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Guide Series

Product Quality Lifecycle Implementation (PQLI®)
from Concept to Continual Improvement

Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example



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Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example

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This Guide intends to show development of the drug product formulation and process, and also aspects of the drug substance process development. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

This Illustrative Example (IE) gives a practical approach on how to implement Quality by Design (QbD) principles for an oral solid dosage product containing a small molecule. Readers should understand that only one approach is illustrated, whereas in practice companies may choose alternative approaches, depending on the product, process, and business drivers.

The intent of the document is to show development of the drug product formulation and process, and also aspects of the drug substance process development. It provides information on the implications for manufacturing in a QbD environment, and introduces opportunities for continual improvement.

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Table of Contents

1 Introduction 7
1.1 Overview 7
1.2 Objectives 7
1.3 Scope 7
1.4 Benefits 8
1.5 Key Concepts 9
1.6 Guidance Structure 10

2 Drug Product 13
2.1 Introduction 13
2.2 Development of Formulation and Process 14
2.3 Overall Conclusion 89

3 Drug Substance 91
3.1 Introduction 91
3.2 Development of Drug Substance Process 94
3.3 Conclusion 131

4 Control Strategy 133
4.1 Introduction 133
4.2 What Must Be Controlled – CQAs Impacted by the Manufacturing Process 134
4.3 Real-Time Release Testing Summary 160
4.4 Control Strategy Summary 161
4.5 Conclusion 164

5 Implementation in Manufacturing 167
5.1 Introduction 167
5.2 Technology Transfer 168
5.3 Knowledge Management (Information Transfer) 169
5.4 Identifying Gaps in the PQS Using Quality Risk Management 169
5.5 Readying Personnel for Implementation 170
5.6 Implementing Some Elements of the Control Strategy 170
5.7 Process Validation/Qualification and Continuous Process Verification 177
5.8 Batch Release 180
5.9 Conclusion 181

6 Continual Improvement 183
6.1 Introduction 183
6.2 Product Lifecycle and Opportunities for Continual Improvement 185
6.3 Continual Improvement Methodology Examples 186
6.4 Conclusion 196

7 Conclusion 197

Documents
Document Sharing Hub
Full document details: ISPE Guide Series PQLI Part 2 - Product Realization using Quality by Design (QbD) - Illustrative Example 2011

8 Appendix 1 199
8.1 Risk Identification 200
8.2 Risk Analysis 200
8.3 Risk Evaluation 202

9 Appendix 2 – Risk Assessment after Formulation Development and IVIVC Studies Using FMEA 205

10 Appendix 3 – Risk Assessment of PaQLInol Tablet Process Using Failure Mode, Effects, and Criticality Analysis (FMECA) 209

11 Appendix 4 215

12 Appendix 5 – References 219
12.1 References 220
12.2 Further Reading 222

13 Appendix 6 – Glossary 223
13.1 Acronyms 224
13.2 Definitions 225

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1 Introduction

1.1 Overview

This Illustrative Example (IE) gives a practical approach on how to implement Quality by Design (QbD) principles for an oral solid dosage product containing a small molecule. Readers should understand that only one approach is illustrated, whereas in practice companies may choose alternative approaches, depending on the product, process, and business drivers.

ICH terms are used throughout and the name chosen for the product is PaQLInol tablets, which contains 30 mg PaQLInol drug substance.

The intent of the document is to show development of the drug product formulation and process, and also aspects of the drug substance process development. It provides information on the implications for manufacturing in a QbD environment, and introduces opportunities for continual improvement.

Development of drug product formulation and process is written to follow the principles of and exemplify enhanced, science- and risk-based, i.e., Quality by Design (QbD) approaches given in Part 1, Topic 1: Overview of Product Realization.

1.2 Objectives

This Illustrative Example shows the development and introduction into manufacturing of a small molecule formulation and associated manufacturing process, and part of the drug substance synthetic route using enhanced, quality by design approaches as described in ICH Guidelines Q8(R2) (Reference 1, Appendix 5) Pharmaceutical Development, Q9 (Reference 2, Appendix 5) Quality Risk Management, Q10 (Reference 3, Appendix 5) Pharmaceutical Quality System, and Q11 (Reference 4, Appendix 5) Development and Manufacture of Drug Substances.

1.3 Scope

This Guide discusses the following:

- development of a formulation and associated process for a tablet using direct compression
- development of some late stages in the synthesis of a small molecule
- elements of the chosen control strategy derived from enhanced, QbD approaches
- considerations when introducing these processes into manufacturing
- some opportunities for continual improvement

The example illustrated in this Guide concentrates on development of a tablet formulation and process for a stable small molecule, PaQLInol, with biopharmaceutical properties of low solubility and high permeability. The intent is that the reader can focus on the science- and risk-based approach and hence the science is relatively uncomplicated.

This Guide exemplifies technical approaches to product and process development and introduction to manufacturing using the science- and risk-based approach. It does not discuss how the data and conclusions from the work should be summarized in a regulatory submission.

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Application of the risk management and iterative nature of the enhanced, science- and risk-based approach is discussed in detail for PaQLInol tablet formulation and process. The last steps in the synthesis of PaQLInol, which are a Grignard reaction, crystallization, and drying are also discussed. Linkage is explained between drug substance and drug product material attributes and process parameters and drug product critical quality attributes. In relevant cases, design spaces are proposed as well as control strategy elements resulting from the science- and risk-based approach. A section on control strategy summarizes the chosen control strategy elements derived from the enhanced, quality by design approach. This section only discusses some elements of the control strategy, for example, discussion of many of the GMP elements is omitted.

There is a section describing considerations when introducing PaQLInol product and processes into manufacturing and a short discussion on continual improvements that may result from development and technology transfer studies, and from initial introduction to manufacturing.

The examples in this Guide show how product realization (i.e., introduction to the market) using Quality by Design (QbD) could be achieved and be of assistance in meeting Stage 1, Process Design of the FDA Guidance on Process Validation (Reference 5, Appendix 5). Some of the considerations for Stage 2, Process Qualification are briefly discussed; however, this stage is not covered in detail, nor is Stage 3, Continued Process Verification. Insufficient data of production scale manufacture are given to allow discussion in detail of statistical measures of process capability.

Examples are given of the iterative nature of formulation and process development, particularly iteration between risk assessment exercises and subsequent experimental studies. Some examples of risk management tools are given.

For development of the formulation, detail of the risk assessment exercise is given providing examples of risk identification, risk analysis, and risk evaluation. In other cases later in the document, outputs from risk assessment exercises are summarized. Similarly, examples are given of systematically-designed experimental studies using Design of Experiments (DoE). Again, these are examples of types of design and how one study may be related to another and are not definitive approaches or examples.

Both univariate and multi-factorial studies are discussed; however, the IE concentrates on how multi-factorial studies and fundamental science are used in the enhanced, quality by design approach. In reality, companies develop products and processes using a combination of “minimal” and enhanced, quality by design approaches.

Only some parts of formulation and process development are discussed to provide examples of the science- and risk-based approach and introduction to manufacturing. Development and application of some analytical methods is discussed at a high level, for example, dissolution methods and in-line NIR. However, detailed description, development, and validation of analytical methodsare not discussed, but it is recognized they are an important part of ensuring science- and risk-based approaches are developed and implemented

1.4 Benefits

Part 1 of this Guide Series suggests a number of benefits of QbD. This Illustrative Example includes examples of the following benefits:

- Understanding product and process design and relating this to patient requirements has the potential to bring benefits to manufacturing efficiency and process capability.
- Applying a science- and risk-based approach to product and process development and manufacturing enables clearer prioritization of where resources should be used.
- Using supporting tools and techniques such as risk management and DoE enables greater understanding of multi-factorial interactions and hence product and process understanding.

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- The use of ICH terms (such Critical Quality Attributes and Critical Process Parameters and terms applied to risk management) enables a common language and understanding to be gained by all functions.
- A clear understanding of product Critical Quality Attributes enables understanding and development of factors that impact patient safety and efficacy and product quality.
- Real time release testing using predictive algorithms enables potential business benefits to be gained, such as reduced end product testing.
- Continual improvement is an important part of QbD and can lead to improved flexibility during manufacture and enable learning and knowledge to be transferred from development to manufacturing and vice-versa.
- A clear Control Strategy provides the foundation for guidance on what must be controlled during manufacture.
- There are many options for control strategies and companies can choose what is appropriate to meet their business requirements.
- Challenges implementing into manufacturing products and processes developed using the enhanced, QbD approach can be overcome.
- Developing products and processes in line with this Guide should assist in meeting the expectations of Stage 1 of FDA Process Validation Guidance, and be a baseline for progressing to Stages 2 and 3.

1.5 Key Concepts

This Illustrative Example provides many key concepts including the following:

- uses ICH terms throughout to ensure a common language and understanding of terms
- illustrates science- and risk-based approaches to pharmaceutical development and manufacturing for a small molecule example
- illustrates the importance of linking development and manufacturing functions and processes
- shows the importance of quantifying patient requirements and developing drug product Critical Quality Attributes (CQAs) and the importance of understanding the links between drug product and drug substance for ensuring patient safety and efficacy and product quality
- is structured so that the quality target product profile and drug product CQAs are discussed first with the technical exemplification of meeting CQA acceptance criteria following in order, drug product formulation and process development then drug substance process development
- shows the relationships between manufacturing unit processes that impact particular Critical Quality Attributes
- illustrates the concepts using a direct compression oral solid dosage manufacturing process with drug product unit operations of dispensing, blending, lubrication and compression, and drug substance unit operations of a Grignard reaction, crystallization, high shear wet milling and drying
- shows the importance of using Quality Risk Management at all stages both in development and manufacturing
- shows how tools such as risk assessment and design of experiments can be applied iteratively to ensure a high degree of product and process understanding

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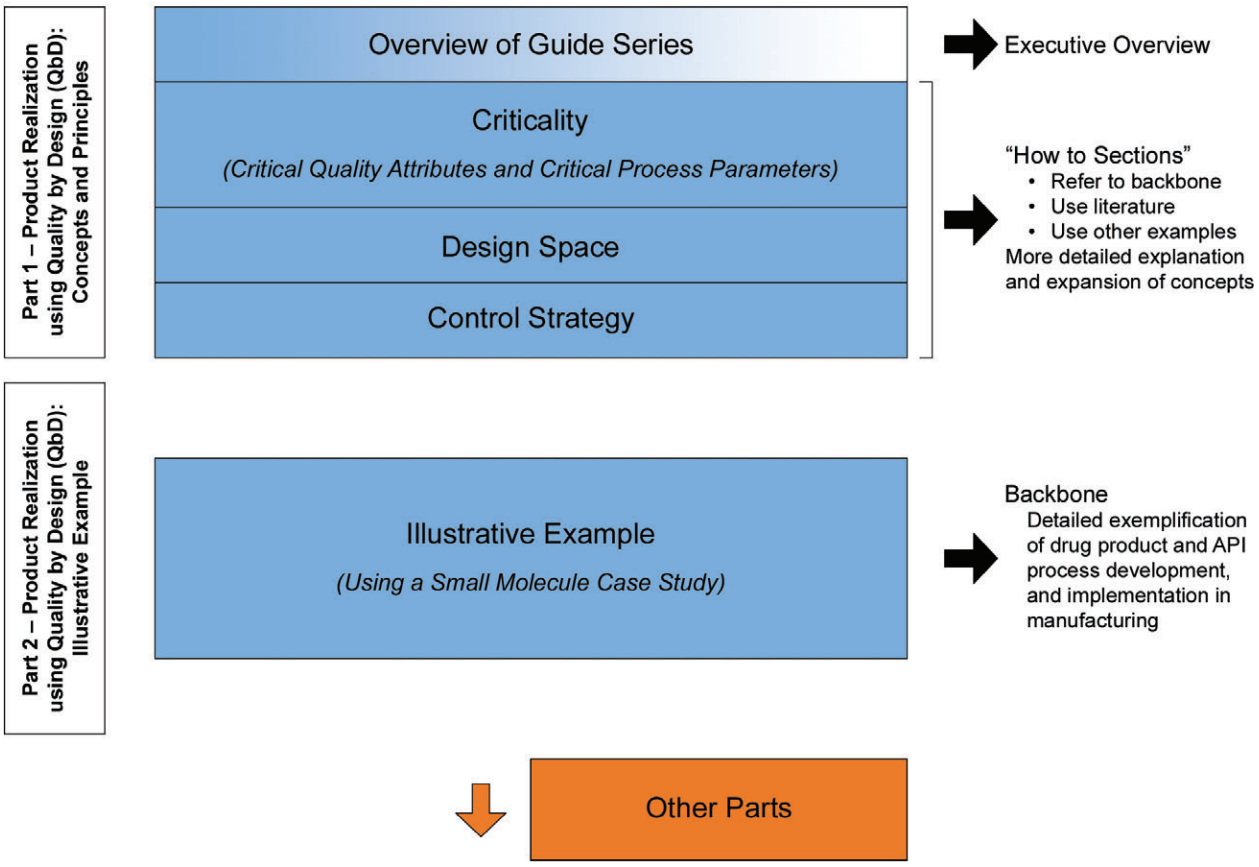
- shows the importance of adopting an iterative approach during development
- shows the need to understand multi-factorial interactions
- shows an example of Real Time Release testing using a predictive algorithm
- Shows examples of how continual improvement can be made during development and manufacturing and the importance of knowledge transfer.
- shows how understanding the technology of unit operations and impact on the processes can lead to improved manufacturing efficiencies
- shows how control strategies are directly linked to the Critical Quality Attributes and that control strategies proposed during development influence equipment controls and manufacturing operations
- shows the need to clearly understand how control strategies are founded on understanding the impact of process parameters and material attributes on drug product Critical Quality Attributes and that these control strategies must be implemented from development through to manufacturing unit operations together with personnel training, process validation, batch release and other factors
- gives examples of control strategies options
- gives examples of control strategies meeting product and GMP requirements and illustrates what needs to be controlled and how this is achieved
- gives examples of tools that can be used for product quality and process monitoring to enable continual improvement
- shows where Process Analytical Technology (PAT) can be used during development and manufacturing to enable improved process understanding and control

1.6 Guidance Structure

The Illustrative Example is Part 2 of the ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement. This series is described in Figure 1.1, which also gives a summary of the relationship between Part 1 and Part 2.

