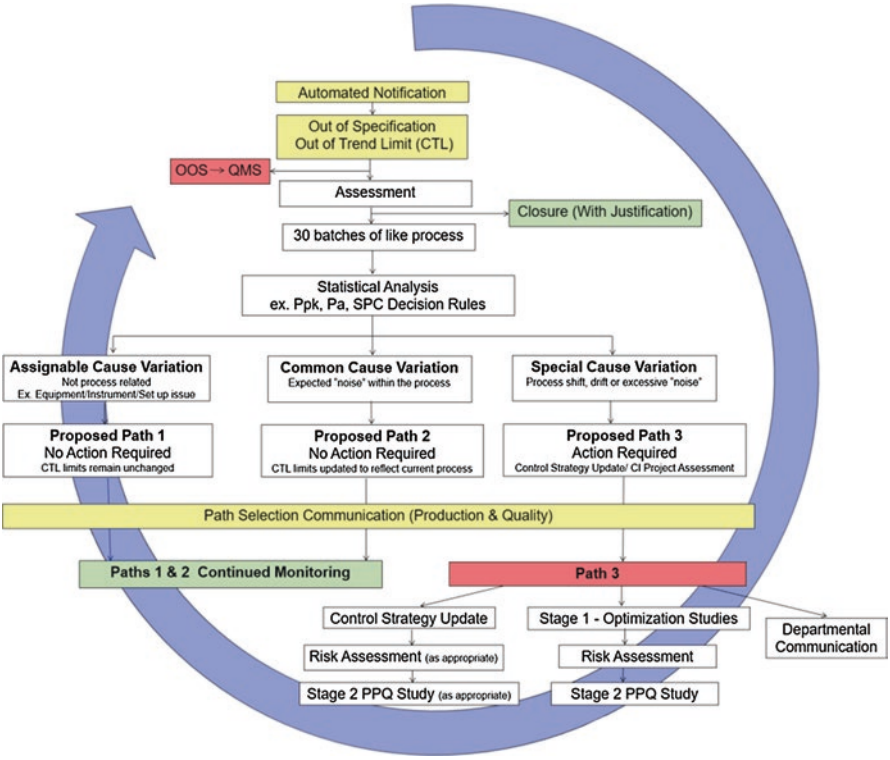


Fig. 5.29 Stage 3B program

References

1. Q8, Q9, & Q10 Questions and Answers — Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider). July 2012.
2. EMA Guideline on process validation for finished products – information and data to be provided in regulatory submissions, 21 Nov 2016.
3. Noskievičová D. Complex control chart interpretation. Int J Eng Bus Manag. 2012.
4. Pazhayattil A. Annual Product Reviews: How to Conduct an Effective Annual Product Quality Review. Pharma Manuf. 2012.
5. *ISPE Discussion* Paper: PV lifecycle implementation for existing ("*Legacy*") *Products.*

Index

A. Pazhayattil et al., *Solid Oral Dose Process Validation, Volume Two*, AAPS Introductions in the Pharmaceutical Sciences,
https://doi.org/10.1007/978-3-030-27484-9