APPLICATION OF A QUALITY BY DESIGN APPROACH TO OPTIMISE AN EXISTING PRODUCT

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DECLARATION:

In accordance with Rule G5.6.3, I hereby declare that the above-mentioned treatise/ dissertation/ thesis is my own work and that it has not previously been submitted for assessment to another University or for another qualification.

SIGNATURE:

DATE: 28 Nov 2017

DEDICATION

This study is dedicated to my mother and father, I would not be the woman I am today were it not for your love and support.

Dad, I wish you were here to see me graduate, I know that you would be proud of what I have achieved.

Mom, thank you for inspiring me to always do my best and to work hard in the face of adversity

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List of Acronyms

ANOVA – Analysis of variation

API – Active pharmaceutical ingredient

BCS – Biopharmaceutics classification system

BMR – Batch manufacturing record

CCD – Central composite design

CFU – Colony forming unit

CI – Carr's compressibility index

CMAs – Critical material attributes

CpK – Process capability

CAPA – Corrective and preventative action

CPPs – Critical process parameters

CQAs – Critical quality attributes

DoE – Design of experiments

FDA – The United States food and drug administration

FDL – Formulation development laboratory

FMEA – Failure mode effects analysis

FMECA – Failure mode effects and criticality analysis

FTA – Fault tree analysis

HACCP – Hazard analysis and critical control points

HAZOP – Hazard operability analysis

HPLC – High performance liquid chromatography

ICH – The international council for harmonisation

IPC – In-process control

IPI – Inactive pharmaceutical ingredient

IR – Infrared

ISPE – International society for pharmaceutical engineering

LOD – Loss on drying

MCC – Medicines control council

OFAT – One-factor at a time

OOS – Out of specification

PHA – Preliminary hazard analysis

PpK – Process performance

PQLI – Product quality lifecycle implementation

QbD – Quality by design

QbT – Quality by testing

QRA – Quality risk assessment

QTPP – Quality target product profile

RH – Relative humidity

RPM – Rotations per minute

RSD – Relative standard deviation

ROI – Return on investment

RSM – Response surface methodology

SLS – Sodium lauryl sulphate

UOM – Uniformity of mass

USP – United States pharmacopeia

UV/VIS – Ultraviolet/visible spectrophotometry

XRD – X-ray diffraction

XRPD – X-ray powder diffraction

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SUMMARY

Purpose: Quality by design (QbD) is a science and risk-based approach whereby quality is built into the product or process during pharmaceutical development. Although QbD is encouraged for pharmaceutical development, it is possible to apply QbD principles to optimise an existing product as part of a continual improvement strategy. The purpose of this study is to determine which factors should be considered to justify the application of QbD to optimise an existing product.

Methodology: A formalised stepwise approach based on QbD principles was applied to perform this study to optimise an existing problem product. First the QbD business case was evaluated, after which the pharmaceutical quality target product profile (QTPP) was confirmed. Once the QTTP was confirmed, the critical quality attributes (CQAs) were determined. Following the identification of the CQAs, the knowledge baseline for the product was evaluated. A quality risk assessment (QRA) was conducted using a risk ranking system to identify the critical processing parameters (CPPs) and critical material attributes (CMAs). Product and process understanding was developed by conducting Design of Experiments (DoE) using Minitab® statistical software version 17.0 (Minitab Inc., United Kingdom). A screening trial using a full factorial design was performed to identify significant factors which could affect the product CQAs.

Based on the outcome of the screening trial, a pivotal study was conducted using a response surface methodology (RSM) approach with a central composite design (CCD). The aim of the pivotal study was to investigate the effects of the significant factors on the responses and to determine the design space. The current quality assurance control strategy for the product was evaluated to determine whether any additional measures should be implemented. The success of the QbD project was evaluated by retrospectively reviewing the cost of the time spent on QbD activities, and determining the actual cost of implementing the QbD approach. The return on investment (ROI) and payback period were also calculated in order to determine the financial implications of the optimisation project.

Results: A formalised stepwise approach using QbD principles was successfully applied to optimise the existing product at a laboratory scale. The large knowledge base for the existing product resulted in fewer product CQAs being investigated. The DoE study identified wet mixing during granulation and feeder speed in compression as parameters which could significantly affect tablet mass variation. The learnings from the laboratory scale studies will

be applied during scale-up submission batch manufacture. Application of QbD resulted in a 20% increase in project cost; however, the intervention should result in good ROI, and the development cost should be recouped within a 3 year period as a result of reduced batch failures.

Conclusion: Based on the outcome of the laboratory scale batches, the adoption of a formalised approach when embarking on a QbD improvement project for an existing product proves that the development cost and the gain in institutional knowledge supports the business case.

Keywords: Quality by Design (QbD), Product Optimisation, Existing Product, Business Case

CHAPTER 1: INTRODUCTION

1.1 Background

Due to an increase in product complexity, fierce competition and a difficult economic climate, the pharmaceutical industry is undergoing a large scale paradigm shift in order to provide higher quality pharmaceutical products to patients at a reduced cost. Historically, most pharmaceutical development and manufacturing systems have relied on a quality by testing (QbT) model to ensure that a product meets the desired specifications. This has resulted in the industry incurring high costs to achieve quality while continuing to sustain value at risk in order to maintain acceptable levels of product supply quality (Blackburn *et al.*, 2011).

The United States Food and Drug Administration (FDA) have moved away from the QbT approach and instead have implemented a scientific framework for reducing risk and increasing continuous improvement and innovation, known as Quality by Design (QbD). The FDA's vision for pharmaceutical manufacturing in the 21st century requires that that quality be built into product and process design by using a science- and risk-based approach. Many older products currently on the market have not been formulated to have quality built into the product; instead, quality is ensured using a QbT approach. With quality standards in pharmaceutical industry becoming stricter, products formulated using traditional approaches and registered with more lenient quality standards may not be able to meet the new requirements due to insufficient product or process understanding. In cases like this, companies may be forced to either discontinue or explore the option of redeveloping these legacy or existing products (IBM Business Consulting Services, 2005).

Product X (so named to avoid divulging proprietary information of the company at which this study is conducted) is a high volume product currently manufactured by a pharmaceutical company based in Port Elizabeth. Based on the current batch size of 1,000,000 tablets, 104 batches per annum were required to meet the market demand in 2016. The product has a history of irreproducible granulation end points which can result in over-granulation. The product also displays poor granule flow, difficulty in achieving optimum tablet hardness, capping of tablets, high tablet friability, and slow compression machine speeds of less than 72,000 tablets produced per hour during tableting.

Optimisation of the manufacturing process and formulation is required for Product X to improve process efficiency and product quality. Product X has been reformulated at an outsource development facility with limited formulation studies being performed. This was part of the development activities prior to scale up using the traditional one factor at a time approach (OFAT). Other than formulation changes, no changes were proposed in terms of the control strategy for the product (Alphamed Formulations PVT Ltd, 2015). A production scale development batch was manufactured with the proposed changes. A suitable granule was obtained and no tablet defects were observed during the compression process; however, granule flow was very poor and the tablet mass and hardness were extremely variable. The formulation and processing changes proposed by the outsource development facility were used as the base formulation for QbD activities conducted at the Port Elizabeth site.

1.2 Research Question

It is well known that QbD is the modern and systematic approach to pharmaceutical development and optimisation, but what factors should be considered to support the business case for the application of QbD to upgrade problematic products?

1.3 Aims and Objectives

1.3.1 Primary Aim

The aim of this research is to determine whether the development cost and the gain in institutional knowledge when optimising an existing product using a QbD approach supports the business case.

1.3.2 Objectives

The objectives derived from the aim are as follows:

1. To determine which factors should be considered when evaluating whether there is value in proceeding with a QbD project for an existing product.
2. To establish a pharmaceutical target product profile and Critical Quality Attributes (CQAs) using current product knowledge.

3. To determine what data should be used in order to identify the knowledge baseline when applying a QbD approach to an existing product. The knowledge baseline refers to current product and process knowledge as well as the quality of the manufacturing process.

4. To apply design of experiments to assess the impact of variables on the CQAs in order to gain a better understanding of the product and its manufacturing process.

5. To develop a control strategy.

6. To evaluate the project and business case to determine whether the QbD project has been successful. Success of the project would be measured in terms of whether the product fulfils the business case objectives, namely:

    6.1 Whether application of QbD has resulted in an optimised product or process.

    6.2 Whether the application of QbD has resulted in a change in the control strategy.

    6.3 Determining the actual cost of the QbD activities.

    6.4 The projected return on investment (ROI) payback period required in order to recoup the QbD development costs.

CHAPTER 2: QUALITY BY DESIGN IN THE PHARMACEUTICAL INDUSTRY

2.1 Introduction

Major changes have been observed in the pharmaceutical industry over the last three decades. This has resulted in increased demands on pharmaceutical manufacturers to improve product quality and process efficiency (Blackburn *et al.*, 2011). When using a QbT approach, product quality is ensured by end product testing with little emphasis placed on understanding the root causes which may adversely affect product quality. As a result there is usually limited understanding of the process and critical process parameters. In an attempt to improve pharmaceutical product quality, regulatory authorities are imposing stringent specifications and guidelines for the registration of drug products with no flexibility to modify the manufacturing process without performing a regulatory submission (Jain, 2014).

2.2 Evolution of Quality by Design

The idea of QbD was first proposed by Dr Joseph M. Juran, and is based on the concept that the primary reason for product quality issues is that quality has not been designed into the product (Yu *et al.*, 2014). The term QbD is explained as a logical, science- and risk-based approach for pharmaceutical development (International Council for Harmonisation Expert Working Group, 2009).

The International Council for Harmonisation (ICH) has developed three guidance documents to support the science- and risk-based approach currently advocated by the FDA. The ICH Q8 (R2) provides guidance on pharmaceutical development, the ICH Q9 deals with quality risk management, and the ICH Q10 deals with pharmaceutical quality system (Potter *et al.*, 2010). The objectives of the ICH Q10 model are:

- To achieve product realisation by establishing, implementing, and maintaining a system that ensures the drug product or substance has the appropriate quality attributes to be fit for its intended purpose.
- To establish and maintain a state of control by developing and using effective monitoring and control systems to ensure that process performance and product quality are suitable and capable.

- To facilitate continual improvement by identifying and implementing quality or process improvements to improve product quality.

(International Council for Harmonisation Expert Working Group, 2008)

A QbD approach to development of a pharmaceutical product begins by defining the objectives for the development and requires an understanding of the product, its manufacturing process, as well as the process controls. Quality by design advocates the incorporation of prior knowledge, design of experiments (DoE), and the use of quality risk management and knowledge management throughout the lifecycle of the product (International Council for Harmonisation Expert Working Group, 2009). The aim of this approach is ultimately to reduce process variation by improving manufacturing process understanding and implementing control strategies based on this improved process understanding (Jain, 2014).

The product lifecycle approach spans across the entire lifecycle of the product. The lifecycle of a product has different stages, beginning at product development, followed by marketing, and ending with product discontinuation (International Council for Harmonisation Expert Working Group, 2009). Figure 2.1 provides a graphical representation of the different stages in the lifecycle of a pharmaceutical product.