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Figure 1.1: Structure of Guide Series, Product Quality Lifecycle Implementation from Concept to Continual Improvement



The Guide concentrates on a particular example; however, it is recognized that there are other case studies in the public domain.

- A-Mab: A Case Study in Bioprocess Development (Reference 6, Appendix 5)
- Pharmaceutical Development Case Study, "ACE tablets" (Reference 7, Appendix 5)
- Quality Overall Summary, Sakura Tablets (Reference 8, Appendix 5)
- EFPIA Mock P2, Examplain Tablets (Reference 9, Appendix 5)

This Illustrative Example builds on these case studies and makes appropriate references throughout.

The flow of the science- and risk-based approach to development and introduction to manufacturing of this example follows the flow given and discussed in Part 1, Topic I Overview of Product Realization, for example, as presented in Figures 3.1, 3.2, and 3.3 in Part 1, Topic I Overview.

The approach of this Illustrative Example is a simplification of the Conceptual Application of QbD through a product's lifecycle given in Figure 3.1 of the Part 1, Topic I Overview, but it results in giving more detail of the steps of applying QbD.

To assist readers, shaded "boxes" are included in the text. The purpose of the content of the "boxes" is to give background information, assumptions, omissions, references to other examples in the public domain or provide definitions immediately in the text.

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2 Drug Product

2.1 Introduction

The purpose of this section is to give examples of:

- some quality risk management processes applied to development of a formulation and a process
- application of different quality risk management processes
- the iterative nature of formulation and process development
- the link between output from risk assessment exercises and design of experiments
- show how increased understanding leads to reduction of risk
- show how increased understanding leads to development of control strategy options

Owing to limitations of size of the document, detail of some of these steps is given only once or on a few occasions; thus later in the section many of the above steps are summarized, so that a reasonable, but not complete story is given.

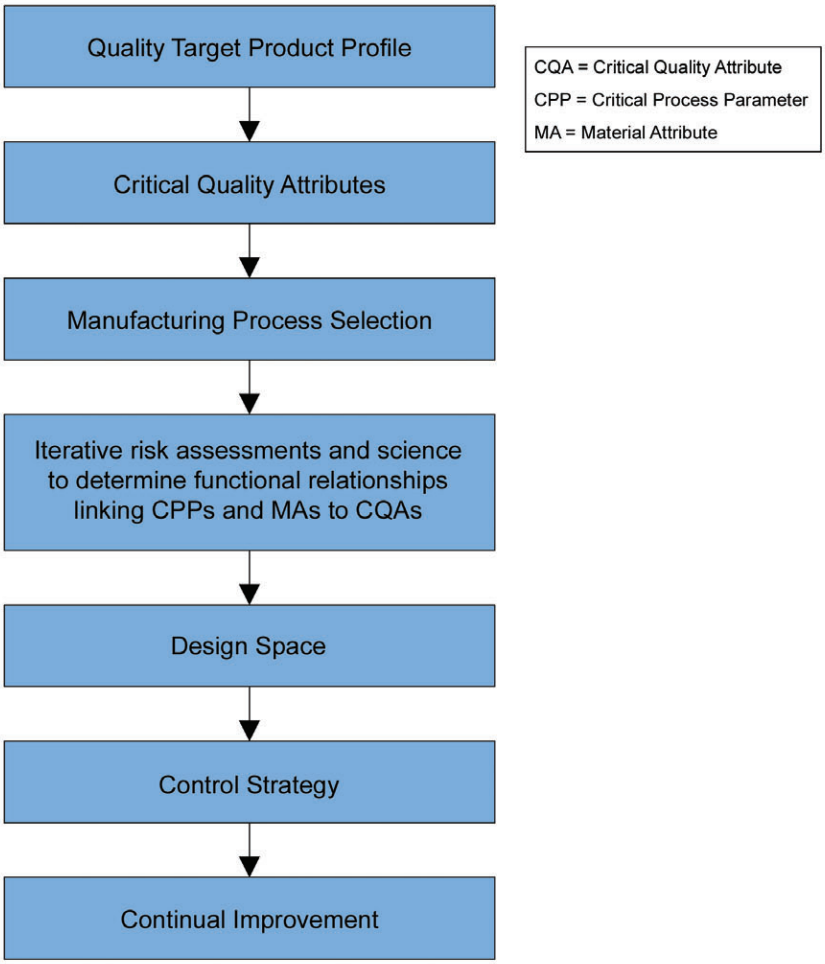
As discussed in Q8(R2) and the Introduction to this Illustrative Example, it is not necessary for companies to develop products and processes using the enhanced, science- and risk-based approach for all studies. It is the choice of the company to decide how it will approach development and what studies to perform. It is the intention of this section to give some examples of science- and risk-based approaches that companies may wish to adapt to their situation.

Development of drug product formulation and process is written to follow the principles of the enhanced, science- and risk-based approach, i.e., Quality by Design (QbD) approach given in Part 1, Topic I Overview.

The formulation and process development flow is shown in Figure 2.1.

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Figure 2.1: Development Flow for PaQLInol Tablet in this Illustrative Example



2.2 Development of Formulation and Process

2.2.1 Defining the Quality Target Product Profile

An initial Quality Target Product Profile (QTPP) is recommended prior to the commencement of Phase 2 clinical studies although it is recognized that not all necessary information may be available at this stage, such as final dose(s). A further iteration of the QTPP should be established prior to the commencement of the development of the proposed commercial dosage form (often after Proof of Concept).

In addition to the QTPP, some companies include in their project scope other business factors that are desired from the project, such as measures to assure security in the supply chain although these are not part of the QTPP since they do not directly impact patient safety and efficacy.

Quality Target Product Profile (QTPP):

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. (ICH Q8(R2))

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When establishing a QTPP, it is recommended that a team comprising pharmaceutical development experts together with production, quality, process engineering, regulatory, clinical, drug safety, and metabolism colleagues discuss the QTPP to ensure that the therapeutic target, clinical usage of the product, and characteristics of the target patient population are understood.

During the development of the product, the QTPP evolves because some information is uncertain in the earlier phases of the project. With PaQLInol, the final dosing regimen and packaging configuration is finalized during clinical Phase 3, the initial QTPP being given in Table 2.1.

Table 2.1: Initial QTPP for PaQLInol Tablets

Therapeutic Indication:	Major Depressive Disorder associated with schizophrenia (final therapeutic indication to be agreed)
Clinical Setting:	Use in home
Route of Administration:	Oral administration by patient
Posology:	20 to 60 mg PaQLInol daily, as a single dose
Pharmaceutical Form:	Round, convex, immediate-release, orange coated tablet of size acceptable to the patient
Container-Closure System:	Calendar pack (28 tablets) to facilitate compliance
Drug Product Quality Criteria:	
Shelf-Life:	Not Less Than (NLT) 2 years (store at 15 to 30°C as US label)
Degradation Products:	Meets criteria of Q3B (Reference 10, Appendix 5).
Bioavailability:	Immediate release; Cmax NMT 4 hours
Uniformity of Dose:	Meets pharmacopoeial criteria
Microbiological Limits:	Meets pharmacopoeial criteria

2.2.2 Initial CQA Selection and Risk Ranking

Determining a list of potential CQAs for a tablet dosage form of a small molecule is relatively straightforward and guidance can be obtained from ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Reference 11, Appendix 5).

Using all the information above as prior knowledge as well as experience from the development team, an initial list of potential CQAs for PaQLInol tablets is derived as given in Table 2.2.

Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (Q8(R2))

Q8(R2) says “CQAs are generally associated with drug substance, excipients, intermediates (in-process materials), and drug product.”

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Table 2.2: Potential Critical Quality Attributes for PaQLInol tablets and their relationship to QTPP

Attribute	Proposed Initial Acceptance Criteria	Relationship to QTPP
Dosage Form Appearance	Round, convex, orange coated tablet	Pharmaceutical Form
Identity	PaQLInol confirmed	Pharmaceutical Form
Assay	95% to 105% of nominal 30 mg dose at time of manufacture	Posology
Impurities Impurity (C) Any other impurity as a degradation product Total	Meet qualified limits NMT 0.5% NMT 0.2% NMT 1.0%	Degradation Products and Container/Closure
Uniformity of Dosage Units (UDU)	Meets pharmacopoeial criteria	Uniformity of Dose
Dissolution	NLT 80% release in 45 minutes, using suitable in-vitro test	Bioavailability
Microbiological Quality	Meets pharmacopoeial criteria	Microbiology
Water Content	To be established both as a limit at time of manufacture and potentially at end of shelf life as related to moisture vapor transmission rate of container/closure	Degradation Products, Microbiology, and Container/ Closure

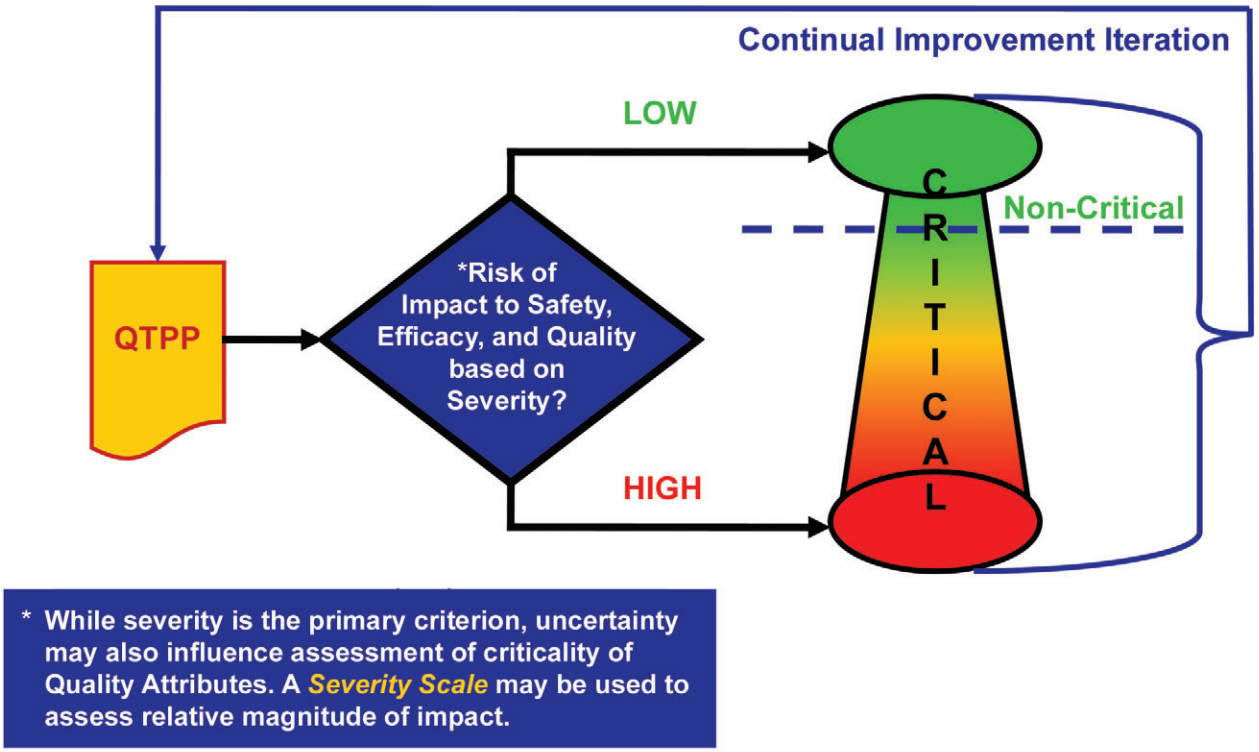
Impurity C is a drug substance process impurity (see Drug Substance Chapter) and from stress studies is a very unlikely potential degradation product. It is included for completeness; however, if shown from subsequent accelerated and long term stability studies it is not a degradation product, it can be removed as a drug product CQA. As a drug substance impurity, it will remain as a drug substance CQA. At this stage of development, fast release for Dissolution can be Q = 80%; however, the time interval requires establishment from development studies. Similarly, the need or not for specific moisture protection in the container closure system requires definition from development stability studies.