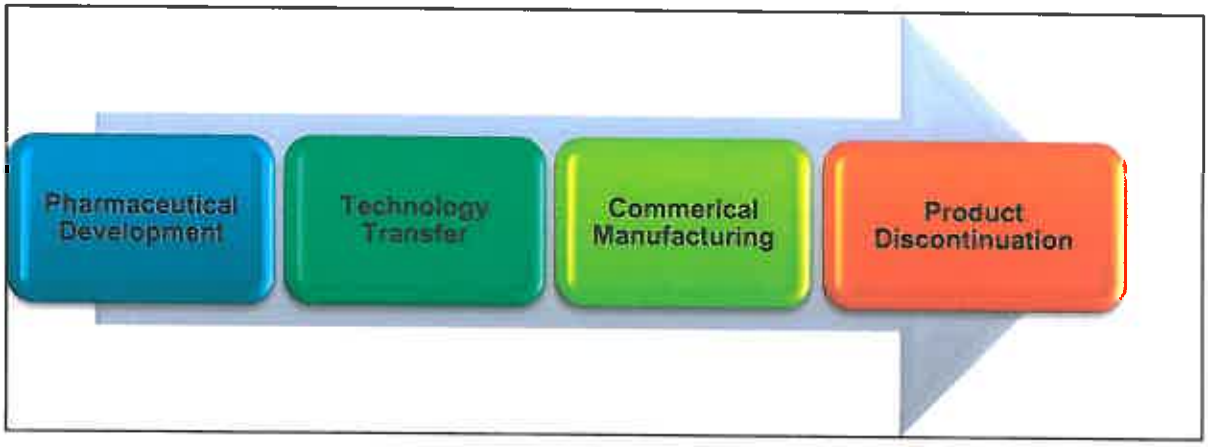

Figure 2.1: Stages in the product lifecycle approach (Adapted from International Council for Harmonisation Expert Working Group, 2008)

One of the primary objectives mentioned in the ICH Q10 model is continual improvement. Continuous improvement can be defined as an ongoing activity to improve the ability of a

product or process to fulfil the necessary requirements (International Council for Harmonisation Expert Working Group, 2008). When used as part of the lifecycle approach in the product quality system, the goals of continual improvement will change along with the lifecycle stage of the product. The ultimate goal, however, is to reduce and control variability by optimising processes, as this will result in increased product quality (Department of Health and Human Services U.S Food and Drug Administration, 2004; McConnell *et al.*, 2011). The ICH Q8 guidance document promotes the use of QbD for pharmaceutical development but also encourages implementation of this concept throughout the lifecycle of the product as product and processing understanding is updated over time (International Council for Harmonisation Expert Working Group, 2009).

The minimal requirements of a QbD approach for pharmaceutical development should include the following steps:

- Defining the quality target product profile (QTPP).
- Identification of the critical quality attributes (CQAs) for the drug product, determining the CQAs of the drug substance and excipients.
- Selecting a manufacturing process and determining the critical process parameters (CPPs) and critical material attributes (CMAs) by means of risk assessment.
- Establishing a design space and finally defining a control strategy.

(International Council for Harmonisation Expert Working Group, 2009)

The elements required for a QbD approach for development are illustrated in Figure 2.2 (Jain, 2014; Zhang and Mao, 2017; Yu *et al.*, 2014).

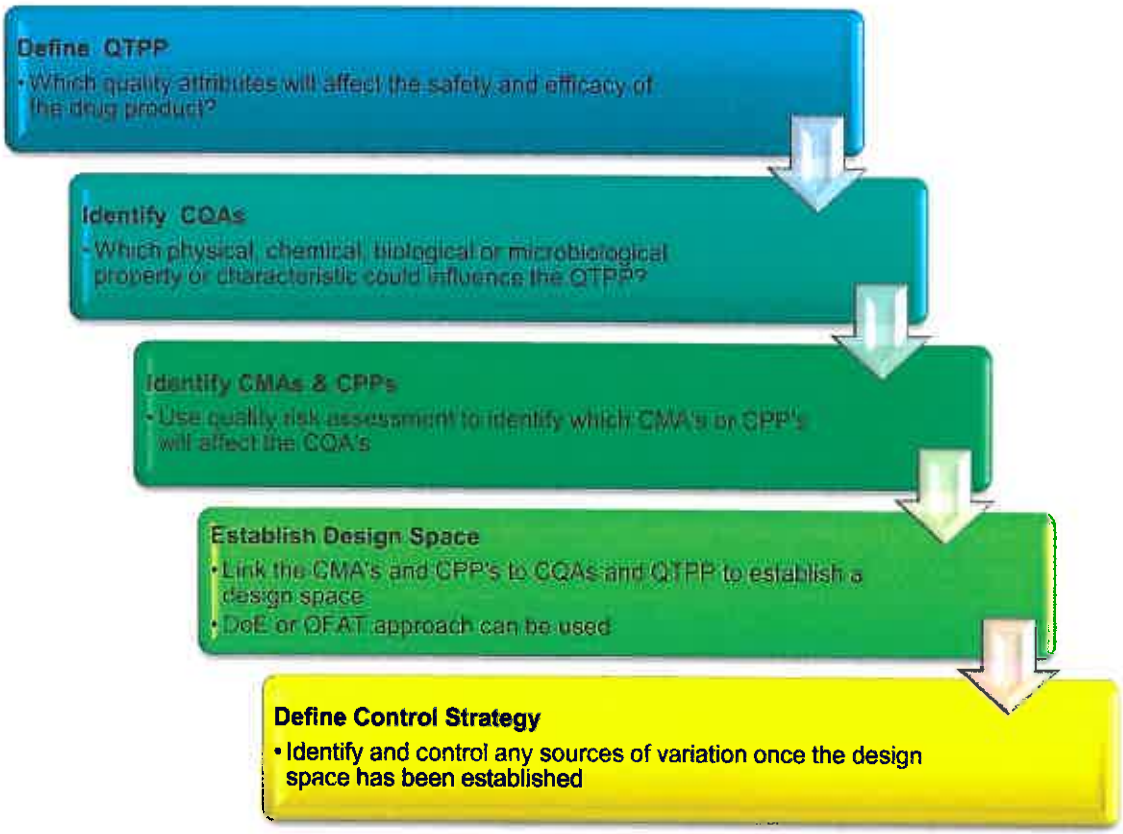

Figure 2.2: Elements required for a QbD approach (Adapted from Jain, 2014, Zhang and Mao, 2017, Yu *et al.*, 2014)

The first step when using a QbD approach for development is establishing the Quality Target Product Profile (QTPP) for the product. This refers to the quality characteristics which have the potential to affect the safety and efficacy of the product (Jain, 2014). The elements which are usually considered when determining the QTPP for a product are shown in Table 2.1 (United States Food and Drug Administration, 2012).

Table 2.1: QTPP elements (Adapted from United States Food and Drug Administration, 2012)

QTPP Element
Route of administration
Dosage form
Dosage strength
Dosage design
Pharmacokinetics
Stability
Drug product quality attributes
Container closure system
Administration/concurrence with labelling

Once the QTPP has been identified, the product's CQAs must be established. The ICH Q8 (2009) defines a CQA as a physical, chemical, biological, or microbiological characteristic that must fall within an appropriate limit range, or distribution to ensure that the product meets the desired quality standards (International Council for Harmonisation Expert Working Group, 2009). Product CQAs may be affected by certain process parameters or raw material attributes. If a physical, chemical, or microbiological property or attribute falls outside a pre-determined range or fails to meet desired limit or specification and has the potential to affect the purity, stability, strength, or release of the drug product, it is deemed to be a CQA (International Council for Harmonisation Expert Working Group, 2009; Potter, 2009). Purity, strength, stability and release are factors which affect the safety, efficacy and bioequivalence of a drug product (Department of Health and Human Services U.S Food and Drug Administration, 2004).

When a QbD approach is used for development, the expectation is that enhanced product and processing knowledge should be utilised to evaluate functional relationships between raw material attributes, processing parameters, and the product's CQAs. Risk assessment can help to identify areas where additional experimentation is required in order to fully understand which product or process parameters could affect the performance of a product (Hwang and Kowalski, 2005).

Design of Experiments (DoE) is an example of a formal experimental design that can be used in cases where additional experimentation is required (Hwang and Kowalski, 2005). Design of Experiments is a structured, organised method that can be used to determine the relationship between factors that may influence the product or process (International Council for Harmonisation Expert Working Group, 2009). An analysis of the data available for an existing product can give an indication of variability of raw materials, processes, or failure modes, and assist in establishing the design space for the product (Hwang and Kowalski, 2005).

Design space can be defined as the combination and interaction of material attributes and process parameters that have been proven to produce a product of the desired quality (International Council for Harmonisation Expert Working Group, 2009). Post-approval, any parameter adjustments outside of the registered design space would be considered to be a

change. In cases like these, a regulatory post-approval change process would need to be initiated in order to evaluate the effect the changes may have on product quality, safety, and efficacy (Yu *et al.*, 2014). When establishing a design space a one-factor-at-a-time (OFAT) or a DoE approach can be used. In an OFAT approach, only one factor is varied while all the other factors remain the same. The use of DoE makes it possible to evaluate a number of elements at the same time and uses statistical analysis to identify critical factors faster than when using a traditional OFAT approach (Jain, 2014). Another advantage of DoE compared to an OFAT approach is that it assists in identifying how different variables may jointly influence a response or process (Yu *et al.*, 2014). Application of multivariate statistical analysis and DoE can assist in identifying the optimal operating conditions, the critical material attributes (CMAs), and CPPs; thereby increasing process understanding. This ultimately results in establishing or optimising the design space of a particular process when applying QbD to a product or process (Yacoub *et al.*, 2011; Yu *et al.*, 2014).

Once the design space has been established, a suitable control strategy can be developed based on improved product understanding (Jain, 2014). A control strategy can be described as a planned set of controls which is based on current product and process understanding that assures process performance and product quality (International Council for Harmonisation Expert Working Group, 2008). It is important to note that design space is intended to evolve over time and throughout the product lifecycle as additional knowledge and information is generated. Together with a suitable control strategy, understanding the design space can reduce the focus on end product testing and increase process performance and robustness (Lepore and Spavins, 2008).

2.3 Implementation of a Quality by Design Approach to an Existing Product

The term 'legacy product' can be used interchangeably with 'existing product' and refers to a product which has already been commercialised. A commercialised product is an item which is manufactured for distribution within a specified market place. Manufacturing activities for existing products during the commercial manufacturing stage of the product lifecycle should be focussed on ensuring that product quality routinely meets the desired expectations and that process performance is suitable and well controlled. Areas of improvement should also be identified and evaluated using the risk assessment strategies outlined in the International Council for Harmonisation's Guideline on Quality Risk management (ICH Q9) (International Council for Harmonisation Expert Working Group, 2005). In this manner, knowledge

regarding the quality and performance of the commercialised product will continually be expanded.

The decision to apply a QbD approach to a legacy product involves less risk to the company because the product history is known, the business environment is established, the product is already approved and marketed, and it has an established regulatory history. In most companies there are also more opportunities to apply QbD to existing products as part of the continual improvement process to ultimately reduce variation, increase product quality, and improve process efficiency (Potter, 2009). Applying the strategies outlined in the ICH Q8 guideline to existing products has the benefit that manufacturing processes will be designed around realising the quality attributes of the drug product. This approach will enforce the concept of design of product quality versus testing of product quality with manufacturers having a better understanding of product and process performance. Testing of quality will still form part of the quality control system. However, when used in conjunction with QbD, it will be performed for verification purposes only (Yacoub *et al.*, 2011).

A paper entitled Product Quality Lifecycle Implementation (PQLI) Application of Science- and Risk-Based Approaches to existing products (Potter, 2009), proposed that QbD can be applied to existing products in the following sequence:

- Evaluation of QbD business case.
- Confirmation of the QTPP and CQAs.
- Identification of knowledge base.
- Development of product and process understanding.
- Understanding the design space.
- Development of the quality assurance strategy and finally evaluation of the project and business case.

The process flow for the implementation of a QbD approach to optimise a legacy product is outlined in Figure 2.3.