A flow that could be used to rank potential CQAs is summarized in the chart given in Figure 2.2 (taken from Part 1, Topic II Criticality) where a suitable risk management tool, such as Preliminary Hazard Analysis, is used in this example to identify potential CQAs and classify them based on a severity rating as varying levels of “criticality.”

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Figure 2.2: CQA Decision Tree Analysis



In order to produce the risk ranking, it is recommended to:

- Use a multi-disciplinary team with appropriate expertise and a trained facilitator.
- Define a methodology (such as Preliminary Hazard Analysis) with defined qualitative or quantitative criteria.
- Record the rationale for the assessments.

The methodology and outcomes are used to support the next steps in development and may provide valuable information for regulatory submissions.

The rating scales used for PaQLInol are shown in Table 2.3 based only on a qualitative severity scale. Because data about the attributes may be limited at this stage of development a qualitative rating system is recommended.

Table 2.3: Severity Scale Used to Rank Potential CQAs

Severity Rating	Description of Impact on Patient if Non-Compliance with CQA
High	Adverse event, lack of efficacy, or unknown impact on a CQA impacting patient safety and efficacy
Medium	Customer complaints (including patient fails to take product) or impact on other quality attribute
Low	No measureable effect on patient

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The output from this risk ranking and filtering quality risk assessment is shown in the Table 2.4. In this example, the "uncertainty" factor in Figure 2.2 is factored in by defaulting the severity ranking to a higher level when there is not a clear link between non-compliance with a CQA and impact on the patient. For example, PaQLInol drug substance is stable and there is probably a high chance that PaQLInol will be stable in PaQLInol tablets. However, in the absence of evidence (data), the impact of "moisture" (water content) on PaQLInol stability is not known (it is uncertain); therefore, the criticality is assigned as "high" rather than "medium." Also Microbiology is rated "high" criticality since severity of microbial contamination even by the oral route may be "high" for example by ingestion and subsequent infection by an objectionable organism such as E Coli.

Table 2.4: Potential Drug Product CQAs with Criticality Ranking

Critical Quality Attribute	Criticality Rating	Rationale and Comments
Dosage Form Appearance	M	Variation in product appearance may lead to non-compliance with treatment regime in this target patient population.
Identity	H	Important for patient safety to have correct active.
Assay	H	Overdose – side effects; under dose – lack of efficacy; however, dose response curve is not precipitous.
Uniformity of Dosage Units	H	Variability in plasma levels may lead to side effects or poor clinical response; however, dose response curve is not precipitous.
Dissolution	H	Poorly soluble (BCS Class 2) drug substance – dissolution characteristics important for bioavailability; however, linkage of dissolution to bioavailability is not known.
Impurities	H	Impurity C as a drug substance process impurity must be limited. Hydrolytic degradation of API in drug product requires further investigation.
Microbiological Quality	H	Presence of an objectionable organism, such as E Coli, could lead to an adverse event.
Water Content	H	Moisture may affect degradation of dosage form performance, i.e., dissolution. API stable; however, API in drug product requires further investigation. Could also impact microbiology.
H = High, M = Medium, L = Low		

Note that stability requirements are identified in the QTPP in terms of desired storage conditions and shelf-life, but stability is not a CQA itself. Stability is reflected in the CQA list as those attributes which could change as a result of stability changes during manufacture and storage, and in relevant risk assessments, the impact of Material Attributes (MAs) and potential CPPs on stability should be assessed. All drug product CQAs must be assured throughout the shelf life of the product. The above list of potential CQAs applies to bulk drug product and it could be useful to consider separately material attributes applicable to design of primary packaging (container/closure), particularly for products which are unstable or where the drug product is highly dependent on choice of primary pack, for example sterile products.

For PaQLInol tablets, the team establishes that the appearance of the tablets is very important because minor defects or variability in color may adversely affect compliance in this target patient population. Appearance of tablets may be less important for tablets used in other indications.

This initial risk assessment helps rank the priority and amount of work required to develop understanding of the impact of variability of material attributes and process parameters on each quality attribute. The higher the criticality ranking of the attribute, the greater the importance given to developing product and process understanding, and this increased importance may or may not lead to more work. For example, the Dissolution CQA warrants higher effort than Appearance.

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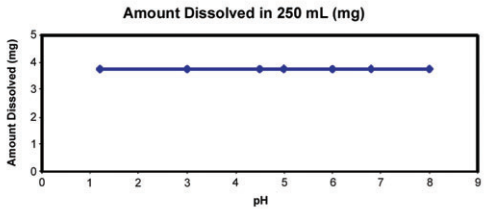
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The next step is to use the information from Table 2.4 together with prior knowledge about the drug substance to identify potential manufacturing options and then formulation components.

2.2.3 Prior Knowledge and Company Strategy

Companies will have different approaches to their product development strategy for determining physicochemical properties of their candidates. In general, the more information that is available, the more straightforward formulation development will be. While final clinical doses may not be known at the start of clinical Phase 3, it is recommended that Phase 3 uses the intended commercial formulation. For facile commercial formulation development, Table 2.5 illustrates the information that would normally be a minimum that is accumulated during earlier clinical phases.

Table 2.5: Physicochemical Properties of PaQLInol Drug Substance

Molecular Weight	450
Chirality	Achiral
Acid/Base pKa	Neutral compound, pKa 6.5
LogD(octanol)	2.6
Solubility: Water Fasted State Simulated Intestinal Fluid (FaSSIF) pH Profile	 0.015 mg/ml at 20°C 0.020 mg/ml at 20°C 
Solid State	Monohydrate as a crystalline solid with single polymorph
Hygroscopicity	Monohydrate is stable at 25°C at humidities down to 5%RH and does not pick up water at humidities up to 85%RH. There is further discussion in Section 3.5 in the Drug Substance Chapter.
Compaction Properties: Yield Pressure (slow) Yield Pressure (fast) Strain Rate Sensitivity	 50 MPa 80 MPa 38% Moderately ductile
Flow Properties	Good to excellent dependent upon particle size
Bulk Density (unmilled)	Untapped 0.40 g/cm3 Tapped (50 taps) 0.48 g/cm3
Wettability	Good by Dynamic Contact Angle (DCA) Measurements
Stability	Drug substance is stable (no degradation products detected) from results from stress, accelerated and long term studies on batches of drug substance used in toxicology and clinical studies manufactured using the same route of synthesis as that proposed for production. Stress studies include ICH light stability studies, and studies of drug substance powder at elevated temperatures stored in the dark. Methods are stability indicating as determined from forced degradation and other stress studies of solutions/suspensions of drug substance. Phase 1 suspension and Phase 2 tablet formulations are also stable over the period of the clinical programs.

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The pharmacokinetic properties of the drug substance are given in Table 2.6.

Table 2.6: Pharmacokinetic Properties of PaQLInol

Results from Phase 1 studies in normal subjects using a suspension of drug substance in water	T_{max} 1.3 hours $T_{½}$ 24 hours Linear pharmacokinetics from doses 0 to 80 mg
Results from Phase 2 studies in patients using prototype tablet	T_{max} 1.5 hours $T_{½}$ 24 hours Linear pharmacokinetics from doses 5 to 80 mg Relative bioavailability of PaQLInol in tablet is 100% compared to suspension

Other valuable information that is recommended to assist in formulation design and the understanding of linkages of MAs and CPPs to CQAs and clinical performance is:

- solubility in simulated gastric and intestinal fluids
- stability in simulated gastric and intestinal fluids
- impact of surfactants on solubility and dissolution
    - (may have utility if a food effect is seen)
- susceptibility to efflux
    - (may be valuable in case efflux inhibitor should be added to formulation)
- permeability, usually measured by Caco-2 cell

PaQLInol drug substance is shown to be stable in gastrointestinal fluid, displays high permeability when investigated using Caco-2 cell monolayers, and is not susceptible to efflux by P-glycoprotein (P-gp). Solubility of PaQLInol is low (0.015 mg/ml, solubility should be greater than 0.04 mg/ml for PaQLInol to be assigned a high solubility drug for a dose of 10 mg) and constant across the physiological pH range due to the lipophilic nature of the molecule. As such, PaQLInol can be classified as Class 2 (low solubility, high permeability) based on the Biopharmaceutics Classification System (BCS) (Reference 12, Appendix 5) assuming a dose of greater than 10 mg.

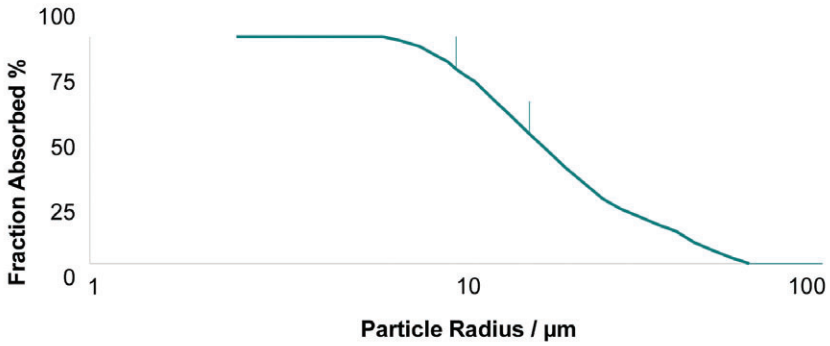
PaQLInol appears to exhibit linear single-dose pharmacokinetics across the investigated dose range 0 to 80 mg in both healthy volunteers and patients. The apparent mean clearance and volume of distribution are approximately 2.3 l/h and 80 l, respectively. The mean elimination half-life is 24 hr, and median T_{max} of 1.3 to 1.5 h.

As PaQLInol is a BCS Class 2 compound, prior literature knowledge regarding the properties of this class means there is potential for variability in formulation and processing factors to impact the rate of dissolution in vivo. In silico modeling (Reference 13, Appendix 5) of the impact of drug substance particle size for Class 2 compounds shows the fraction absorbed decreases as particle size increases, giving further evidence that this could be a risk, see Figure 2.3.

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Figure 2.3: In silico Modeling of Fraction Absorbed versus Drug Substance Particle Size



In summary, there is a good basis of physicochemical and pharmacokinetic information relating to PaQLInol to progress development using the enhanced QbD approach.

2.2.4 Product and Manufacturing Process Selection

Reference to the QTPP indicates that a tablet is required so alternative solid dosage forms can be discounted without need for exploratory studies. Patients are familiar with tablet dosage forms for the proposed indication; however, there is a business need to differentiate with other products using, for example, shape, intagliation, or film coat color, and this aids patient compliance. Film coated tablets generally are considered easier to swallow and are less prone to tampering.

Since the company has several other products on the market using direct compression, there is significant expertise both in manufacturing and development relevant to development of PaQLInol tablets, 30 mg, which gives opportunities for application of prior knowledge.

Consideration could be given using risk management to selection of the manufacturing process between the three most common options, direct compression, dry granulation, and wet granulation using a high shear mixer. In some circumstances, it may be necessary to perform some studies to help select a suitable process; however, prior company knowledge and literature (Reference 14, Appendix 5) could be used to produce Table 2.7 as an example to compare processes.

Table 2.7: Comparison of Potential Tableting Processes

Property	Risk to Direct Compression	Risk to Dry Granulation	Risk to Wet Granulation
Stability of Tablet	Low	Low	Low
Flow of Granule	Low	Low	Low
Uniformity of Content of Tablet	Medium	Low to Medium	Low to Medium
Bulk Density of PaQLInol	Low	Low	Low
Compaction Properties of PaQLInol	Low to Medium	Low to Medium	Low
In vitro Dissolution from Tablet	Medium (Unknown)	Medium (Unknown)	Medium (Unknown)
Tablet Size/Drug Load	Medium (Unknown)	Low to Medium	Low
Company Expertise	Low	Low	Medium
Company Equipment	Low	Low	High

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Review of Table 2.7 suggests that wet granulation could be the lowest risk; however, in this case and for this company, there is less expertise and very little wet granulation equipment, which, therefore increases risk and cost. Some preliminary relatively small studies are desirable to give some assurance that larger studies are justified to optimize the "dry" process. Due to the good flow and low dose of PaQLInol tablets, direct compression has similar risk to dry granulation with one less unit operation; therefore, this process is chosen to progress.

When the proposed process has been selected, a risk management team (for example, that which evaluated criticality of CQAs) could review the proposed process with respect to formulation composition and unit operations to estimate risk to CQAs from the product and process. A cause and effect discussion within the team could lead to a matrix as given in Table 2.8. In this case, the severity scores are taken from Table 8.2 in Appendix 1, which is repeated below for ease of comparison.

Table 8.2 (from Appendix 1): Severity Scores

Severity	Score	Description of Impact on Patient if Failure to Meet CQA Acceptance Criteria
Minor	1	No impact on patient.
Major	2	Some impact on patient, but reversible.
Critical	3	Impact on patient, but not life threatening.
Catastrophic	4	High impact on patient which is irreversible and potentially life threatening.