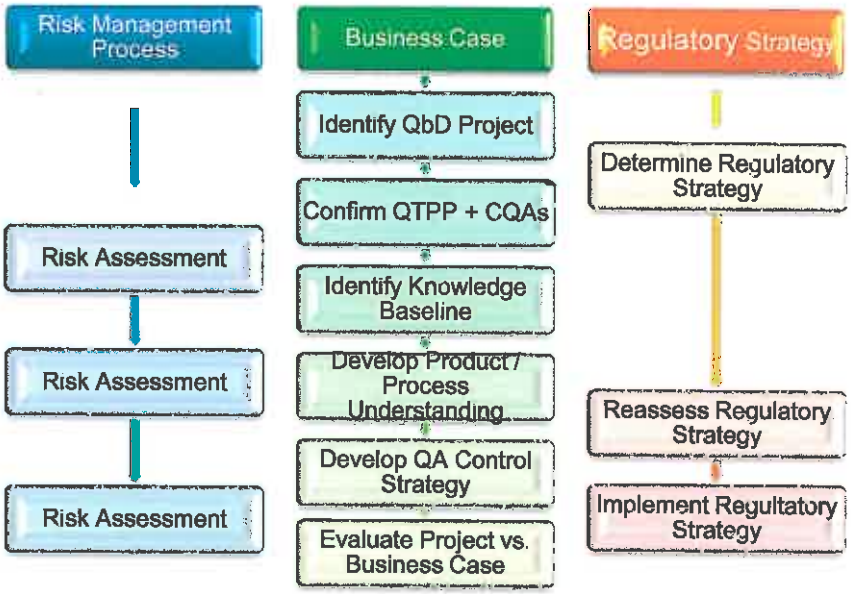

Figure 2.3: Process of applying QbD to an existing product (Adapted from Potter, 2009)

2.4 Evaluation of the Quality by Design Business Case

The first step is to evaluate the business case for the proposed change and determine whether there is value in proceeding with a QbD project. A business case summarises the costs, benefits, and the impact of the investment for the company (Maes *et al.*, 2014). At this initial stage, the regulatory strategy must also be determined along with the business case. Depending on the proposed change, a regulatory submission may or may not be required (Potter, 2009). Due to the fact that in this case, the product is an existing and marketed product, changes to the formulation or manufacturing process may require approval from the regulatory authority in the territory where the product is registered prior to being implemented. In South Africa, the Medicines Control Council (MCC) is the regulatory authority responsible for applying the standards that govern the manufacture, distribution, sale, as well as marketing of medicines as per the Medicines and Related Substances Act (Act 101 of 1965) (Medicines Control Council, 2017). The four different amendment types which are applicable to a product registered with the MCC are described in Table 2.2 (Medicines Control Council, 2012).

Table 2.2: Different amendment types in South Africa for products registered with the Medicine Control Council (Adapted from Medicines Control Council, 2012)

Amendment Type	Description
Type A	Can be implemented immediately without prior approval. The changes are unlikely to affect product quality and performance.
Type B	Prior notification must be submitted to the MCC 30 days before the intended date of implementation. The changes could have a significant effect on product quality and performance.
Type C	Prior approval is required from the MCC before implementation. The changes may have a significant effect on product quality and performance.
Type D	The amendments are considered new applications.

It is important to identify the type of post-approval change required as a result of the proposed QbD improvement project because this could impact the cost and complexity of the project. Different amendment types have different requirements in terms of the supporting data necessary to perform a regulatory submission. As a result, the regulatory strategy could potentially affect the business case. During an interview in 2015, Alicia Tébar of the International Society for Pharmaceutical Engineering (ISPE) Spain Steering Committee discussed how QbD could be applied to legacy products. In the interview she outlined the ranking system and methods used to choose which products need improvement. The main criteria used by her team to determine which product should be selected to undergo continuous improvement were: product quality, process performance, and manufacturing volume.

For the ranking system, aspects of product quality were evaluated and scored by considering the percentage of batches that were rejected during the evaluation period, as well as the percentage of deviations encountered during this time. The lower the percentage of non-conformance, the lower the final score. In addition, process performance (PpK) and process capability (CpK) indicators were used to evaluate product quality (Tébar, 2015). Process performance can be defined as a capability statistic that can be used to determine whether a process is capable of meeting specifications. This capability statistic takes the variation within subgroups into account and gives a better indication of how the process is performing at present. Process capability can be referred to as the potential capacity; it represents the potential of the process to produce a product that falls within the specification. Process capability is an important tool in evaluating key process performance and is usually used more commonly than PpK (Paret, 2012).

Using the ranking system described by the ISPE Steering Committee QbD team, the product quality process performance was evaluated by ranking PpK. The lower the PpK (less than 1), the higher the weighting, as a lower PpK value indicates a process that has room for improvement. Conversely, the higher the PpK value, the lower the score for process performance. Lastly, manufacturing volume was measured in millions of units per year with a higher score being given to higher manufacturing volumes. In order to identify the high-volume-low-quality candidates, risk scores for all of the priority factors were multiplied resulting in a final score. These numbers helped to determine high, medium, and low priority projects (Tébar, 2015).

In a practical setting, annual product reviews which capture release results for products could serve as a dataset which could use process capability or performance capability tools to determine whether the product is meeting the desired specifications and if the process is capable. The proposed method for selecting existing products that would be suitable to undergo a QbD improvement is a useful and practical way of identifying projects where the most value could be obtained by implementing a change (Potter, 2009).

This concept used by the ISPE Steering Committee QbD team to select products for continuous improvement is very much in line with the methodology employed for six-sigma programs (Tébar, 2015). Six-sigma is not a statistical system but uses statistics as a major tool for the analysis and interpretation of the data. The ultimate goal for six-sigma is to change the mind-set and culture of an organisation to create systems and processes that are as close to perfect as they are achievable, thus ensuring that they are functioning at the best possible performance levels (Jerbelid and Roan, 2009).

A survey to evaluate the business benefits of applying QbD revealed that companies that have applied elements of QbD have experienced a reduction in batch defects, a more robust manufacturing processes, reduced variability, an improved process capability, as well as reduced failures at batch release (Davis *et al.*, 2012) (Kourti and Davis, 2012). Compilation of a QbD submission for an existing product will take longer to compile. Considering this, fewer post-approval submissions would be required for any changes to the manufacturing process, provided those changes fall within the established design space. From a business point of view, an improved understanding of the product and process also enables more

flexibility to move the product between sites or changes to manufacturing scales (Potter, 2009).

2.5 Confirmation of the Pharmaceutical Target Product Profile and Critical Quality Attributes

Once the business case and regulatory strategy have been finalised, the QTPP must be reviewed. Once the QTTP for the product has been confirmed, the CQAs which are expected to affect safety and efficacy must be verified (Potter, 2009). Potential CQA's are selected based on the QTPP and prior knowledge (International Council for Harmonisation Expert Working Group, 2009). The review will usually conclude that the approved specification is appropriate due to the fact that the product is already being supplied to the market. Evaluation could provide opportunities to amend the current specifications by removing unnecessary tests, amending acceptance criteria, or facilitating improvements of analytical methods (Potter, 2009).

2.6 Identification of the Knowledge Baseline

Current product and process knowledge is assessed and the quality of the manufacturing process is evaluated. Product and process knowledge can be obtained from numerous sources. Some examples include: development and validation data; annual product reviews; batch release information; stability data; deviations, and; customer complaints. Evaluation of this data helps to determine which parameters are critical to achieve the product CQAs. A risk assessment should be performed to evaluate any gaps in the knowledge base of the product or process (Potter, 2009). According to the ICH Q9, a risk assessment can be described as the systematic process whereby available information related to the product or process is organised to support the risk decision. A risk assessment consists of the identification of hazards, as well as the analysis and evaluation of risks associated with exposure to those hazards (International Council for Harmonisation Expert Working Group, 2005). There are a number of recognised risk assessment tools within the pharmaceutical industry that can be used to determine criticality. Critical processing parameters or material attributes can directly or indirectly affect the product's quality, safety, or efficacy (Nosal and Schultz, 2008). The ICH Q9 lists some of the primary risk management tools which can be used to perform a risk analysis within the pharmaceutical industry. Examples of risk assessment tools include: Failure Mode Effects Analysis (FMEA); Failure Mode Effects and Criticality Analysis (FMECA); Fault Tree Analysis (FTA); Hazard Analysis and Critical Control

Points (HACCP); Hazard Operability Analysis (HAZOP); Preliminary Hazard Analysis (PHA) and Risk Ranking and Filtering. It is important to note that it is not always necessary to use a formal risk management process. The use of informal risk management tools such as risk ranking system whereby attributes are ranked as high, medium and low is also considered to be acceptable (International Council for Harmonisation Expert Working Group, 2005). The decision as to which risk management tool should be selected in order to perform the risk analysis will be dependent on each situation, the reason for performing the quality risk assessment, as well as the available information. Depending on the situation, the ICH advocates the use of quality risk management methods and the supporting statistical tools in combination if required (International Council for Harmonisation Expert Working Group, 2005). The availability of a large amount of data can assist in performing a more effective pharmaceutical risk assessment as there is a larger knowledge base from information can be gathered. Alicia Tébar of ISPE Spain cautioned that, although prior product and process knowledge is greater for legacy products than for a new product, greater knowledge could also make it challenging to identify gaps in knowledge (Tébar, 2015). Despite the fact that it could be difficult to identify knowledge gaps, the knowledge available regarding the product's process performance and quality for an existing product should be vast, which would be beneficial for a risk assessment.

2.7 Development of Product and Process Understanding

Once the knowledge base has been identified, product and process understanding must be developed. The risk assessment that is performed once the knowledge base has been established will highlight factors that require further investigation (Potter, 2009). In this step, gaps in knowledge or process understanding will be investigated by performing experiments to evaluate whether there are functional risks between parameters or attributes (Nosal and Schultz, 2008).

Design of experiments (DoE) and multivariate analysis are excellent tools to establish the design space for a product or process (Zhang and Mao, 2017). Design of experiments is an example of a multivariate mathematical approach that can be used to develop relationships between the CQAs and controlled process variables (Yacoub *et al.*, 2011). The objective for DoE is to gain a better understanding of the behaviour and process factors which may impact the CQA's of a product with the ultimate goal of developing a robust process which will not be affected by external sources of variability. Experiments conducted as part of a

DoE study have three primary aims. Firstly, they help to determine which controllable factors have the greatest influence on the response. Secondly, experiments help to identify which controllable variables are significant to ensure that the response is as close to the target value as possible. Lastly, the experiments help to determine the set points for the significant controllable variables to ensure that the effects of the uncontrollable factors on the response is minimal (Forooq *et al.*, 2016). A DoE approach is preferred to the traditional method of changing one factor at a time (OFAT). An OFAT approach requires a large number of experiments and also does not reveal interactions between factors (Korakianiti and Rekkas, 2011). Other multivariate approaches include response surface methodologies, process simulation, and pattern recognition tools; these approaches are intended for use in conjunction with knowledge management systems. By using these tools, critical product quality and performance attributes can be identified and this could assist in recognising potential failure modes and the resultant effect on product quality (Department of Health and Human Services U.S Food and Drug Administration, 2004). The steps shown in Figure 2.4 are usually required when planning DoE studies (Jain, 2014).

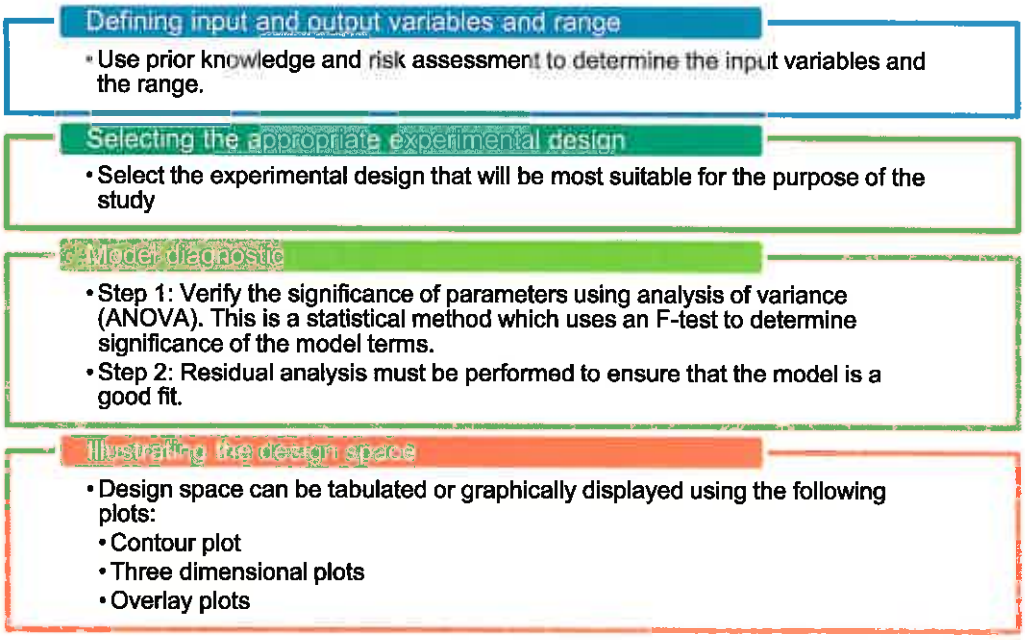

Figure 2.4: Basic steps involved in a DoE approach (Adapted from Jain, 2014)

A variety of user-friendly software packages are currently available. These can be used to conduct design of experiment studies and to understand multivariate models. Availability of these software packages makes it easier to perform studies to develop product and process understanding. The use of DoE studies are intended to generate sufficient data to establish a design space (Potter, 2009). Understanding the design space is extremely important as

operating within the design space will ensure that the product will meet the predefined quality standards (Sangshetti *et al.*, 2017). The experiments conducted to develop product and process understanding must aim to address knowledge gaps in the following areas (Jain, 2014):

- The design space must be clearly described and should include the critical material and process parameters.
- Any interactions between the material inputs and process parameters and their relationship between the CQAs will be understood.

Depending on the proposed change to a product or process, development of a design space is not always applicable when applying QbD principles to an existing product. The design space should be supported using historical product knowledge and must include quality risk management principles as well as experimental studies. The DoE study should support the design space. A suitable control strategy must be determined and must ensure that the process will remain within the limits of the design space for the product or process. A shift outside of the established design space may negatively affect product CQAs which could ultimately compromise the safely and efficacy of the finished product (Potter, 2009).

2.8 Development of a Control Strategy

A control strategy can be described as a planned set of controls that ensure process performance and product quality. According to the International Council for Harmonisation Expert Working Group (2008), controls usually include the following parameters and attributes:

- The active pharmaceutical ingredient, inactive pharmaceutical excipients, and components such as packaging materials.
- Facility and equipment operating conditions.
- In-process and finished product controls and specifications.

Once the product history review has been completed and product and process understanding has been determined, the product quality control strategy must be reviewed. An improved understanding of the product and process due to the previous activities already discussed could result in changes to the control strategy for the product (Potter, 2009). Depending on when drug development was performed, a minimal control strategy could

already be in place. When a minimal control strategy is in place, drug product quality is controlled mainly by intermediate or end-product testing. In an enhanced control strategy, drug product quality is ensured by using a risk-based control strategy or a product and process that is well understood (Davis *et al.*, 2008).

2.9 Evaluation of the Project and Business Case

Following approval of the regulatory submission and implementation of the proposed change, the outcome should be evaluated against the original business case in order to determine whether the QbD project was successful. This is an important activity as it could influence how future projects are undertaken (Potter, 2009). Management review is an important part of continual improvement of process performance and product quality, and it is therefore essential that this step be performed in the spirit of embracing an effective Pharmaceutical Quality Management System as outlined in the ICH Q10 (International Council for Harmonisation Expert Working Group, 2008).

2.10 Summary

Major changes have been observed in the pharmaceutical industry over the last three decades. This has resulted in increased demands on pharmaceutical manufacturers to improve product quality as well as process efficiency. There has also been a move away from the traditional QbT approach with companies being encouraged to build or design quality into their products and processes. The ICH Q8, Q9 and Q10 guidelines support a more holistic approach to quality management throughout the lifecycle of a product. Although QbD is encouraged in pharmaceutical development, it can and should also be applied to existing or legacy products as part of a continual improvement strategy. This is in line with the product lifecycle concept. Adoption of a more formalised approach when embarking on a QbD improvement project for an existing product described by Potter (2009) should be considered as it should facilitate better management of the process. With pressure to implement QbD for pharmaceutical development, it is only logical for regulatory authorities to consider formalising the implementation of a science- and risk-based approach to existing products to bring them in line with the current expectations. The ICH Q10 and Q9 have already paved the way for this change and in the future there will be no room for "satisfactory" manufacturing processes, regardless of where the product is in its lifecycle. Embracing continual improvement to produce the best quality product at a competitive price will be the difference between success and failure pharmaceutical industry going forward.

CHAPTER 3: METHODOLOGY

3.1 Introduction

In order to realise the aims and objectives of the study, the following stepwise approach developed by Potter (2009) was applied to Product X, which is an existing product manufactured by a Pharmaceutical Company based in Port Elizabeth:

Step 1: Evaluation of QbD Business Case

Step 2: Confirmation of the Pharmaceutical Quality Target Product Profile & Critical Quality Attributes

Step 3: Identification of Knowledge Baseline

Step 4: Application of Design of Experiments to Develop product or process understanding

Step 5: Development of a control strategy

Step 6: Evaluation of Project and Business Case

3.2 Evaluation of the Quality by Design Business Case

In order to evaluate the business case before deciding whether QbD should be applied to an existing product, the following factors must be considered: the reason for embarking on a product optimisation, product volumes, cost of development, and the regulatory implications of the development (Potter, 2009).

The data required to determine the business case was gathered by means of evaluating the historical data available for Product X. Product X is marketed in a number of different pack types (28's, 56's, 84's, and 100's) in both the private and state markets. The product volumes from 2014 to 2016 were obtained from the planning department. Product X is a problem product in both granulation and compression and is currently listed on the problem product forum at the manufacturing site. This forum highlights problem products where process or product optimisations are required. Product optimisation was outsourced to an offsite development facility where small scale trials were conducted in order to resolve the granulation and compression issues experienced with Product X. The formulation and

processing changes proposed by the outsource development facility were used as the basis to plan for subsequent QbD-related activities.

As part of the project initiation process prior to commencing with product optimisation, a quote must be generated. A project costing template is used within the company to calculate the estimated project costs for optimising an existing product. This template is a password protected Microsoft Excel spreadsheet that is adjusted according to the scope of the project. The costing template uses standard rates based on the cost of time spent for the relevant development activities such as: project management; formulation development; analytical activities; stability; raw materials and specifications; bioequivalence study (if applicable); regulatory support activities; cost of reference product or any project specific expenses, and; batch manufacturing costs including the cost of the active pharmaceutical ingredient. The development project costing template was used to generate a projected costing to optimise product X.

Due to the fact that Product X is a registered and marketed product within South Africa, the proposed changes will be submitted as an amendment to the current registered product dossier and will be supported by comparative *in-vitro* dissolution data.

3.3 Confirmation of the Pharmaceutical Quality Target Product Profile & Critical Quality Attributes

Following finalisation of the business case and regulatory strategy, the QTPP must be reviewed (Potter, 2009). The following data was reviewed in order to determine the QTPP for Product X: desired dosage form; dosage strength; dosage design; route of administration; pharmacokinetics; route of administration; stability; drug product quality attributes; container closure system; administration/concurrence with labelling, and; alternative methods of administration (United States Food and Drug Administration, 2012). Once the QTPP was established for Product X, the CQAs that were expected to have an effect on safety and efficacy were identified and verified.

The following quality attributes were considered for Product X: physical attributes; identification; assay (by means of high performance liquid chromatography (HPLC)); content

uniformity (by means of HPLC); dissolution (by means of UV/VIS absorption spectrophotometry); related substances (by means of HPLC); water content, and; microbial content. The quality attributes were selected for evaluation as they are included in the product release specification (Aspen Phamacare, 2016b). Table 3.1 and 3.2 describes the methodology and acceptance criteria for the physical quality attributes for Product X.

Table 3.1: Critical quality attribute characterisation methodology – physical attributes

Physical Testing of Product X		
Quality Attribute	**Methodology**	**Acceptance Criteria (Aspen Phamacare, 2016b)**
Appearance	Examine a suitable quantity of the sample against a white background in diffused light for physical defects to ensure that the sample meets the specifications (Aspen Pharmacare Group, 2013).	A white, round, flat tablet with bevelled edges, plain on one side and bisected on the other side.
Thickness	Select a sample size of 10 tablets randomly and measure the thickness of each tablet using a Vernier gauge (dial calliper) and determine the mean value (Aspen Pharmacare Group, 2014d; Aspen Phamacare, 2016b).	4.0 mm (3.6 to 4.4 mm).
Diameter	Select a sample size of 10 tablets randomly and measure the diameter of each tablet using a Vernier gauge (dial calliper) and determine the mean value (Aspen Pharmacare Group, 2014d; Aspen Phamacare, 2016b).	9.0 (8.6 to 9.5 mm).
Disintegration	Place 1 dosage unit in each of the 6 tubes of the basket. Suspend the basket assembly in a beaker containing purified water maintained at 37 °C ± 2 °C and operate the apparatus. The tablets pass the test if all 6 of the dosage units have disintegrated completely (Aspen Pharmacare Group, 2014b).	Not more than 15 minutes.
Friability	Take a sample of whole tablets as near as possible to 6.5 g (a minimum of 20 tablets must be used). Dedust the tablets using a soft brush to remove any loose dust before testing. Accurately weigh the sample and place the samples into the friability apparatus (M1). Rotate the drum 100 times at 25 rotations per minute (rpm) for 4 minutes. Remove the tablets from the friability apparatus, remove any loose dust from the tablets, and accurately weigh the sample again (M2). Percentage loss is calculated by subtracting the mass after rotation (M2) from the initial mass (M1) and dividing that difference by the initial mass. This result is multiplied by 100 so that it can be expressed as a percentage. (Aspen Pharmacare Group, 2014c).	Not more than 1% is lost after 4 minutes.

Table 3.2: Critical quality attribute characterisation methodology – physical attributes (continued)

Physical Testing of Product X continued		
Quality Attribute	**Methodology**	**Acceptance Criteria (Aspen Phamacare, 2016b)**
Hardness	Select a sample size of 10 tablets randomly and measure the hardness of each tablet using a suitable hardness tester and determine the mean value (Aspen Pharmacare Group, 2014d).	60 N (40 to 100 N).
Tablet Mass	Select a sample of 20 tablets at random and weigh in total on a suitable analytical balance (Aspen Pharmacare Group, 2014d).	277.0 mg (265.0 – 289.0 mg).
Uniformity of mass (UOM)	Weigh 20 units individually at random and determine the average mass. Average mass is calculated by adding all of the tablet masses and dividing the total mass by the number of units weighed. The 5 and 10% limits are calculated based on the average mass for the 20 units (Aspen Pharmacare Group, 2007).	Not more than 2/20 cores may deviate from the average mass by more than 5% and no tablet by more than 10%.
Sub-division	Take 30 tablets at random and break the tablets by hand. From all the parts obtained from 1 tablet, take part 1 for the test and reject the other part. Weigh each of the 30 parts individually and calculate the average mass (Aspen Phamacare, 2016b).	The tablets comply with the test if not more than 1 individual mass is outside the limits of 85% - 115% of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75% - 125% of the average mass.