Table 2.8: Cause and Effect Matrix for Impact of Product and Process on Proposed CQAs

Unit Ops/CQAs (Severity)	Formulation Composition	Blending	Lubrication	Compression	Coating
Appearance (3)	H	L	M	M	M
Identity (4)	L	L	L	L	L
Assay (4)	M	M	L	L	L
UDU (4)	H	H	M	M	L
Dissolution (4)	H	L	H	H	L
Impurities (4)	H	L	L	L	L
Microbiology (3)	M	L	L	L	L
Water Content (4)	M	L	L	L	L
Severity values in parenthesis. H = High Risk, M = Medium Risk, L = Low Risk					

This matrix gives an overview of where development effort should be placed. For this dry manufacturing process, initial efforts should be placed on establishing a formulation composition. Development of a formulation should have goals of optimizing and balancing the impact of the formulation on the highest risk CQAs of Appearance, UDU, Dissolution, and Impurities. Depending on excipients selected, there also could be significant reduction of impact on Microbiology and Water Content. For this company, there is significant prior knowledge that coating will have low impact of Microbiology and Water Content.

2.2.5 Formulation and Package Selection for Direct Compression

In this section, the iterative nature of a systematic approach to development of a tablet core formulation is described using a formal risk management process, Preliminary Hazard Analysis (PHA) (Reference 15, Appendix 5) allowing comparison of risk evaluations at the end of formulation development with that at the beginning.

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At the very end of the tablet core formulation development section, risk assessment is performed using Failure Mode and Effect Analysis (FMEA) to give some comparison with PHA.

The Formulation and Process Development Section has been written to consider largely quality-dependent variables. These sections also could have been written to consider other project and business factors as dependent variables such as yield, cost, impact on environment, process safety, process robustness, and total process time. Similarly, the same risk management tools could be used to compare and decide for the project and business the relative importance between dependent variables. Please refer to Part 1, Topic I Overview of Product Realization for further discussion.

Discussion of development of the formulation and process has focused on the tablet core. The coating formulation and process is considered platform technology in this case, for which there is great prior knowledge and expertise.

Selection of Excipients

Many textbooks have been written on pre-formulation studies and these will not be addressed here.

In this instance, the desired commercial dosage form is to be a tablet. From pre-formulation work, compaction studies have indicated that PaQLInol drug substance has ductile properties with a low yield pressure and relatively high strain rate sensitivity, indicating that compression to form tablets with high quality (e.g., absence of “picking” and “capping”) may be difficult on a high speed press.

> Materials with high strain rate sensitivity exhibit time-dependent plastic deformation when compressed. As the tablet press speed increases, there is less time for the material to deform and form strong bonds with other particles in the tablet, but this problem can be reduced by including more brittle materials in the formulation where the hardness of tablets is much less sensitive to increases in tablet press speed.

Considerations influencing choice of excipients should include:

- Functional properties – flow, compressibility, solubility, etc.
- Quality – compliance with relevant pharmacopoeias
- Sourcing – familiarity with suppliers
- Utility – are they already in use within the company
- Multiple supply options

A series of soluble and insoluble fillers suitable for use in direct compression formulations is screened for chemical compatibility with the drug substance. The first materials studied should be those which are used in other products; therefore, there is good knowledge of suppliers. Given the conflicting properties of the drug substance, as described above, a dual filler system is proposed as this would increase the likelihood of achieving the right balance of brittle and plastic deformation properties, and solubility of the excipients. Given the good flow and “wettability” properties of PaQLInol, it is not considered in this instance that a flow agent such as talc and a surfactant are required.

An excipient compatibility study showed the following excipients are compatible with PaQLInol:

- Fillers:
  - Dicalcium Phosphate (dihydrate) – brittle deformation
  - Mannitol DC (direct compression) grade – plastic

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- Lactose DC grade – plastic
- Microcrystalline Cellulose – plastic

• Disintegrants:

- Sodium Starch Glycollate
- Crospovidone

• Lubricants:

- Magnesium Stearate (MgSt)
- Sodium Stearyl Fumarate

Only lactose shows some minor evidence of formation of degradation products. Thus, any of these excipients could be taken forward. To reduce risk in the first series of manufacturing process studies, lactose is not included and would only be considered if other combinations of fillers are not found suitable.

The fundamental properties (Reference 16, Appendix 5) of the components to be studied in the formulation selection with respect to their impact on the key identified priority risks of dissolution and compression characteristics can be found in Table 2.9 and this information is factored into risk assessment discussions and into design of subsequent experiments.

Table 2.9: Properties of Excipients Relevant to Formulation Selection for a Direct Compression Tablet

Material	Solubility (in Water)	Impact on Compression	Typical Ranges for Immediate Release Tablets
Mannitol	1 in 5.5	Lower hardness values/compression force compared to MCC and DCP. More sensitive to increase in press speed.	10 to 90%
Microcrystalline Cellulose (MCC)	Practically Insoluble in water	Higher hardness values/compression force compared to mannitol. More sensitive than DCP, but less sensitive than mannitol with respect to press speed.	20 to 90%
Dicalcium Phosphate (Dihydrate) (DCP)	Practically Insoluble	Brittle, so therefore needs approximately 1% lubricant. Less sensitive to press speed.	10 to 80%
Sodium Starch Glycolate (SSG)	Practically Insoluble	Increase in compaction force does not correlate to increase in disintegration. Disintegrant action not impacted by lubricant. Works well with insoluble fillers.	2 to 8%, optimal 4%
Crospovidone (CP)	Insoluble	NA	2 to 5%
Magnesium Stearate (MgSt)	Practically Insoluble	Increase in concentration decreases tablet hardness.	0.25 to 5.0%
Sodium Stearyl Fumarate (Sod St Fum)	Practically Insoluble	Increase in concentration decreases tablet hardness.	0.5 to 2.0%

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In light of these properties and the direct compression process evaluated in initial studies, the following aspects should be considered:

- Low solubility of the drug substance typically requires soluble fillers, but these tend to have lower yield pressure and higher strain rate sensitivity.
- Low yield pressure of the drug substance would require brittle inorganic fillers to assure good compression properties of the product but these are insoluble.
- Poor properties of the drug substance could be "diluted out" with excess filler, but this would impact on the size of the dosage form.
- Given the low solubility of the drug substance, the use of a hydrophobic lubricant could further impact on the performance of the product and so the amount of lubricant and the duration of the lubrication step would need to be assessed.
- Excessive compaction force could produce tablets of low porosity and thereby limit the ingress of water and the subsequent disintegration and dissolution steps.

While multi-factorial experiments are necessary if a design space is to be proposed, univariate studies are often valuable to:

- Screen variables to confirm feasibility of proposed manufacturing process.
- Determine appropriateness of initial formulation(s).
- Establish potential experimental ranges for subsequent DoEs.

For PaQLInol, these preliminary studies (not discussed further here) indicate that a direct compression process can be developed to produce a tablet with good compression, *in vitro* dissolution properties, and of a suitable size for patients. However, the formula and process require optimization.

The manufacturing process selected for formula optimization for the drug product is summarized below:

- Dispense
- Blend
- Lubricate
- Compress
- Coat

Some important considerations are the relative solubility of the excipients, appropriate levels for effective performance, mechanical and physical properties with knowledge of their interdependencies for optimal performance. For example, increased lubrication levels are required to prevent tablet sticking and edge damage due to the inclusion of dicalcium phosphate, which is necessary to balance the elastic properties of the drug substance.

The information gathered in Table 2.9 guides the risk assessment process, subsequent selection of the levels of excipient to be studied in the DoE and helps interpret the data derived from the dependent responses.

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In addition to the information in Table 2.9, it is important to have an appreciation of the factors that affect the dependent variables, that is the Critical Quality Attributes (CQAs) of PaQLInol tablets or surrogate measures of these CQAs. The theoretical cause and effect relationships between the dependent variables with respect to the potential DoE inputs can be found in Table 2.10. As with information in Table 2.9, the information summarized in Table 2.10 acts as prior knowledge in a risk assessment exercise as well as assisting in design of resulting experiments.

Table 2.10: Theoretical Cause and Effect Relationships for Dependent Variables for Measuring Success of Formulation Selection (Relevant to Inputs)

Dependent Variable	Positive Response		Negative Response	
	Primary Cause	Secondary Cause	Primary Cause	Secondary Cause
Uniformity of Dosage Units (UDU)	Narrow particle size distribution, free flowing spherical particles	Good flow, meeting acceptance criteria	Wide particle size distribution, particle shape, cohesion, moisture content	Poor flow/ segregation/ agglomeration
Dissolution	Soluble filler, correct level of lubricant and disintegrant, appropriate tablet hardness/porosity	Meets acceptance criteria	Insoluble fillers, too much lubricant, too little disintegrant, hard tablets	Fails to meet acceptance criteria
Flow	Narrow particle size distribution, free flowing	Good compression speed, good tablet weight control, meets UDU	Wide particle size distribution, particle shape, cohesion	Poor yield, poor weight control, low compression speed, in worst case, unacceptable levels for these factors
Appearance	Appropriate tablet hardness and friability for handling and coating, appropriate mechanical properties and lubrication for particle bonding, good flow, bonding of particles due to balance of brittle and elastic properties, appropriate particle size/shape and moisture content, target strain rate sensitivity	Absence of picking, sticking and capping, smooth surface, appropriate lubrication and ejection force, meets friability and hardness acceptance criteria	Soft tablets due to non-optimal fillers/or ratios, non-optimal lubrication level, increase in dwell time needed to form bonds	Evidence of picking, sticking, and capping, and a rough pitted surface

Table 2.10 shows that there are multiple factors to be considered when planning DoEs and these include CQAs and business factors, such as press speed.

An initial risk management exercise is required to assist with formulation development and this uses as input prior knowledge of the drug substance (e.g., Tables 2.5 and 2.6), potential excipients (Table 2.9), and the direct compression process (Table 2.10).

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Initial Quality Risk Management for Formulation Development

The following Section and Appendix 1 give an example of the detail of a risk assessment exercise following the steps given in ICH Quality Risk Management Q9 (Reference 2, Appendix 5) using one tool, Preliminary Hazard Analysis (PHA) (Reference 15, Appendix 5). There are other tools and approaches that could be used. An overview of the risk management process is given in the text and more detail relating to the scoring system is given in the Appendix.

Risk priority numbers (scores) are derived as examples based on experience; however, other teams may assign slightly different scores based on their experience. A key feature of these scoring systems is that they are most useful when scores are compared relatively to show differences and scales of differences between factors. Absolute values are less useful, and if different scoring systems are used, it is not sensible realistically to compare scores; however, relative differences between factors may still be applicable.

It is recommended that a team of subject matter experts in formulation and process development, and an expert and facilitator in quality risk management conducts a risk assessment exercise to assess the available prior knowledge. Deciding the participants in a risk management team is important. Experience from other industries suggests that presence of multidisciplinary expertise is highly desirable.

The team identifies potential hazards, analyzes, and evaluates the information using questions such as:

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?

As summarized in ICH Q9, Quality Risk Management (Reference 2, Appendix 5) and always with the end user in mind.

For a drug substance with similar properties having, however, some potential for instability, and a similar manufacturing process, a description of the initial risk assessment process is given in Section 3.2.P.2.2 of Sakura Mock QOS (Reference 8, Appendix 5).

A similar exercise was used in the ACE case study and a summary of the output for formulation development is given in Table 5, page 16 (Reference 7, Appendix 5).

The following sections illustrative details of an analogous iterative, science- and risk-based approach as applied to PaQLInol tablets cores. For this first risk assessment example, the steps are described in some detail in Appendix 1, which are not repeated for other risk management processes later in this document.

In Appendix 1, part of a relatively formal Preliminary Hazards Analysis risk process is summarized. This tool is useful in the early stages of development when accurate quantitative estimates of risk parameters, such as probability and detectability, are hard to make owing to absence of significant experimental data on the proposed formulation and process. The tool consists of:

1. the identification of the possibilities that the risk event happens
2. the qualitative evaluation of the extent of possible injury or damage to health that could result
3. a relative ranking of the hazard using a combination of severity and likelihood of occurrence
4. the identification of possible remedial measures

The first step in the process is risk identification.

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Risk Identification

Using prior knowledge summarized in the above sections for this case, this risk step addresses the question "What might go wrong?" and naturally identifies possible consequences.

Some specific questions to ask for this product are:

- Drug Substance:
  - How will the Particle Size Distribution (PSD) impact *in vivo* performance?
  - How will the particle size and morphology affect the flow?
- Excipients:
  - What excipients should be chosen and at what level?
  - How will insoluble inorganic excipients impact dissolution?
  - How will insoluble organic excipients impact compression (appearance and dosage form)?
  - How will hydrophobic excipients (e.g., lubricant) impact dissolution?
  - How will excipient variability impact on product quality (specifically the impact of magnesium stearate particle size/surface area)?
- Process:
  - How will moisture impact the product during processing?
  - How will the different processing steps such as blending, lubrication, compression, and coating impact the CQAs?