A high level description of the methodology and acceptance criteria for the other quality attributes identified for Product X is shown in Table 3.3 – 3.5 below. Chemical testing is required in order to characterise each of these quality attributes.

Table 3.3: Critical quality attribute characterisation methodology – chemical testing

Chemical Testing of Product X		
Quality Attribute	**Methodology**	**Acceptance Criteria (Aspen Phamacare, 2016b)**
Identification	Identification A: High Performance Liquid Chromatography (HPLC) Procedure: Compare the retention times of the principal peak of the sample preparation in the Assay (HPLC) to that of Active X reference standard preparation (Aspen Phamacare, 2016b).	a. The retention time of the peak due to Active X in the chromatogram obtained with the sample solution corresponds to the retention time of the peak attributable to the active in the appropriate standard chromatogram.
	Identification B Infrared (IR) absorption spectrophotometry Procedure: Boil a quantity of powdered tablets containing 0.2 g of Active X with 15 ml of acetone. Filter the hot solution; wash the filtrate with two 5 ml quantities of hot acetone. Cool in an ice bath and evaporate the combined filtrates to dryness. Prepare the Potassium Bromide disc of the crystals. Determine the Infrared absorption spectrum of the crystals and compare with the reference spectrum of Active X (Aspen Phamacare, 2016b).	b. By Infrared (IR).
Water content Karl Fischer	Grind 20 tablets into a fine powder. Weigh and transfer 0.2 g of the powdered sample to a measuring scoop. Use a suitable Karl Fischer titrator in order to determine moisture content of the sample (Aspen Pharmacare Group, 2014a).	1.0 – 5.0% m/m
Assay	High Performance Liquid Chromatography (HPLC) Procedure: Separately inject 20 µl of blank (solvent), system suitability, standard solution, and sample solutions into the chromatographic system. Record the chromatograms at 230 nm and measure the peak responses. The retention time of Active X related compound A is about 9.8 and Active X is about 11.1 minutes (Aspen Phamacare, 2016b).	200.00 mg (190.00 to 210.00 mg)

Table 3.4: Critical quality attribute characterisation methodology – chemical testing (continued)

Chemical Testing of Product X continued		
Quality Attribute	**Methodology**	**Acceptance Criteria (Aspen Pharmacare, 2016b)**
Dissolution	Ultraviolet/visible (UV/VIS) absorption spectrophotometry Medium: 1 % Sodium Lauryl Sulphate (SLS) in water Volume: 900 ml Apparatus: USP II (Paddles) Speed: 75 rpm Temperature: 37.0 °C ± 0.5 °C Sampling point: 60 minutes (Aspen Pharmacare, 2016b). Procedure: Measure the absorbance of the standard solution (five replicates) and each sample's solution in a 1 cm cell at 288 nm using the dissolution medium as a reference.	Not less than 80% of active is released within 60 minutes (Q = 75%).
Uniformity of dosage units (weight variation)	High Performance Liquid Chromatography (HPLC) Procedure: Accurately weigh 10 tablets individually. Calculate the active substance content as a % of the label claim of each tablet from the weight (mass) of the individual tablets and the result of the assay. Calculate the acceptance values (Aspen Pharmacare, 2016b; Aspen Pharmacare Group, 2014f).	Acceptance value of the 10 units is less than or equal to L1% (L1 is 15).
Related Substances	High Performance Liquid Chromatography (HPLC) Procedure: Separately inject 20 µl of blank (solvent), placebo, system suitability solution, standard solution, and sample solutions into the chromatographic system. Record the chromatograms at 230 nm and measure the peak responses. Disregard the peaks due to the blank and placebo from the sample solution. Disregard any peak with an area less than 0.25 times the area of the peak due to Active X in the chromatogram obtained with the standard solution (0.05%). The retention times of Active X related compound A and Active X are about 9.2 and 10.5 minutes respectively (Aspen Pharmacare, 2016b).	Any individual impurity: Not more than 0.2%. Total impurities: Not more than 0.5%.

Table 3.5: Critical quality attribute characterisation methodology – chemical testing (continued)

Chemical Testing of Product X continued		
Quality Attribute	**Methodology**	**Acceptance Criteria (Aspen Phamacare, 2016b)**
Microbial Limits Total Viable Microbial Count: Bacteria Fungi Escherichia coli	Dilute Finished product sample 1: 10 using Casein Soya Bean Digest Broth. Dilute 1:100 using Casein Soya Bean Digest Broth if required: 1. Incubate sample at 30-35 °C for 18-24 hours and test for the specified microorganisms using specific incubation periods for each microorganism. Following incubation if colonies are suspected, perform a gram stain test followed by identification testing to confirm the identity of the microorganism. 2. Test Total Aerobic Microbial Count by incubating the samples at 30-35 °C for 3-5 days 3. Test Total Yeast and Mould Count by incubating the sample at 20 to 25 °C for 5 – 7 days (Aspen Pharmacare Group, 2014e).	Total Viable Microbial Count: Not more than 10^3 cfu/g. Bacteria: Not more than 10^2 cfu/g. Fungi: Absent. Escherichia coli: Absent.

For each of the quality attributes for Product X listed in Table 3.1 – 3.5 the following question was posed "Is this a CQA?". A yes or no response was reflected along with a justification for the response.

3.4 Identification of Knowledge Baseline

The product and process knowledge and the quality of the manufacturing process was evaluated for Product X. Product and process knowledge for Product X was obtained from development and validation data, the Product Quality Review Report for Product X, as well as the Pharmaceutical Development Report prepared by the outsource development (Alphamed Formulations PVT Ltd, 2015; Aspen Port Elizabeth Pty Ltd, 2015; Aspen Pharmacare Port Elizabeth Site, 2012).

As part of the quality system at the Port Elizabeth Manufacturing Site, a Product Quality Review Report is prepared for commercial products. The Product Quality Review is conducted over a 12 month period and consists of the following sections:

1. Description of the Product
2. Manufacturing Composition
3. Packaging Material and Packing Details

4. Flow Chart of Current Manufacturing Process and Packaging Flow
5. Number of Batches Manufactured, Batch Size and Yield
6. In-process Product Specifications and Results
7. Finished Product Specification and Results
8. Review of Changes
9. Stability Review
10. Deviations/Investigations/Out of Specification (OOS) review
11. Complaints/Returned Goods/Product Recalls Review/Corrective and Preventative Action (CAPA)
12. Rework/Rejected Batches
13. Review of Marketing Authorisation and Technical Agreement
14. Review of Qualification Status of Equipment/Utilities associated with the Product
15. Summary of Review and Conclusions
16. Recommendations and/or Corrective Actions
17. Report Approval and Authorisation

(Aspen Port Elizabeth Pty Ltd, 2015).

A review of the latest Product Quality Review Report available for Product X was conducted. Problematic areas where batches were rejected or failed to meet the requirements in terms of quality or performance were noted. Process capability (CpK) was calculated using the finished product batch release results for all of the batches of Product X manufactured during the review period. A CpK of 1.33 or more indicates that the process is capable and represents the potential of the process being able to produce a product which falls within the specification (Paret, 2012). Validation data for Product X was also reviewed and compared to the data available in the Product Quality Review Report.

Product X is manufactured by means of wet granulation using a high shear mixer granulator, followed by drying, screening, blending and finally compression. During the granulation process, fine or coarse particles are transformed into larger agglomerates which are called granules by mixing the dry powder blend with a granulating fluid which can be easily compressed (Bhanu, 2016; Shanmugam, 2015). The process flow and excipients used to manufacture Product X are shown in Figure 3.1.

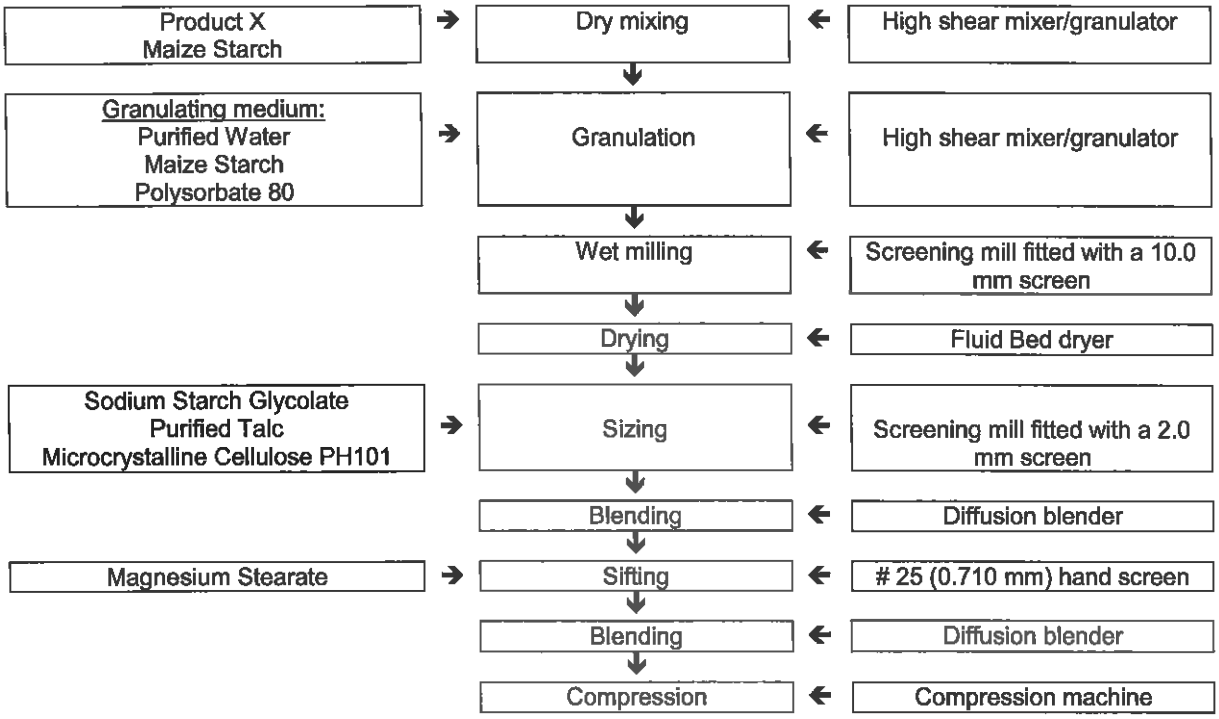

Figure 3.1: Manufacturing process flow for Product X

Based on the above information, a quality risk assessment was performed for Product X in order to identify the CMAs and CPPs. It is not always necessary to use a formal risk management process, and the use of informal risk management tools is also considered to be acceptable according the ICH Q9 Quality Risk Management guideline (International Council for Harmonisation Expert Working Group, 2005). Material attributes and manufacturing process parameters were assessed using a quantitative risk ranking system in order to determine which material attributes and process parameters could influence the CQAs identified for Product X. Attributes were ranked as either high, medium, or low risk. In instances where an attribute's risk is categorised as high or medium, the risk will be reduced by means of an appropriate control strategy. Low risk attributes were considered to be acceptable and required no further investigation (United States Food and Drug Administration, 2012).

The Quality Risk Assessment evaluated the following areas: the material attributes for the Active Pharmaceutical Ingredient (API), the material attributes for the Inactive Pharmaceutical Ingredients (IPIs), and the manufacturing process parameters. Evaluation of this data assisted in determining which parameters are deemed to be critical in achieving the CQAs to ensure that Product X meets the required quality, safety, and efficacy standard. In

addition, the risk assessment is an important tool in identifying any gaps in the knowledge base of the product or process (Potter, 2009). Table 3.6 provides an overview of the risk ranking system used to evaluate and determine which material attributes and process parameters are deemed to be critical.

Table 3.6: Ranking system (Adapted from United States Food and Drug Administration, 2012)

Risk Ranking	Description
Low risk	No impact on product CQA – risk is acceptable and no further action is required.
Medium risk	Known or potential impact on the product CQA but the current in-process and release specifications or controls mitigate the risk.
High risk	Known or potential impact on the product CQA and warrants further investigation to reduce risk.

3.5 Application of Design of Experiments (DoE)

Once the knowledge base has been identified and the risk assessment has been completed, product and process understanding must be developed (Potter, 2009).

Prior to the manufacture of the DoE batches, small scale trial batches were manufactured to investigate an order of addition change to the microcrystalline cellulose from the extra-granular phase to the intra-granular phase which was proposed by the outsource development site (Alphamed Formulations PVT Ltd, 2015). In addition, the inclusion of colloidal silicone dioxide was evaluated in order to improve granule flow and thus compression performance. On completion of these trials the formulation was finalised. Based on the risk assessment that was performed for Product X, factors that required further investigation were highlighted. Missing or additional information was generated by performing studies using DoE and multivariate analysis. The statistical software package Minitab® Version 17.0 (Minitab Inc., United Kingdom) was used to conduct design of experiment studies for Product X.

3.5.1 Materials

The raw materials which were utilised in the DoE studies are shown in Table 3.7. The formulation remained constant for all of the DoE batches based on the outcome of the risk assessment and therefore the quantities per tablet of each raw material have not been included in Table 3.7. Only processing variables and their impact on the CQAs for Product X were evaluated as part of this study.

Table 3.7: Raw Materials and Suppliers used to manufacture Product X

Raw Material	Raw Material Supplier
Active X	Amoli Organics Pvt Ltd, India
Maize Starch	Roquette, Spain
Microcrystalline Cellulose	Gujarat Microwax PVT Ltd, India
Polysorbate 80	Croda, Singapore
Purified Water	N/A
Sodium Starch Glycolate	Amishi Drugs and Chemicals Pvt Ltd, India
Magnesium Stearate	FACI S.p.A Spain
Purified Talc	Imery's Talc, Italy
Colloidal Silicone Dioxide (Aerosil 200)	Evonik Industries, Germany

3.5.2 Methods

Manufacture of the DoE batches was performed on a 10 L scale, using equipment which has similar operation principles as the equipment used for commercial batch manufacture. A batch size of 8000 tablets was used for each DoE batch.

The raw materials dispensed for each DoE batch were weighed (Mettler Toledo Balance SR 3200, Switzerland) as per the experimental trial batch plan. All of the batches were manufactured using a 10 L bottom driven high shear mixer/granulator (Rapid Mixer & Wet Granulator; Model number: RMG 10 LTR; India). The granulating medium was prepared by mixing the purified water and polysorbate by hand using a spatula. Once the polysorbate was dissolved, the maize starch that is used as part of the granulating medium, was added to the polysorbate-water dispersion and mixed. Boiling water was added to the polysorbate-starch slurry to form a starch paste, adding cold water to thin the paste out following activation of the starch. Dry mixing and granulation of Active X, maize starch, and microcrystalline cellulose using the granulating medium (starch paste & polysorbate 80) was performed in the high shear mixer/granulator. The granules were wet milled using a screening mill fitted with a 10.0 mm screen set at 200 rpm (Quadro Co-Mill; Model Number 197; Canada) and dried in a fluid bed dryer (Retsch Fluid Bed Dryer: Model Number TG100; Germany) set at 75 °C until a moisture content (loss on drying) of 1.0 to 2.0 % was achieved. The dried granule, purifed talc, collodial silicone dioxide and sodium starch glycolate was dry milled using a screening milled fitted with a 2.0 mm screen set at 300 rpm (Quadro Co-Mill; Model Number 197; Canada). The screened granule and extra-granular material were blended using a diffusion blender (IMA Pharma Canguro Turbula Bin; Model Number: J50; Italy) for 10 minutes at 11 rpm. The lubricant, magnesium stearate, was

screened through a size 20-mesh hand screen, added to the granules, and blended for 5 minutes at 11 rpm. The final blend was compressed into tablets using a Korsch XL 100 Pro Compression Machine (Korsch AG; Model number: K1510247; Germany). The following compression tooling was used to compress the lubricated granule: top punch: 9.0 mm round, flat, bevelled, bisected; bottom punch: 9.0 mm round, flat, bevelled, and; die: 9.0 mm round (Eliza-Tool, India).

3.5.3 Screening Trial

The factors which required further evaluation were identified by means of the risk assessment. A screening trial was performed to assess the following factors:

- Dosing impeller speed in granulation ranging from 80 rpm to 120 rpm.
- Dosing time in granulation ranging from 300 to 420 seconds. Dosing time includes the total time to dose the starch paste (16 ml polysorbate 80, 122.36 g starch maize, 975 ml purified water), as well as a set quantity of additional purified water (100 ml).
- Wet mix time in granulation ranging from 60 to 120 seconds.
- Feeder speed in compression ranging between 20 rpm and 50 rpm, which equates to 66.7 % to 166.7 % of turret speed (similar to speeds employed for the currently registered product).

A 2-level full factorial design with centre point was chosen to assess how each individual factor affected the responses, based on the assumption that the factors may have a linear relationship with the responses. Based on the number of factors which were required to be evaluated, a fractional factorial design (1/2 factorial with 1 centre point) could have resulted in a study design resolution of IV. A study with a resolution of IV could have resulted in the main effects not being aliased with two way interactions. Higher resolution designs are usually preferred to lower resolution designs, but usually require more experimental conditions (Collins *et al.*, 2009). Minitab® statistical software package version 17.0 (Minitab Inc., United Kingdom) was used to for the statistical designs and analysis. In order to perform a full factorial design with a centre point a total of 17 batches were required. The use of a fractional factorial design would have required 9 batches to be manufactured with the resultant study design having a low resolution. After comparing the number of batches required and taking the study resolution into account, the decision was made to select a full factorial design. The 17 experimental runs were randomised to prevent bias. The screening trial study design is shown below in Table 3.8.

Table 3.8: Screening trial study design

Run Order	Dosing impeller speed (rpm)	Dosing time (seconds)	Wet mix time (seconds)	Feeder speed (rpm)
1	80	300 (240 + 60)	60	50
2	120	420 (300 + 120)	120	20
3	120	300 (240 + 60)	120	20
4	100	360 (300 + 60)	90	35
5	120	300 (240 + 60)	120	50
6	80	420 (300 + 120)	60	20
7	120	300 (240 + 60)	60	20
8	120	420 (300 + 120)	60	50
9	120	420 (300 + 120)	120	50
10	120	300 (240 + 60)	60	50
11	120	420 (300 + 120)	60	20
12	80	420 (300 + 120)	120	50
13	80	300 (240 + 60)	120	50
14	80	420 (300 + 120)	120	20
15	80	300 (240 + 60)	60	20
16	80	420 (300 + 120)	60	50
17	80	300 (240 + 60)	120	20

Processing parameters that were not identified as being critical remained constant for all the batches. The details of the process parameter setting used for screening trial batch manufacture are described in Table 3.9.

Table 3.9: Process parameter settings for the screening stability batches

Processing steps	Settings
Dry mix	
Impeller speed	100 rpm
Chopper speed	500 rpm
Time	10 minutes
Dosing	
Impeller speed	As per experimental design in Table 3.5
Chopper speed	2500 rpm
Time	As per experimental design in Table 3.5
Wet mix	
Impeller speed	100 rpm
Chopper speed	2500 rpm
Time	As per experimental design in Table 3.5
Wet milling	
Screen size	10.0 mm
Speed	200 rpm
Drying	
Inlet temperature	75 °C
LOD	1.0 – 2.0%
Dry milling	
Screen size	2.0 mm, round hole
Speed	300 rpm
Blending	
Time	10 minutes + 5 minutes (with magnesium stearate)
Speed	11 rpm
Compression	
Feeder speed	As per experimental design in Table 1
In-process Control (IPC)	Average tablet mass: 277.0 mg (265.0 – 289.0 mg)
	Target tablet hardness: ± 90 N
	Friability: not more than 1.0% after 4 minutes
	Disintegration: not more than 15 minutes

The registered specification for tablet hardness for Product X is 60 N (40 – 100 N). However, an average hardness of approximately 90 N was targeted in order to maintain satisfactory friability results at a 10 L scale. The responses, which were monitored for the screening trial batches, are shown in Table 3.10.

Table 3.10: Responses monitored during screening trial batches

Processing Stage	Monitored Response
Granulation	Torque after wet mix (Amps)
Dry milling & Blending	LOD after lubrication (% m/m)
	Granule flow
	Bulk density (g/ml)
	Tap density (g/ml) – not considered for experimental analysis as it is used in the Hausner ratio and Carr index calculations
	Hausner Ratio
	Carr Index
	Particle size distribution % greater than 0.105 mm % less than 0.105 mm
Compression	Fill depth (mm)
	Compaction force (kN)
	Average % RSD compaction force (in automatic mode)
	Ejection force (N)
	% RSD of tablet mass
	Average tablet thickness (mm)
	Disintegration (s) – not considered for experimental analysis as the tablet typically disintegrates within 30 s.
	Dissolution % active X released after 15 minutes

Torque measures the load on the impeller and is influenced by granule properties (Gokhale and Triveli, 2010). Measuring torque following wet mixing is a means of measuring the granulation end-point (Sakr *et al.*, 2012).

Loss on Drying (LOD) after lubrication was measured using a Moisture Analyser (Mettler Toledo HB43-S, Switzerland). A granule sample of 100 g was placed into the heating pan, weighed, and heated to a temperature of 105 °C with the drying timer set to the automatic switch-off function (2 mg/30 seconds). The moisture content in the lubricated sample was calculated by determining the percentage of the difference in the initial weight less the final weight. The difference is expressed as a percentage of the initial weight (Aspen Phamacare, 2015b).

There are a number of different methods that can be used to measure powder flow. Bulk and tap density are examples of two compendial methods which were used to evaluate the powder flow properties of Product X (Shah *et al.*, 2008). After blending and prior to compression, a 100 g sample of the lubricated granule was placed into a pre-weighed dry

graduated 250 ml cylinder. The mass of the sample was weighed (M) and the volume of powder was read to the closest graduated unit (V_0). The bulk density, measured in g/ml, was calculated by dividing the mass of the test samples (M) by the volume (V_0). The tapped density was calculated by measuring the bulk volume after manually tapping the cylinder using a mechanical tester (Electrolab Tap Density Tester, Boksburg, South Africa) at a nominal rate of 250 taps per minute (USP Method II) on a flat table top surface (United States Pharmacopeial Convention, 2017). The measured bulk and tapped densities were used to calculate the Carr's compressibility index (CI) and the Hausner ratio using the following two equations:

Where:

V_0 = unsettled apparent volume
V_F = final tapped volume

$$100(V_0-V_F)/V_0$$

Equation 3.1: Compressibility Index (United States Pharmacopeial Convention, 2017)

$$V_0/V_F$$

Equation 3.2: Hausner Ratio (United States Pharmacopeial Convention, 2017)

The results obtained provided an indication of the compressibility and flow properties of the lubricated Product X granule. The Carr's compressibility index measures bridge strength and stability of a powder, where powder flowability prediction is based on densities (Crouter and Briens, 2014). Although the Hausner ratio is also used to predict granule flow, it measures inter-particulate friction which provides an indication of the powder cohesiveness (Crouter and Briens, 2014; Shah *et al.*, 2008). Lower Hausner or Carr's compressibility ratios indicate better flow properties than higher ones. Table 3.11 provides guidance on how to interpret Carr's CI and Hausner ratios (Shah *et al.*, 2008).