In this first hazard identification process, it is important to consider the scope of the exercise; for example, are only the hazards arising from formulation to be considered or are all possible factors including formulation components, processing variables, and eventual handling hazards in routine manufacture to be included? Definition of this scope helps decide who should be in the risk assessment team.

In this exercise, formulation factors are considered in the first risk identification exercise and hence the questions can be more focused on formulation design, such as what and how much ingredients/excipients to incorporate:

- With brittle compression characteristics?
- With plastic compression characteristics?
- Which lubricant?
- What disintegrant?
- Is a flow agent (glidant) required?
- Is a surfactant required to assist with dissolution?
- What are the highest risk process steps or variables when developing a direct compression formulation?

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Prior knowledge can answer some of these questions, such as a flow agent is probably not required due to the inherent good flow of the drug substance and compression excipients suitable for direct compression, and a surfactant is also probably not required due to the inherent good wetability of PaQLInol and excipients.

Ishikawa diagrams can be used to identify potential cause and effect linkages as suggested in Appendix 2 of ICH Q8(R2) (Reference 1, Appendix 5) and an example of their use is given later in this Illustrative Example for developing the direct compression process.

A hazard list is then generated of the formulation factors that could impact potential CQAs based on prior knowledge from literature, company experience, and initial tableting screening studies. The hazard list for development of PaQLInol tablet for formulation factors could be:

- level of active ingredient, i.e., size of tablet, which according to the QTPP has to be a size acceptable to a patient, for example a round tablet no larger than 7 mm
- choice and level of excipients
- particle size of PaQLInol and magnesium stearate
- tablet press speed, since this is judged the most significant process variable with potential to impact on formation of a good tablet compact, i.e., interact with selection and amounts of excipients chosen for the formulation

Hazards are listed probably in some form of chart – see Appendix 1, Table 8.1.

Risk Analysis

Risks associated with the identified hazards are considered to be inability to meet CQAs and this risk could be estimated using scores for severity of impact on the patient, and probability of occurrence of such an event of non-compliance using the knowledge of the risk management team.

In this case, scores are estimated by the team using definitions of severity and probability as given in the charts 8.2 and 8.3 respectively in Appendix 1 as examples to produce a chart such 8.4. Please note that the severity 4 point scale in this exercise uses as input estimates of severity of impact on the patient of non-compliance with a CQA acceptance criterion; therefore, severity scores in Table 8.4 are different from those in Table 2.3 used in the initial CQA priority ranking exercise.

Alternative scoring systems could be used or developed by the team.

Risk Evaluation

Risk evaluation involves placing the scores in perspective to give a summary of the overall risks based on formulation, and a summary chart is produced as given in Table 2.11 for levels of PaQLInol and mannitol. Table 2.11 is a summary matrix of Table 8.6 in the Appendix with the rationale for the scores and colors being given in Table 8.5 in the Appendix. CQAs are selected as those appropriate for an uncoated tablet which is suitable for coating and meet the CQA acceptance criteria given in Table 2.2. At this early stage of risk assessment for development of tablet cores, Appearance, Friability, and Hardness are treated as separate CQAs; however, later in the manufacturing process development section these CQAs are consolidated and listed under Appearance in risk assessment tables (e.g., Tables 2.19 and 2.24). Identity CQA is low risk from Table 2.8, and Assay is not included since it is lower risk and can be estimated from UDU values.

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Table 2.11: Summary of Risk Evaluation Using PHA for Levels of 2 Independent Variables, PaQLInol and Mannitol

CQA (Severity Rating)/ Hazard	App (3)	Impurities (4)	Water (4)	UDU (4)	Disso (4)	Micro (3)	Fria (3)	Hard (3)
Level of PaQLInol	High chance (4) of failure	Low chance (2) of failure	Extremely low (1) chance of failure	Medium chance (3) of failure	Medium chance (3) of failure	Extremely low (1) chance of failure	Medium chance (3) of failure	Medium chance (3) of failure
Level of Mannitol	High chance (4) of failure	Extremely low (1) chance of failure	Extremely low (1) chance of failure	Medium chance (3) of failure	Medium chance (3) of failure	Extremely low (1) chance of failure	Medium chance (3) of failure	Medium chance (3) of failure

Table 2.11 is the outcome of a formal risk management process applied to levels of PaQLInol and mannitol with individual risk assessment steps given in more detail in Appendix 1. The risk assessment process is completed in Table 2.12 to give the risk evaluation using the list of all potential hazards relating to formulation development given in Table 8.1. This is summarized in the columns of Table 2.12 with detail of individual steps not being given in the Appendix. Independent variables in this exercise include both levels and material attributes of active ingredient and magnesium stearate, and one process parameter, press speed. As noted above, press speed is judged the most significant process variable to interact with level and amount of excipients to form a good tablet compact.

Table 2.12: Summary of Risk Evaluation of Remaining Independent Variables

CQA (Severity Rating)/ Hazard	App (3)	Impurities (4)	Water (4)	UDU (4)	Disso (4)	Micro (3)	Fria (3)	Hard (3)
Level of DCP	H	M	M	H	H	L	H	H
Level of MCC	H	M	M	H	H	L	H	H
Level of SSG	M	M	M	M	H	L	M	M
Level of CP	M	M	M	M	H	L	M	M
Level of MgSt	H	M	M	M	H	L	H	H
Level of Sod St Fum	H	M	M	M	H	L	H	H
PaQLInol Particle Size	M	M	M	H	H	L	M	M
MgSt Particle Size	M	M	M	M	H	L	M	M
Press Speed	H	M	M	H	M	L	H	H

The total risk profile for the first phase of formulation design is the total list of hazards given in Tables 2.11 and 2.12.

The team including formulation and statistical expertise discusses the output from this risk evaluation step and has options regarding what factors to include in a DoE study, and what type of study to design. For example, this risk assessment process has produced “Medium Risk” for factors which have high severity although low chance of failure and an efficient first DoE study could be designed initially to study only “High Risk” factors with a high chance of occurrence. “High Risk” factors with low chance of occurrence and “Medium Risk” factors would be evaluated in subsequent, probably smaller, studies, which could include small 4 to 10 batch DoEs or simple univariate experimentation.

From this matrix, CQAs to measure as responses in a first DoE are Appearance of tablet, tablet uniformity, or surrogates for UDU such as blend uniformity, powder flow or shear, and dissolution. At this early stage, it is desirable to evaluate as many compatible excipients with the relevant properties as possible since choice of qualitative formula is extremely important as the basis for delivery of the drug substance, and as the foundation for a robust process.

For further similar approaches, please refer to ACE Section 3.4 (Reference 7, Appendix 5).

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Conclusion

From the risk assessment, a DoE study or studies is required to evaluate as independent variables:

- size of tablet up to a pre-defined size (level of PaQLInol is set at 30 mg)
- level of brittle filler, dicalcium phosphate dihydrate (DCP)
- level of plastic filler or fillers, microcrystalline cellulose (MCC), and mannitol
- level of disintegrant, sodium starch glycollate (SSG) or crosspovidone (CP)
- level of lubricant, magnesium stearate (MgSt) or sodium stearyl fumarate (Sod St Fum)
- particle size of drug substance and magnesium stearate
- press speed

And dependent response variables (or surrogates for these) are:

- appearance, i.e., absence of picking and capping
- uniformity of dosage units
- dissolution
- friability
- hardness

Assay and impurities are analyzed on some samples, and samples with extremes of properties (e.g., high and low dissolution) are placed on a stress stability program.

In this Illustrative Example, Hardness CQA during development of the formulation is measured kilopond, kp units, whereas later in this Section, Hardness is determined as crushing force and measured in units of Newton, N. 10 N crushing force is approximately equal to 1 kp.

Experimental Program

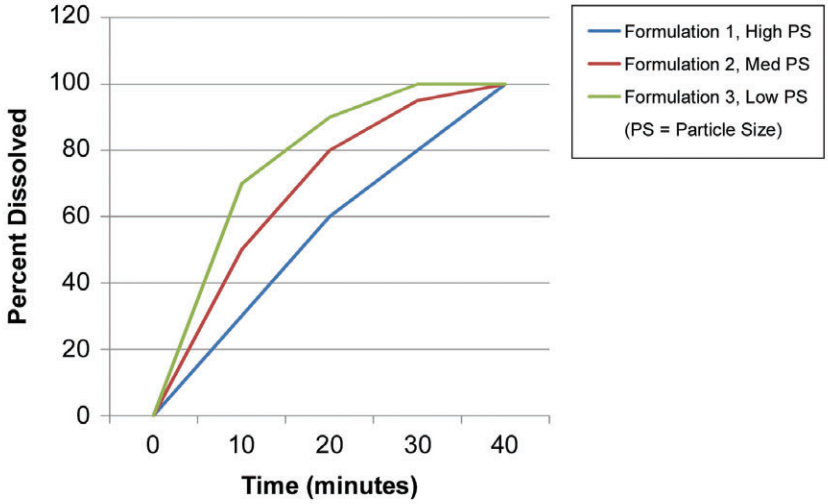
Analytical Methods

Before progressing the DoE studies, consideration is given to the methods to employ. The UDU method and assay methods should be developed and validated as fit for purpose, for example, in the hands of the analyst(s) performing the work for appropriate accuracy, precision (repeatability), linearity, and specificity. At this stage of development, it is not necessary to validate fully for example to assure that the method is validated for multiple analysts or multiple laboratories. The scope of this document does not extend to exemplifying how the detail of validation should be performed.

With regard to the dissolution method, a method is required which is discriminating for formulation and processing variables and in this case, the method could be developed using USP dissolution media pH 6.8 containing 0.5% surfactant (Polysorbate 80, Paddle method, 50 rpm, 900 ml, 37 ±0.5°C). This method is able to discriminate between samples generated from preliminary univariate studies and subsequently in this first series of DoE studies, for example, between large differences in drug substance particle size as shown in Figure 2.4.

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Figure 2.4: Curves showing Discriminatory Performance of First Dissolution Method



This method is suitable for formulation development and process optimization. Further studies are required, potentially *in vivo* to establish if an *In Vitro – In Vivo* Correlation (IVIVC) can be established using this method. It may be necessary to develop an improvement to this method or develop an alternative method in order for an IVIVC to be derived.

Appearance can be established as some internal subjective criteria, and friability and hardness should be standard pharmacopoeial methods

Design of Tablet Core

This section describes one approach to design of the formulation. It describes in this case approaches to selection of study design and levels of factors to study as an example. Other designs and levels to study could be equally acceptable.

The approach to development of the formulation and process should be based on another review of prior knowledge both for this formulation and from the company's experience. The team with subject matter experts and statistical expertise reviews prior knowledge and performs a high level and informal risk assessment to work out the optimum strategy for development of the formulation and process. Among several alternative approaches which could be considered are:

- Optimize the formulation, and then optimize excipient material attributes and process parameters in a subsequent series of studies.
- Optimize the formulation and process as a series of combined studies including both formulation, material attributes, and process parameters as independent variables.
- Optimize formulation and excipient material attributes in one series of studies, and then optimize in-process material attributes, and process parameters in a second series of studies.

In all the above cases, there is the possibility of:

- studying all unit operations together or
- studying one unit operation at a time. For initial formulation work, this option is probably more risky since interactions between unit operations will not be detected; however, this option does have utility when "fine tuning" a proposed process.

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Based on prior knowledge and the informal risk assessment by the development team, a short list is selected of parameters to evaluate. It is assumed that the output from the first DoE would provide a qualitative formulation based on the defined criteria resulting in a formulation that would contain:

- appropriate level of drug substance
- aAppropriate levels of suitable fillers that meet acceptance criteria for compression properties and dissolution

This would be followed by a subsequent DoE to further optimize the formulation and define the quantitative composition of the tablet. In doing so, the output from the second DoE would provide the following:

- fillers with different compression properties (plastic and ductile) and at suggested levels
- a preferred disintegrant
- a preferred lubricant

In addition to understanding the influences on the dependent variables, it is also important to establish the acceptance criteria and the relative importance of the factors that are being measured. In this example, the acceptance criteria of some relevant CQAs are based on Phase 2 studies and are given in Table 2.13.

Table 2.13: CQAs and Acceptance Criteria for Formulation Development

CQA	Acceptance Criteria	Comment
Dissolution	> 85% released at 30 minutes using USP paddle method, 0.5% polysorbate, pH 6.8	"Must have"
Flow (as a surrogate for UDU)	Good flow, Carr's index < 20	"Want"
Appearance	Absence of major defects picking, sticking, capping, edge damage)	"Must have"
Hardness	Crushing force greater than 60N (approx 6 kp)	"Must have"
Press Speed Sensitivity	NMT 0.5 reduction in kp for 20 to 60 rpm	"Want" – can be modified by process optimization. Strictly this is a process parameter and is an independent variable.

It should be remembered that optimization of the process also can influence the dependent variables. Additional measurements that are also recommended to be collected as part of the manufacturing process for the first DoE include friability, ejection force, compression force variability (Relative Standard Deviation (RSD)) and tablet weight variation (RSD). All of these measurements provide information that is important in determination of a suitable formulation.