Table 3.11: Interpretation of Carr's Compression Index and Hausner Ratio's (Adapted from Shat *et al.*, 2008)

Carr's Compressibility Index	Hausner Ratio	Interpretation
Less than 10	Less than 1.11	Excellent flow
11–15	1.12–1.18	Good flow
16–20	1.19–1.25	Fair flow
21–25	1.26–1.34	Passable flow
26–31	1.35–1.45	Poor flow
32–37	1.46–1.59	Very poor flow
More than 38	More than 1.60	Very very poor flow

In addition to measuring bulk and tap density, the granule flowability was determined using a Flowdex™ flow meter (Hanson Research Chatsworth, CA, United States of America). A 50 g powder sample of Product X was passed through the instrument in order to assess the powder's ability to fall freely through disks with different sized holes (Teledyne Hanson Research, 2017). The test was repeated until the powder could no longer pass through the hole in the disk. At this point, the size of the hole that the powder previously passed through is recorded.

Based on historical data obtained from development and validation batches, the majority of particles were usually less than 0.105 mm in size (Aspen Pharmacare Port Elizabeth Site, 2012). In order to evaluate this response, particle size was separated into material where the average percentage of particles was greater than 0.105 mm in size, and material where the average percentage of particles was less than 0.105 mm. Particle size distribution was evaluated by performing sieve analysis using the United States Pharmacopeial (USP) dry sieving method with mechanical agitation (United States Pharmacopeia, 2017).

A number of responses were evaluated in compression. The parameters shown in Table 3.11 are all responses that are displayed on the control screen of the compression machine. Fill depth determines the tablet mass and was evaluated because uniformity of mass violations have been experienced with the existing product. Compaction force determines the tablet thickness, which is linked to tablet hardness. Tablet hardness can influence dissolution performance. The amount of variation in tablet mass as well as the compaction force was also evaluated in order to determine how much variation was present during tablet compression.

The main effects and interactions were assessed using analysis of variance (ANOVA) in order to evaluate the effect the identified factors had on the monitored responses. The probability value (p value) was set at 0.05, which means that a value below 0.05 has strong evidence against the null hypothesis (Rowe, 2007). The null hypothesis for this study was that the factors have no statically significant impact on the monitored responses. The linearity of the model was also analysed using ANOVA with the p-value set at 0.05. A p-value below 0.05 indicates non-linearity of the relationship between the investigated factors and the monitored responses. The suitability of the model in terms of how well it fits the data were evaluated using the R^2 statistical measure. For example, an R^2 value which is close to 100% would indicate that the model is a good fit for the data. It must however be noted that,

even in the presence of a low R^2 value, it is still possible to draw conclusions on how changes in the factors may impact the measured responses if there are statistically significant predictors present (Frost, 2013).

3.5.4 Pivotal Study

Once the significant factors were identified following the outcome of the screening trial, a pivotal study was conducted. A surface response methodology approach with a central composite design (CCD) was used in order to establish or verify a design space for the significant factors identified for Product X. The reason for selecting a CCD was due to the fact that non-linear relationship was observed for some of the factors investigated. A full CCD model was used to confirm the relationship between the factors and the monitored responses. The same batch size of 8000 tablets employing the same equipment used for the screening trial was used in order to manufacture 20 batches. The factors and levels which were investigated are shown in Table 3.12.

Table 3.12: Factors and the levels investigated

Factors	Units	Factor Level				
		-α	-1	0	1	+α
Dosing impeller speed	Rpm	66	80	100	120	134
Wet mix time	seconds	40	60	90	120	140
Feeder speed	Rpm	18	25	35	45	52

The experimental design that was used for the pivotal trials is shown below in Table 3.13. Processing parameters that were not investigated were set to a predetermined value. As with the screening trial, the pivotal trial batches were randomised to prevent bias. Data was analysed using ANOVA with the p-value set at 0.05.

Table 3.13: Pivotal trial experimental design

Run Order	Dosing Impeller speed	Wet mix Time	Feeder Speed
Units	rpm	seconds	rpm
1	120	60	25
2	100	90	35
3	100	90	35
4	66	90	35
5	80	60	45
6	80	60	25
7	134	90	35
8	120	120	25
9	120	120	45
10	100	90	35
11	100	140	35
12	80	120	25
13	100	90	52
14	120	60	45
15	100	90	35
16	100	90	18
17	100	90	35
18	100	40	35
19	80	120	45
20	100	90	35

3.5.5 Verification

Following the pivotal study, a follow-up experiment using the "best" processing parameters is required in order to confirm the optimisation results and verify the design model and its predictive capability (Minitab, 2005).

Based on the outcome of the pivotal studies, significant factors on the measured responses were identified. The results optimiser function in Minitab was used to predict the optimal parameters for these significant factors in order to achieve a 95 % confidence interval for the measured response. These parameters were used to manufacture a 10 L verification batch. Processing parameters that were not being investigated were set to a predetermined value.

3.6 Development of a Control Strategy

Following the outcome of the DoE studies, the quality risk assessment was reviewed and, where required, the product control strategy was adjusted (Potter, 2009). During this stage, the same risk ranking system that was used to determine the knowledge baseline in Section 3.3 was employed.

3.7 Evaluation of the Project and Business Case

Following the adjustment of the control strategy for Product X, the original business case was evaluated in order to determine whether the QbD project was successful (Potter, 2009). The business case was evaluated by: determining whether an optimised product or process was achieved by applying a QbD approach; comparing the control strategies between the QbD and traditional development approach; comparing the theoretical development cost to optimise the process versus the actual time spent on the QbD-related activities, and; by calculating the projected payback period required to recoup the costs of the development spend.

3.7.1 Determining whether the application of QbD resulted in an optimised product or process

In order to evaluate whether the application of QbD resulted in an optimised product or process, the over-granulation and compression issues encountered with this product must have been resolved. Over-granulation will be evaluated by visually inspecting the granule following fluid addition and wet mixing. No tablet defects should be observed during compression. In addition, the lubricated granule should demonstrate flow of properties that are similar or better when compared to the product reformulated using a traditional approach, and better than that of the current product where no process or formulation changes have been implemented. Powder flow will be evaluated by measuring the bulk and tap density of the granule prior to compression and calculating the Hausner ratio and Carr Index using the same methodology described in Section 3.5.3.

3.7.2 Comparison of the control strategies between the QbD and traditional development approaches

In order to determine whether the application of QbD resulted in a change in the control strategy when compared to a traditional approach, the control strategies were evaluated by

comparing each step in the manufacturing process. The control strategies proposed by each approach for the various manufacturing stages were compared to each other and any differences were noted. Where differences were found, a discussion regarding the reason for these differences was included.

3.7.3 Determining the actual cost of the QbD activities

The development project costing template was used to generate a projected costing that includes QbD-related activities. For the purposes of this activity, QbD-related activities involved the time spent manufacturing the screening and pivotal batches, material costs for laboratory scale batch manufacture, and any analytical costs related to analysis of the QbD batches. Each development project at the site is allocated its own unique project number. The man hours spent on each product are logged by the employees using an electronic timesheet system. This system is used to ensure that the employee's labour costs are charged to the specific project and are captured in the total project cost. The costing template used to generate the original project quote takes the labour costs of the persons involved in the DoE batch manufacture into account. Table 3.14 shows a breakdown of the activities, personnel, and budgeted time for QbD activities used to generate the project quote.

Table 3.14: Hours and cost of QbD activities in unit activity costing model

Activity	Personnel	Hours allocated for activity
Production control sheet	Formulation Scientist	60
Dispensing	Warehouse Co-ordinator	90
Manufacture	Formulation Development Laboratory (FDL) Team Leader	30
Manufacture	Operator	480
Manufacture	Formulation Scientist	480
Review meetings	Formulation Scientist	10
QbD report	Formulation Scientist	240
QbD report	Regulatory Support Pharmacist	4
Cost		R 25,795.09

The allocated hours for each activity are multiplied by the standard hourly remuneration rate for each employee. A retrospective review of time spent by the employees involved in DoE batch manufacture was conducted by reviewing the actual time logged. The cost per hour of labour for the formulation scientist, warehouse co-ordinator, formulation development laboratory team leader, and the formulation development operators was multiplied by the

time per activity to determine the actual cost of the QbD batch manufacture in terms of labour. The actual cost of the time spent manufacturing the QbD batches was compared to the theoretical time and cost that was used to calculate the original project quote.

3.7.4 Calculating the projected Return on Investment (ROI) and payback period

In order to support the business case to optimise Product X, it is important to understand the profit margins for Product X. If the profit margins are low, the development spent would not be justified. The total revenue as well as the cost of sales for Product X for the 2018 financial year was requested from the company's finance department. The finance department provided the total number of units required to satisfy market demand, projected sales income, as well as the cost of sales. Nett profit was calculated by subtracting the cost of sales from the total sales in order to determine the projected net profit for the 2018 financial year.

The ROI was calculated for the estimated development cost based on the original project quote. In addition, ROI was calculated for the development costs which included the actual cost of time spent on QbD-related activities. The projected return on investment was calculated using Equation 3.3.

$$\text{ROI:} \qquad \frac{\text{Profit} - \text{Development Cost}}{\text{Development Cost}} \times 100\ \%$$

Equation 3.3: Return on Investment

The projected payback period was determined by measuring the time taken to pay back the cost of the development based of the product profit (Burke, 2013). The payback period was calculated for both the estimated and actual development costs. Equation 3.4 was used to determine the payback period for original development cost, where time spent on QbD-related activities was estimated.

$$\text{Payback Period} = \frac{\text{Development Project Cost}}{\text{Profit}}$$

Equation 3.4: Projected payback period

In addition to calculating the payback period for the theoretical development cost as per the original development quote (including QbD activities), the payback period based on the time actually spent on QbD-related activities was calculated using the same equation.

3.8 Ethical considerations

The research did not involve any human and/or animal subjects. As a result ethical clearance was not required.

CHAPTER 4 – RESULTS AND DISCUSSION

4.1 Evaluation of the Quality by Design Business Case

The following areas were considered when evaluating the QbD business case: the reason for embarking on the product optimisation, product volumes, cost of the development, and the regulatory implications.

4.1.1 Reason for embarking on the Product Optimisation

The Port Elizabeth manufacturing facility has a problem product forum where different departments have the opportunity to discuss products which are problematic at the site. Product X has been highlighted for optimisation via the Problem Product Forum. Although the manufacturing process for Product X was validated in September 2011, some batches manufactured in subsequent production campaigns have experienced problems in both the granulation as well as compression stages of manufacture. At irregular occurrences, certain production batches were over-granulated whilst using the validated recipe for granulation. Over-granulation led operators to manually intervene during the wet mixing process in order to produce an acceptable granule. While the batches could be salvaged and dried using the validated drying process, problems in compression were noted on both over-granulated and normal production batches. These included problems such as poor granule flow, capping of tablets, and poor hardness control. The product was selected for optimisation in order to resolve the granulation and compression issues

4.1.2 Review of Product Volumes

The product volumes for the last three years were obtained from the planning department. The current commercial batch size for Product X is 1,000,000 tablets. The average number of batches from 2014 to 2016 required to satisfy commercial demand required per annum is shown in Table 4.1.

Table 4. 1: Commercial Volume for Product X from 2014 to 2016

Year	Number of Batches Required
2014	72
2015	80
2016	104

Issues experienced in granulation and compression have resulted in batch write-offs and inefficiency in terms of compression machine output. Based on the number of batches per annum in 2014 to 2016, and problems currently experienced when manufacturing Product X, product optimisation is warranted based on the market demand.

4.1.3 Cost of the Development

The development department's unit activity cost model was used to generate a project costing to optimise Product X. The development project quote was circulated for review and approval with the other formal project initiation documents required in order to formally initiate a product optimisation or reformulation. Development activities for Product X only commenced once project approval was received from the company's head office. A breakdown of the estimated costs required to optimise Product X is shown in Table 4.2.