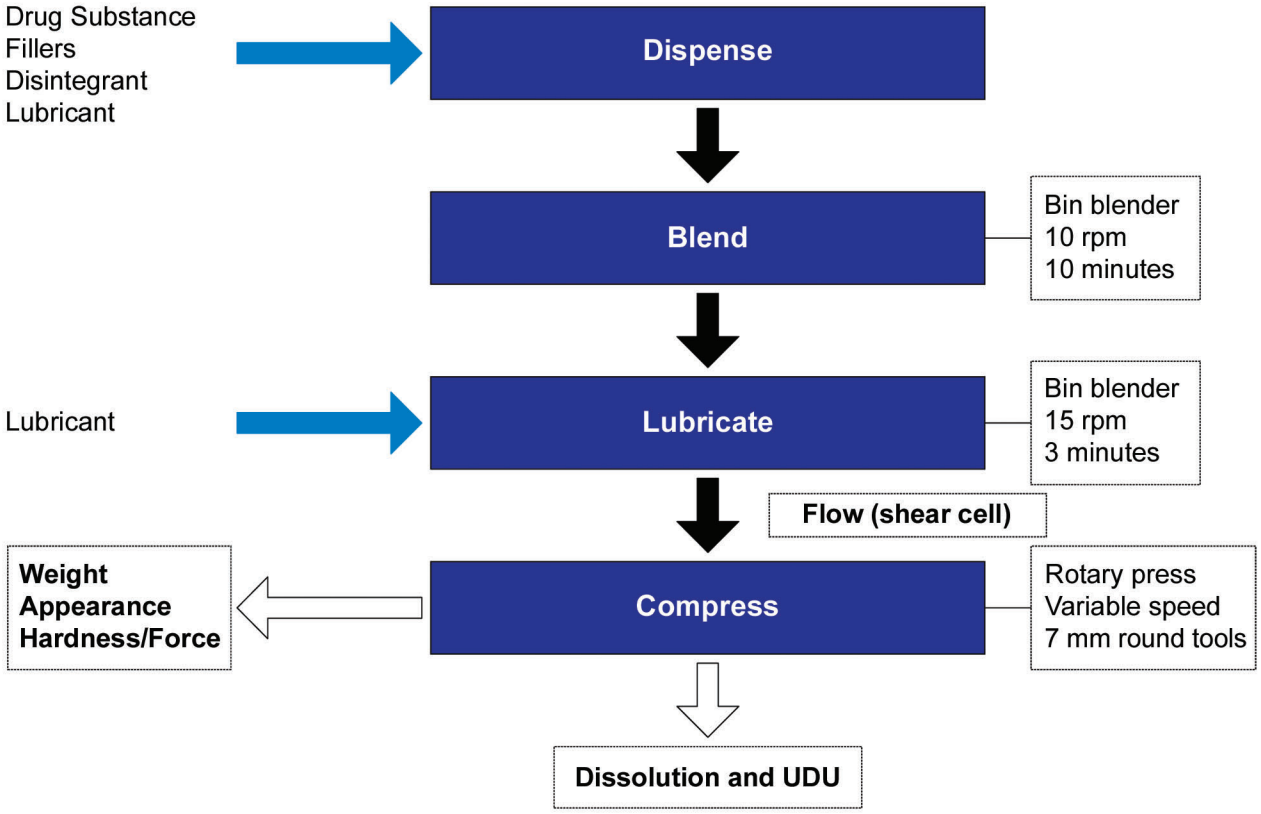
Tables 2.11 and 2.12 show that there are multiple factors to consider in order to explain the output of the data generated from the DoEs.

Tablet cores could be manufactured at small scale. In a subsequent series of studies, the process is optimized by studying material attributes and potential critical process parameters at larger scale.

Using a suitable software package a full factorial design DoE study 1 is developed, built on using 100 g batches of tablet cores manufactured using a direct compression process, see Figure 2.5. Use of a bin blender and blender times are chosen based on prior knowledge and equipment proposed for production scale manufacture

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Figure 2.5: Schematic of Tablet Core Manufacturing Process



Design of the tablet core formulation rather than formulation and process together results in this case in a mixture design rather than a factorial design for the first DoE. The choice of study design is decided by the team. In this case, it is considered that a factorial design is more limited when used for formulation development since it is decided to use a fixed tablet weight. Change of one component (e.g., drug substance content at 20% and 30%); therefore, limits what changes in levels of other components can be made in the design. However, other designs could be used satisfactorily. Before deciding the specific levels and ingredients to investigate, a few screening batches are made using in-house experience to estimate values for the filler and dug substance levels. The results from these screening batches indicated that drug substance levels up to ~30% would be feasible in terms of the general handling characteristics and would be suitable for compression. For the first DoE, the drug load is set at 20% (for the target dose of 30 mg, which results in a 150 mg tablet and satisfies the need for a small tablet) using PaQLInol with a "typical" particle size of 20 µm. Given the criteria and limitations discussed previously, e.g., Table 2.8, the following ranges are used. Single batches of excipients are selected as representative of commercial supply:

- DCP: 20 to 70%
- Mannitol: 0 to 50%
- MCC: 0 to 50%
- Crospovidone: 2 to 8%
- Magnesium Stearate: 0.5 to 2.5%
- Total sum of the above: 80%

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A minimum amount of DCP is estimated to offset the strain rate sensitivity of the drug substance and as a balance against the plastic nature of the other fillers and the drug substance. The mannitol and MCC levels are set at 0 to 50% to allow the evaluation of the effect of each individual component as well as mixtures of these two excipients. The disintegrant and lubricant, crospovidone and magnesium stearate (MgSt), respectively, are chosen based on in-house experience with similar formulations and levels set according to prior knowledge. Alternative disintegrant and lubricant in this case are evaluated in the second DoE. A D-Optimal design that incorporated 21 batches (15 for model development, three for fit testing, three duplicates for reproducibility) is constructed, see Table 2.14, dependent variables and acceptance criteria being the CQAs given in Table 2.13. This design may appear large for a "screening" study; smaller factorial designs that use ratios of excipients or keep levels fixed while varying excipient type (e.g., lactose or starch) could be substituted. However, multiple designs would be needed to cover the same ranges, and in the end, would likely need as many or more batches to get the same amount of information. Furthermore, the effects of formulation variables tend to be asymptotic rather than leading to minima/maxima (i.e., increasing mannitol while keeping all other excipients at the same ratios does not lead to increased hardness at low levels or decreased hardness at higher levels). It is considered that this single study can successfully elucidate the cause and effect relationships between the various formulation components.

Table 2.14: Design of DoE Study 1

Batch	DCP	Mannitol	MCC	Crospovidone	MgSt
1	70.00	7.50	0.00	2.0	0.5
2	20.75	0.75	50.00	8.0	0.5
3	48.75	0.00	28.75	2.0	0.5
4	70.00	0.00	1.50	8.0	0.5
5	20.00	0.00	49.50	8.0	2.5
6	24.50	50.00	0.00	5.0	0.5
7	20.00	25.75	25.75	8.0	0.5
8	20.00	50.00	6.50	2.0	1.5
9	70.00	0.00	5.50	2.0	2.5
10	20.00	50.00	2.75	4.8	2.5
11	69.50	0.00	0.00	8.0	2.5
12	47.75	27.75	0.00	2.0	2.5
13	20.75	50.00	0.00	8.0	1.3
14	20.00	5.50	50.00	2.0	2.5
15	46.17	0.00	26.17	5.9	1.8
16	38.83	18.83	18.83	2.0	1.5
17	29.61	8.86	33.86	6.6	1.0
18	31.11	33.86	8.86	5.1	1.0
19	20.75	50.00	0.00	8.0	1.3
20	69.50	0.00	0.00	8.0	2.5
21	20.00	5.50	50.00	2.0	2.5

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Dependent response variables are:

- Appearance, i.e., absence of picking and capping
- Uniformity of Dosage Units (UDU)
- Flow of blend (potentially to link to UDU results)
- Dissolution
- Friability
- Hardness

Impurities are also analyzed on some samples, and some samples at extremes of excipient levels and with extremes of dissolution behavior could be placed on a stress stability study, for example, 80°C storage for two days in the open, i.e., not packaged. Other data also would likely emerge from such a study depending on equipment used, such as ejection force after compression of a table.

Tablet hardness can be assessed in a number of different ways when running compression studies. For example, tablets can be made at three or five different compression forces, compression force plotted against hardness and the area under the curve measured. Alternatively, tablet hardness can be determined at a single compression force, and/or tablets can be compressed at two press speeds (which can be assessed quantitatively by the change in tablet hardness, or qualitatively as pass/fail). UDU is measured on all samples (RSD from analysis of 10 tablets), and flow is measured by a shear cell method.

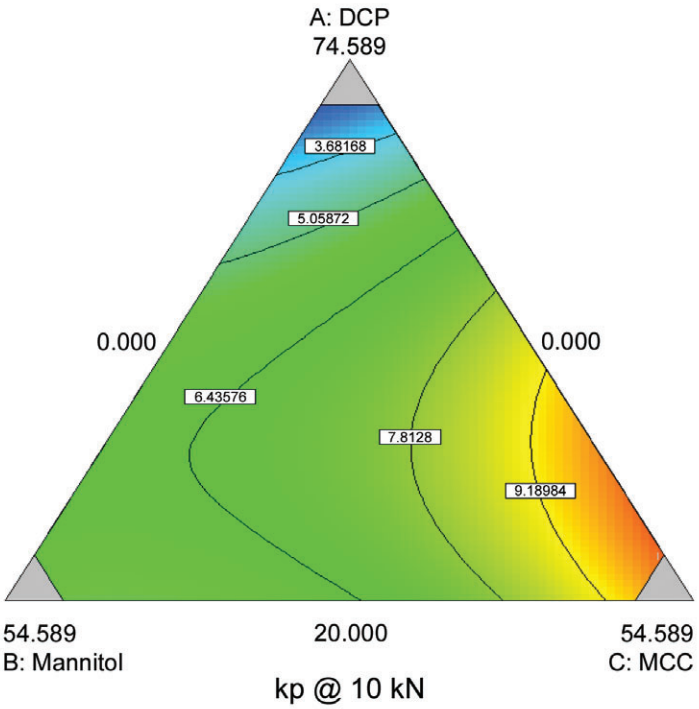
The output from this work is a number of ternary contour plots that identify the impact of changing levels on the output of interest. Example plots are shown in Figure 2.6, in which the effects of changing levels of DCP, MCC, and mannitol at fixed values of crospovidone and magnesium stearate (changing the levels of these components varies the quantitative, but not the qualitative relationships shown in Figures 2.6 and 2.7) is shown on (a) tablet hardness at 10 kN compression force and (b) dissolution at 30 minutes.

The values in the middle of the lines of 0.00, 0.00, and 20.00 represent the level of excipient in the opposite corner, i.e., clockwise, MCC, mannitol and DCP.

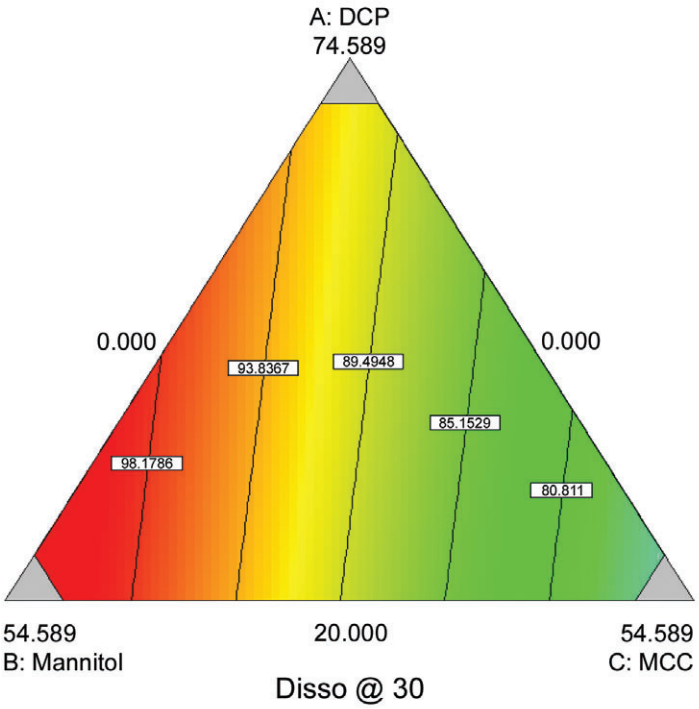
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Figure 2.6: Example Contour Plots for DoE Study 1 Results – a. Hardness at a Compression Force of 10 kN as a function of Mannitol, Microcrystalline Cellulose, and Dicalcium Phosphate levels, b. Dissolution at 30 minutes

Note: a. Hardness is highest in bottom right-hand corner.



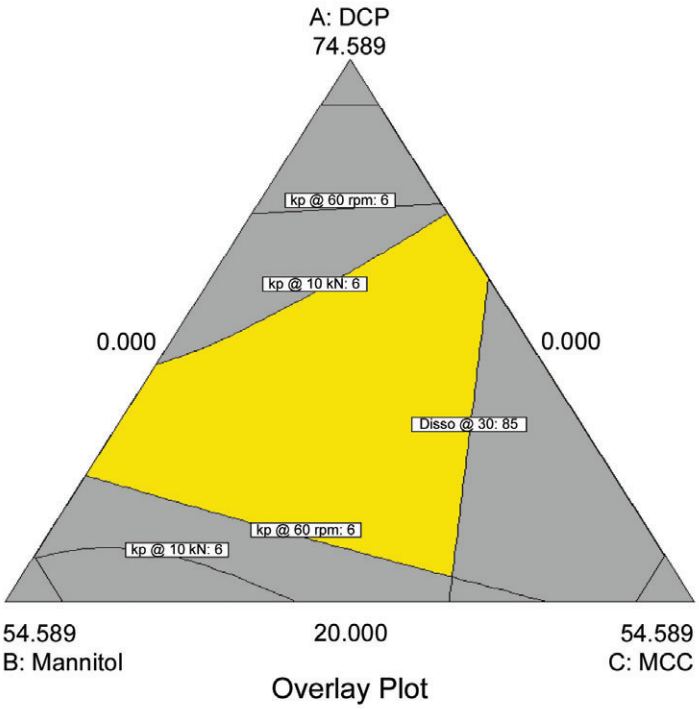
Note: b. Dissolution is highest in bottom left-hand corner.



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In Figure 2.6(a), it is clear that increasing levels of MCC lead to harder tablets and that if DCP levels are too high that sufficient tablet hardness cannot be attained. The reduced binding properties (i.e., lower hardness) of mannitol compared with MCC also can be seen. Figure 2.6(b) demonstrates the decrease in dissolution associated with increased MCC and that DCP has essentially no effect on dissolution. Similar plots are constructed to look at other combinations of variables and outputs. One of the most important balances to maintain is good dissolution performance while achieving acceptable tablet hardness and limiting sensitivity to high press speed (herein defined as the tablet hardness decreasing by less than 0.5 kp upon an increase in tablet turret speed from 20 to 60 rpm). Optimization plots are used to examine simultaneously the effect of filler combinations on these multiple outputs; see Figure 2.7

Figure 2.7: Example Overlay Optimization plot for DoE Study 1



This plot identifies a range of values (light shading) that meet both dissolution and hardness criteria, indicating that a minimal value of DCP is needed to meet press speed criteria while too much MCC has deleterious effects on dissolution, but that relying solely on mannitol may not lead to robust tablets. A summary of the conclusions from this work and other work not shown is:

- UDU/Flow:
  - No significant problems are encountered for the ranges studied.
  - Means met Assay criteria of ±5% label claim
- Dissolution – reduction in release at 30 minutes is caused by:
  - High levels of MCC
  - A lack of mannitol (i.e., mannitol is necessary in the formulation)
  - Very low values of disintegrant (<2.5%)

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- High levels of lubricant (>2%, especially at DCP levels below 30%)

- Appearance – picking and/or sticking is associated with:
  - Very high disintegrant values (>6.5%, exacerbated by low lubricant amounts)
  - Low levels of plastic fillers (<~15%)

- Tablet Hardness – reduction in hardness is caused by:
  - High levels of DCP
  - Insufficient MCC (depends on DCP levels, in some cases, mannitol by itself does suffice)

- Friability:
  - A minimum amount of plastic filler (~20%) is needed for acceptable friability
  - Press Speed – to avoid loss of hardness on press speed increase:
  - A minimum amount of DCP is necessary (~30%)

- Impurities:
  - No impurities are observed from manufacture
  - Stress stability testing (e.g., storage at 80°C for two days of unprotected tablets) showed no evidence of increase in degradation products

- Stress stability:
  - No evidence of chemical degradation or change in dissolution

The evaluation of these results leads to a repeat risk assessment exercise and the output is summarized in Table 2.15. The same assessment criteria are used as that used for Tables 2.11 and 2.12. Some comments are placed in selected squares to indicate the rationale for assignment of risk.

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Table 2.15: Summary Risk Evaluation after DoE Study 1

CQA (Severity Rating)/ Hazard	App (3)	Impurities (4)	Water (4)	UDU (4)	Disso (4)	Micro (3)	Fria (3)	Hard (3)
Level of PaQLInol ("typical" particle size)	Low chance (2) of failure when excipients and their levels optimized.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure. All samples met acceptance criteria.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced. Low levels (<2.5%) of disintegrant and high levels (>2%) of lubricant increase risk.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced. reduced.	Low chance (2) of failure. Acceptable manufacturing space identified Risk reduced.
Level of Mannitol (0 to 50%)	Low chance (2) of failure. Acceptable manufacturing space identified (>15%). Risk reduced.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Low chance 2) of failure. (Acceptable manufacturing space identified. Some mannitol required.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified when level > 20%. Risk reduced.	Low chance (2) of failure. Acceptable manufacturing space identified. Some other excipient required.
Level of DCP (20 to 70%)	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced. High levels a problem.
Level of MCC (0 to 50%)	Low chance (2) of failure. Acceptable manufacturing space identified (>15%). Risk reduced. Low levels a problem.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Medium chance (3) of failure. High levels are a problem.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced. Insufficient MCC is a problem.
Level of SSG (NE)								
Level of CP (2 to 8%)	Low chance (2) of failure. High levels (> 6.5%) are a problem in combination with low lubricant levels. Acceptable manufacturing space identified.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Medium chance (3) of failure. Very low levels (< 2.5%) are a problem.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.

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Table 2.15: Summary Risk Evaluation after DoE Study 1 (continued)

CQA (Severity Rating)/ Hazard	App (3)	Impurities (4)	Water (4)	UDU (4)	Disso (4)	Micro (3)	Fria (3)	Hard (3)
Level of MgSt (0 to 2.5%)	Low chance (2) of failure. Low levels interact with CP. Acceptable manufacturing space identified.	Extremely low chance (1) of failure. No new impurities during manufacture and from stress storage.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Medium chance (3) of failure. High levels (> 2%) with low levels (< 30%) of DCP are a problem.	Extremely low chance (1) of failure.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.	Low chance (2) of failure. Acceptable manufacturing space identified. Risk reduced.
Level of Sod St Fum (NE)								
PaQLInol Particle Size (NE)								
MgSt Particle Size (NE)								
Press Speed	Medium chance (3) of failure. High levels (> 30%) of DCP required.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Extremely low chance (1) of failure.	Medium chance (3) of failure. High levels of DCP are required.	Medium chance (3) of failure. Minimum level of DCP is required.
NE = Not Evaluated								

A review of the data thus far demonstrates wide ranges of the various excipients that give acceptable tablet properties which gives high confidence in the ability to develop an appropriate formulation. The most important factors to investigate in future work are to optimize the relative ratios of DCP, mannitol, and MCC – preferably eliminating MCC if possible (to make a simpler formulation with one less excipient – which is a business benefit). DCP levels must be kept high enough to avoid press speed sensitivity. To facilitate these requirements, a second DoE is constructed to determine optimal DCP levels, ratios of mannitol to MCC as well as to investigate the effects of changing disintegrant and lubricant types. Again single representative batches of PaQLInol drug substance and excipients are used. The ranges chosen are:

- DCP: 35 to 50%
- Mannitol/MCC: remainder (100% mannitol, or 67/33 mannitol/MCC)
- Disintegrant: 5% (Crospovidone (CP) or sodium starch glycollate (SSG))
- Lubricant: 1.5% (magnesium stearate (MgSt) or sodium fumarate (Sod St Fum))

The disintegrant level is purposely set at the higher levels in order to push the effect on tablet appearance as it is indicated that a range of disintegrant levels (3 to 5%) would be sufficient from a dissolution point of view. A resulting fractional factorial design is constructed, consisting of eight batches (see Table 2.16).

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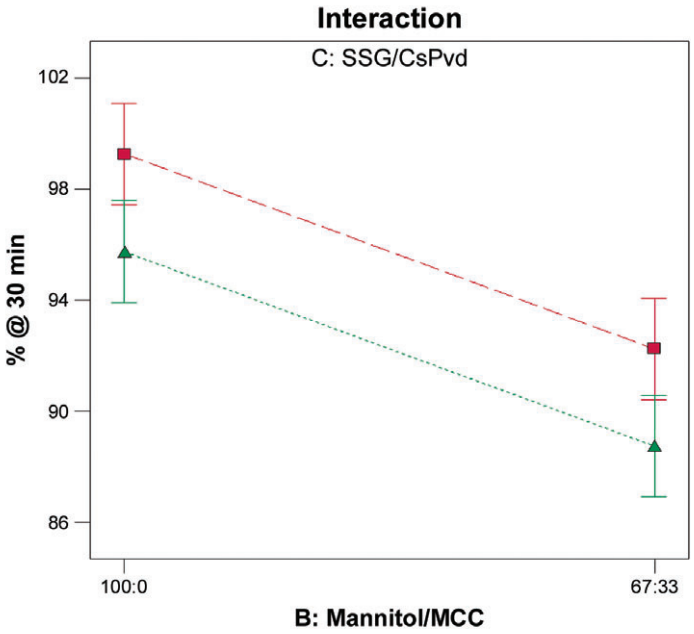
Table 2.16: Design of Study DoE 2

Batch	DCP	Mannitol/MCC	Disintegrant	Lubricant
1	35	100:0	SSG	MgSt
2	50	100:0	SSG	Sod St Fum
3	35	67:33	SSG	Sod St Fum
4	50	67:33	SSG	MgSt
5	35	100:0	CP	Sod St Fum
6	50	100:0	CP	MgSt
7	35	67:33	CP	MgSt
8	50	67:33	CP	Sod St Fum

Dependent variables studies are similar to those in DoE 1. Assay is not performed, and UDU is only performed on some samples at the edge of the design. Stress stability samples are only performed on samples containing SSG after initial evaluation of the data to minimize work. Work is carried out at the same scale and in the same manner as DoE Study 1.

The resulting cause and effect relationships are identified, for instance, Figure 2.8 shows how mannitol/MCC ratios and choice of disintegrant affect dissolution.

Figure 2.8: Example interaction plot for DoE Study 2



SSG is shown as squares and CP as triangles.

In this case, the deleterious effect of including MCC in the formulation on the resulting dissolution performance is clear; SSG shows superior performance compared to crospovidone (labeled in Figure 2.8 as CsPvd).

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The conclusions from DoE Study 2 are:

- DCP:
  - Higher levels (nearer 50%) are needed to avoid press speed sensitivity.
- Mannitol/MCC:
  - Using mannitol alone is sufficient to meet target tablet hardness.
- SSG/crospovidone:
  - SSG showed superior performance.
  - Minor appearance issues seen.
- Lubricant:
  - Both lubricants performed similarly.
- UDU:
  - Meets acceptance criteria on all samples tested.
- Press Speed:
  - Higher levels of DCP led to high press speeds being possible with the proposed formulation with acceptable compliance with other CQA acceptance criteria.

These results led to the identification of a lead prototype formulation and a repeat risk assessment.

The formulation of tablet cores proposed has the following composition:

- Plain round tablets, 7 mm in diameter, target compression weight 150 mg
- PaQLInol: 20%
- 45% Calcium hydrogen phosphate dihydrate
- 29.5% Mannitol
- 4% Sodium starch glycolate
- 1.5% Magnesium Stearate (MgSt)

Another risk assessment exercise is conducted; however, please note that in Table 2.17, the “Hazards” have been changed to reflect the excipients and their amounts chosen for the formulation. Excipients listed in the initial risk evaluation chart, Table 2.11 and 2.12 have been included; however, risk scores have been omitted. Almost all “Hazards” have an extremely low chance of occurrence after this comprehensive formulation development exercise.

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Table 2.17: Summary Risk Evaluation after DoE Study 2

CQA (Severity Rating)/ Hazard	App (3)	Impurities (4)	Water (4)	UDU (4)	Disso (4)	Micro (3)	Fria (3)	Hard (3)
20% PaQLInol (at Typical Particle Size)	L	M	M	M	M	L	L	L
Level of Mannitol, 29.5%	L	M	M	M	M	L	L	L
Level of DCP, 45%	L	M	M	M	M	L	L	L
Level of MCC, not used								
Level of SSG (4%)	L	M	M	M	M	L	L	L
Level of CP, not used								
Level of MgSt 1.5%	L	M	M	M	M	L	L	L
Level of Sod St Fum (NE), not used								
PaQLInol Particle Size (NE)	M	M	M	H	H	L	M	M
MgSt Particle Size (NE)	M	M	M	M	H	L	M	M
Press Speed	L	L	L	L	L	L	L	L
NE = Not Evaluated, H = High Risk, M = Medium Risk, L = Low Risk								

Comparison should be made between the final risk table associated with formulation development, Table 2.17, and the initial risk table, 2.11 where it is clear that for the factors studied:

- All risks have been reduced.
- There are no residual “high” formulation composition risks.

There are factors identified in the initial risk analysis (Table 2.11) which have not yet been studied, for example, the material attributes of PaQLInol and magnesium stearate particle sizes. The project team took the decision for this example to optimize excipient choice and quantities using only typical particle size PaQLInol (20 µm). This decision is based on the risk evaluation Table 2.12 where the factors of PaQLInol particle size and magnesium stearate particle size have reduced number of high risk impacts on CQAs (2 and 1 respectively) compared to all the other factors listed.

Using this formulation as a starting point, a number of one-off experiments are performed to confirm final levels (i.e., reduction in disintegrant, confirming an optimal DCP level, etc.). In addition, batches are made that moved all components in the same direction (i.e., toward poorer dissolution, 5% less DCP, 0.5% more lubricant, 1% less disintegrant) to test formulation robustness.

These studies confirm that the formulation given in Table 2.18 is optimal. This formulation generates uncoated tablets with ideal characteristics of low compression force RSD, low ejection force, low tablet weight RSD, high tablet hardness (> 6 kp) and low friability, as well as meeting Assay, Impurities, UDU and Dissolution acceptance criteria, and from a series of stress studies having predicted good stability. The tablet cores have good properties of Hardness and Friability for film coating.

Although all the above work is performed at small laboratory scale prior knowledge indicates that there is low risk of having to change formulation quantities during further process development and scale up studies.

The process is confirmed as:

- Dispense

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- Blend
- Lubricate
- Compress
- Coat

The process is presented schematically in Figure 2.9.

Figure 2.9: PaQLInol Tablet Manufacturing Process

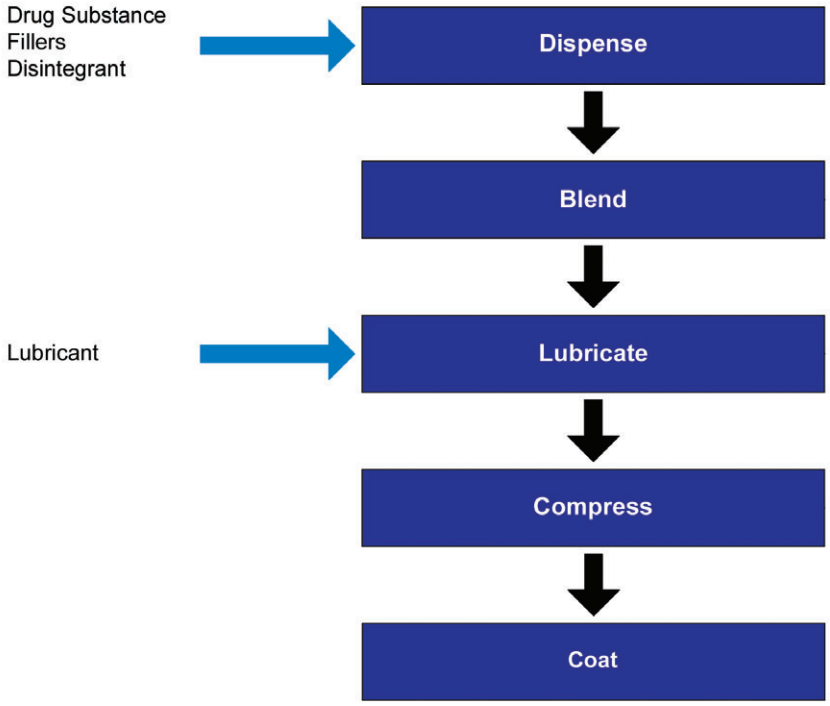


Table 2.18: Quantitative Composition of the PaQLInol Tablet Cores, 30 mg

Component	Purpose	% w/w	mg per Tablet
PaQLInol	Active Ingredient	20	30
Dicalcium Phosphate Anhydrous	Filler	45	67.5
Mannitol	Filler	29.5	44.25
Sodium Starch Glycolate	Disintegrant	4.0	6.0
Magnesium Stearate (MgSt)	Lubricant	1.5	2.25
Total		100%	150 mg

Use of Formulation

The formulation (Table 2.18) is developed for and used in pivotal Phase 3 clinical studies, and subsequently is shown bioequivalent to the extemporaneous suspension used in Phase 1 studies. Chemical and physical stability is confirmed as acceptable, and assay of all batches manufactured for Phase 3 are acceptable.

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Another example of process selection is given in the ACE case study (Reference 7, Appendix 5) in this case, flow properties of the drug substance are not suitable at a drug loading of 10% in the tablet to support direct compression and dry granulation using roller compaction was selected as the process to study.

It is highly desirable to try to understand the biopharmaceutical performance of this formulation and one way of doing this would be to try to develop some kind of in vitro - in vivo relationship and these studies are discussed in the next section.

An informal risk assessment applied to the proposed formulation and manufacturing process can guide further work to develop increased understanding (Table 2.19).

Table 2.19: Overview Risk Evaluation of the Proposed Manufacturing Process

Unit Ops/CQAs	Dispensing (MAs of RMs)	Blending	Lubrication	Compression	Coating
Appearance (3)	H	L	M	M	M
Assay (4)	M	M	L	L	L
Impurities (4)	M	L	L	L	L
Water Content (4)	L	L	L	L	L
UDU (4)	H	H	M	M	L
Dissolution (4)	H	L	H	H	L
Microbiology (3)	L	L	L	L	L
H = High Risk, M = Medium Risk, L = Low Risk					

Severity values in parenthesis (based on scores in Table 8.2).

From Table 2.19, the CQAs of UDU, Dissolution, and Appearance have the highest number of high and medium risk ratings; therefore, the highest priority to study. In addition and if it is possible, it is important to try to understand the linkage between the proposed CQA of Dissolution and *in vivo* performance so that an *in vivo* relevant *in vitro* method can be developed and acceptance criteria set appropriate to *in vivo* performance. Based on learning from the formulation design DoE studies, it is highly probable that dependent variables of UDU, Dissolution, and Appearance can be determined from a single design of independent process parameter and material attribute variables.

Understanding *In Vivo* Impact of Variables and Linking to *In Vitro* Test

The purpose of this section is to explain how an *in vitro* – *in vivo* relationship could be developed for an immediate release tablet. The increased understanding and correlation between in vivo performance and dissolution is used to reduce risk to formulation and process development, to produce acceptance criteria for the Dissolution CQA, and to produce a method with suitable discriminatory power to apply to process development studies.

This work is not always possible to perform for many reasons, for example, clinical safety and non-linear or highly variable pharmacokinetics, and should not be necessary for highly soluble, highly permeable BCS Class 1 drug substances formulated as immediate release tablets.

The lead formulation and manufacturing process for PaQLInol tablets has been identified experimentally. An important next step is to understand the impact on the *in vivo* performance of the product of variability of *in vitro* performance of the product resulting from different dissolution mechanisms. Samples of tablet cores with different dissolution mechanisms can be produced by adjusting appropriately levels and attributes of input materials and manufacturing process parameters (see Tables 2.21 and 2.22).

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An approach to the development of enhanced *in vivo* understanding and its subsequent application in the establishment of a proposed Design Space and use in the Control Strategy is described in Table 2.20.

Table 2.20

Step	Example
1. Conduct Quality Risk Assessment (QRA)	Perform QRA to identify the most relevant risks (product and process variables) to in vivo dissolution using prior knowledge and suitable expertise.
2. Develop Appropriate Dissolution CQA Tests	Develop *in vitro* dissolution test(s) with physiological relevance that is most likely to identify changes in the relevant mechanisms for altering *in vivo* dissolution (identified in Step 1).
3. Understand the *in vivo* Importance of Changes	Perform *in vivo* study. Determine the impact of the highest risks (from Step 1) to clinical pharmacokinetics based on *in vitro* dissolution data using: 1. prior knowledge including BCS and/or mechanistic absorption understanding 2. and/or clinical "bioavailability" data from *in vivo* study
4. Establish Appropriate CQA Limits	Establish the *in vitro* dissolution limit that assures acceptable bioavailability.
5. Use the Product Knowledge Gained in Subsequent QbD Steps	Develop a design space ensuring in vitro dissolution performance within established limits. Develop a control strategy to ensure routine manufacture remains within the design space, e.g., that assures dissolution limits are met during routine manufacture.

An important aspect of this approach (step 3) is when the understanding relating to in vivo impact is developed, resulting ideally in an *In Vitro – In Vivo* Correlation (IVIVC). For some compounds (notably BCS Class 2 and 4), this may require an in vivo relative bioavailability study.

Relative Bioavailability Studies

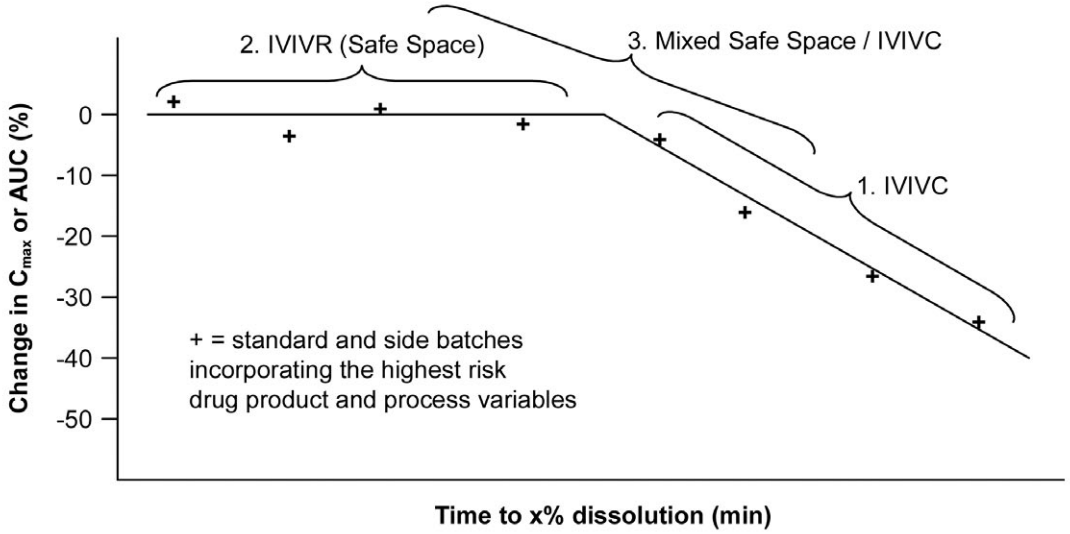
Variation in dissolution rate may not lead to a change in bioavailability, as other physiological absorption processes may dominate (e.g., gastric emptying and intestinal wall permeation). This means that *in vitro* dissolution could vary within a certain range without any influence on pharmacokinetics. This is often the case not only for highly soluble drugs (BCS Class 1 and 3), but also for well formulated, moderately-soluble Class 2 drugs and Class 4 drugs, when the rate of (*in vivo*) dissolution is much faster than the rate of absorption.

Thus, for any product three potential outcomes exist for the relationship between *in vitro* dissolution and bioavailability as illustrated in Figure 2.10 (Reference 12, Appendix 5), these are:

- An IVIVC could be established, where changes in *in vitro* dissolution are correlated to changes in bioavailability.
- An IVIV Relationship (IVIVR) in which no effect on bioavailability would be observed across a range of *in vitro* dissolution rates (referred to in Figure 2.10 as a "Safe Space").
- The final option is a mixed safe space/IVIVC result in which bioavailability is only affected for some of the *in vitro* variants tested clinically.

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Figure 2.10: Potential Outcomes for the Relationship between *In Vitro* Dissolution and Bioavailability



Development of an IVIVC would have the potential benefits of:

- Assisting with producing a design space boundary (i.e., "...an assurance of quality." Given in the ICH Q8(R2) definition and represented by the dissolution CQA).
- Allow establishment of dissolution acceptance criteria based on *in vivo* performance.
- Provide an *in vitro* method to assess the impact of movements within design space or outside design space in support of desired post approval changes.

Development of an IVIVC is in many cases not necessary, for example. for BCS Class 1 and 3 highly soluble drugs, and in some cases is not practical, for example, where relatively straightforward single dose i*n vivo* studies in "normals" are not possible or when pharmacokinetics are complex.

These principles could be applied in the development of the PaQLInol tablets and are described in detail below.

Conduct Quality Risk Assessment (QRA) Relating to In Vivo Performance

The highest risks to the *in vivo* performance are presented in Table 2.21 with their respective dissolution retardation mechanisms.

Table 2.21: Highest Risk Failure Modes with the Potential to Impact Bioavailability

Failure Mode	Dissolution Retardation Mechanism
Changes in drug substance properties (a PaQLInol material attribute)	Impact of drug substance surface area on rate of dissolution
Over-compression (resulting from a potential critical process parameter of unacceptably high compression force)	Reduced porosity of the tablet matrix could lead to retarded ingress of water and thereby reduced dissolution rate
Excess lubrication (either by lubricant level or prolonged lubrication time). (A combination of a formulation design design factor and a potential critical process parameter of excessive lubrication time)	Increased hydrophobicity of the tablet could retard disintegration and dissolution

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