Table 4.2: Breakdown of costs associated with Optimising Product X

Activity	Cost in ZAR
Project initiation and management	129 452.07
Stability management	31 605.43
Analytical	809 932.93
Formulation	76 795.09
Regulatory support	45 070.10
Raw material evaluation & specification and methods of analysis	33 734.44
Overheads	292 913.41
API cost	549 248.58
Production scale batch manufacture costs	616 331.88
10 % contingency	258 508.39
TOTAL PROJECT COST + 10 % contingency	**2 843 592.31**

The project quote did not include development activities conducted at the outsource development facility. It only includes development-related activities which were required at the Port Elizabeth manufacturing site.

4.1.4 Regulatory Implications

Product X is a registered product and therefore the changes proposed in order to optimise this product will need to be submitted to the South African Medicines Control Council and receive approval prior to implementation. In addition to the formulation and process optimisation, an analytical upgrade was also proposed as part of this project in order to bring

the product in line with the latest pharmacopeial monographs. The proposed changes as well as the expected amendment type associated with the changes are shown in Table 4.3.

Table 4.3: Expected amendments related to the optimisation of Product X (Adapted from Medicines Control Council, 2012)

Proposed Change	Type of Amendment
Change in order of addition of pharmaceutical ingredients with the same processing principles and same final product specifications.	A15
Change in Maize Starch from food grade material to Pharma grade material. Replacement of IPI with a comparable IPI.	B8
Granulation solution change greater than 20 % of the original stated granulating solution. Increase is more than allowed for Type A or B changes for immediate release solid oral dosage forms.	C1
Change in process timing and/or operating speeds, but same final product specifications and content uniformity. Change in equipment or process machinery, but with same processing principles.	B5
Final product specification and method for Related Substances upgraded to the latest Pharmacopeial specification but to a less stringent limit.	C4
Addition of an IPI to the formulation.	C1
Batch size change of less than 10 x the registered batch size.	B7

The regulatory submission strategy to support the proposed changes is as follows:

- Reference Product: Commercially manufactured Product X Tablets will be used as the reference product for this product optimisation.
- Proof of efficacy: According to the amendments guidance, proof of efficacy is required to support the proposed amendments (Medicines Control Council, 2012). A bioequivalence study is included in the currently registered dossier and *in-vitro* multi-point, multi-media dissolution testing will be used to support the above-mentioned post-approval changes (Medicines Control Council, 2015).
- Number of batches required for submission purposes

  Only one batch manufactured at a production scale batch size is required at the time of submission to support of the proposed amendments. Three months stability data at 25 °C ± 2 °C/60 % RH ± 5 % and 40 °C ± 2 °C/75 % RH ± 5 % must be submitted with a commitment that the trial will continue until the product reaches its shelf life (Medicines Control Council, 2012).

4.2 Confirmation of the Pharmaceutical Quality Target Product Profile & Critical Quality Attributes

The QTPP and CQAs for Product X are listed in Section 4.2.1 and 4.2.2

4.2.1 Quality Target Product Profile

The Quality Target Product Profile for Product X is shown in Table 4.4.

Table 4.4: Quality target product profile for Product X

QTTP Element	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement. The dosage form of the optimised product and registered reference product is the same.
Dosage strength	200 mg Active X	Pharmaceutical equivalence requirement. Both the optimised and registered reference product contains 200 mg of Active X.
Dosage design	Immediate release tablet	An immediate release product is required to meet label claims.
Route of administration	Oral	Pharmaceutical equivalence requirement. The optimised and registered reference product has the same route of administration.
Container closure system	Suitable container closure system must be used to package the product.	Suitable packaging is essential to achieve the desired shelf life and to ensure tablet integrity during distribution.
Pharmacokinetics	Immediate release to enable T_{max} within 2 – 6 hours (Division of Clinical Pharmacology Faculty of Health Sciences University of Cape Town & Rossiter D, 2010). Bioequivalent to the registered reference product.	A rapid onset is required to ensure efficacy and is a bioequivalence requirement.
Stability	At least a 24 month shelf life at room temperature.	Pharmaceutical equivalence requirement. The optimised product must be equivalent or better than shelf life requirement for the registered reference product.
Alternative methods of administration	None	None are listed for the registered reference product.

Table 4.4: Quality target product profile for product X (continued)

QTTP Element		Target	Justification
Drug product quality attributes	Physical attributes	Pharmaceutical equivalence requirement. The drug product quality attributes must meet the same compendial requirements as well as any additional registered specifications as the reference product.	
	Identification		
	Assay		
	Content uniformity		
	Degradation products		
	Dissolution		
	Water content		
	Microbial limits		
	Sub-division		
Administration/concurrence with labelling		The optimised product must have a similar effect to the registered reference product when administered with food.	Absorption can be enhanced by taking the product with food. However, labelling of the registered reference product does not indicate that doses should be administered with or without food (Division of Clinical Pharmacology Faculty of Health Sciences University of Cape Town & Rossiter D, 2010)

4.2.2 Critical Quality Attributes

The critical attributes for Product X are shown in Table 4.5.

Table 4.5: Critical quality attributes for product X – physical attributes

Attributes of the Drug Product	Target	Is it a CQA?	Justification
Appearance	A white, round, flat tablet with bevelled edges, plain on one side and bisected on the other side.	No	Release and shelf life testing requirement. Tablet appearance does not have a direct link to safety and efficacy. Appearance will be checked as part of the in-process checks during compression as well as batch release to ensure compliance to the finished product specification. Compliance to the specification will ensure patient acceptability. Tablet appearance is not considered to be a CQA.
Thickness	4.0 mm (3.6 to 4.4 mm)	No	Tablet thickness is determined by the tooling used to compress the tablet as well as the compression machine settings. Thickness out of specification could affect tablet hardness which could affect dissolution and friability, and hence safety and efficacy. The same tooling will be used to compress the optimised and registered product. The target thickness for the optimised product will therefore be similar to the registered reference product. Tooling to be used for compression will be specified in the Batch Manufacturing Record (BMR). Thickness is thus not deemed to be a CQA. It will be monitored as part of the in-process checks during compression and will also be tested prior to batch release.
Diameter	9.0 mm (8.6 to 9.5 mm)	No	Tablet diameter is determined by the tooling used to compress the tablet. The same tooling will be used to compress the optimised and registered product. The target diameter for the optimised product will therefore be similar to the registered reference product. Tooling to be used for compression will be specified in the BMR and diameter will be monitored as part of the in-process checks during compression and will also be tested prior to batch release. Diameter is not considered to be a CQA.

Table 4.5: Critical quality attributes for Product X – physical attributes (continued)

Attributes of the Drug Product	Target	Is it a CQA?	Justification
Sub-division	The tablets comply with the test if not more than 1 individual mass is outside the limits of 85% - 115% of the average mass. The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75% - 125% of the average mass.	No	Package insert does require tablets to be broken in half as part of the dosing regimen. All three validation batches of the currently registered reference product passed sub-division at release. This test does not form part of the finished product specification at present but will be tested for development and validation batches. Sub-division is determined by score configuration and is thus tooling dependant. The same tooling will be used to compress the optimised and registered product and therefore sub-division is not deemed to be a CQA.
Tablet Mass	277.0 mg (265.0 – 289.0 mg)	No	Release and shelf life testing requirement. Testing of tablet mass is a routine test as per compendial requirements for tablets and can influence assay and uniformity of content, which are critical to safety and efficacy. Tablet mass will be monitored and controlled as part of the in-process checks during tablet compression and will also be tested as part of batch release. Tablet mass is not considered to be a CQA as operation within the specification ensures a low impact on patient safety and efficacy.
Uniformity of mass (UOM)	Not more than 2/20 cores may deviate from the average mass by more than 5% and no tablet by more than 10%.	No	This is a release requirement and can have a direct effect on assay and uniformity of content, which could compromise safety and efficacy. Uniformity of mass is monitored and controlled as part of the in-process checks during tablet compression and will also be tested as part of batch release. It is therefore not considered to be a CQA.
Hardness	60 N (40 to 100 N)	No	Release and shelf life testing requirement could affect tablet dissolution. Achieving suitable tablet hardness is one of the reasons for optimisation of the registered reference product. A hardness range study was performed on a laboratory scale batch. The study confirmed that all of the physical parameters were satisfactory over the current hardness specification (40 – 100 N). Dissolution profiles were similar at the different hardness ranges. Tablet hardness will be monitored as part of the in-process checks every 30 minutes during compression and will also be tested prior to batch release. Tablet hardness is not considered to be a CQA.

Table 4.5: Critical quality attributes for Product X – physical attributes (continued)

Attributes of the Drug Product	Target	Is it a CQA?	Justification
Friability	Not more than 1% is lost after 4 minutes	No	Friability has a low impact on safety and efficacy. It can however impact patient acceptability. Problems with tablet friability have been experienced with the registered reference product. Improving tablet friability is one of the objectives of this development. Friability results for laboratory trials on stability show results of less than 0.4 % m/m lost after 4 minutes. Friability will be monitored as part of the in-process checks during compression and will also be tested prior to batch release. Friability will also be monitored and trended during stability trials. Friability is not considered to be a CQA.
Disintegration	Not more than 15 minutes.	No	Release and shelf life testing requirement. Disintegration is directly linked to dissolution, which can affect efficacy of the drug product. Disintegration will be monitored as part of the in-process checks during compression and will also be tested prior to batch release, ensuring a low impact on dissolution and hence bioavailability. Release and stability data available for the optimised and existing product showed that all of the batches reviewed disintegrated in less than 6 minutes. This is well within the specification of not more than 15 minutes and disintegration is therefore not considered to be a CQA.

Table 4.6: Critical quality attributes for Product X – chemical attributes

Attributes of the Drug Product	Target	Is it a CQA?	Justification
Identification	a. The retention time of the peak due to Active X in the chromatogram obtained with the sample solution corresponds to the retention time of the peak attributable to the active in the appropriate standard chromatogram. b. By IR	**Yes***	Release requirement. Identification is critical to safety and efficacy; it is considered to be a CQA, but it is not affected by processing parameters or material attributes. Release testing will confirm that the correct API has been used prior to batch release. The material will also be tested to confirm identity before it is released for use in production batches. For this reason this CQA will not be discussed further in this Quality Risk Assessment.
Assay	200.00 mg (190.00 to 210.00 mg)	**Yes**	Release and stability testing requirement. Variability in assay can affect safety and efficacy. Assay can be affected by process variables and is considered to be a CQA.
Uniformity of dosage units (weight variation)	Acceptance value of the 10 units is less than or equal to L1% (L1 is 15).	No	Release requirement. Variation in uniformity of content can affect safety and efficacy. Content uniformity can be affected by process variables, but active X accounts for 72.2 % tablet content. If the product meets the requirements for blend uniformity and uniformity of mass remains within specification during the compression, uniformity of content is unlikely to fail due the high level of active content.
Dissolution	Not less than 80% of active is released within 60 minutes (Q = 75%).	**Yes**	Release and stability testing requirement. Variability in dissolution can influence bioavailability. Dissolution can be affected by process variables and is considered to be a CQA.
Related Substances	Any individual impurity: Not more than 0.2%. Total impurities: Not more than 0.5%.	**Yes**	Release and stability testing requirement. Related substances can affect product safety. Process variables can have an effect on related substances and it is therefore considered to be CQA.
Water content Karl Fischer	1.0 – 5.0%	No	The presence of water may affect degradation products. During the annual product review one batch had a moisture result which was out of trend. Karl Fischer moisture remains constant during stability trials and does not appear to affect related substances.

Table 4.6: Critical quality attributes for Product X – chemical attributes (continued)

Attributes of the Drug Product	Target	Is it a CQA?	Justification
Microbial Limits Total Viable Microbial Count: Bacteria Fungi Escherichia coli	Not more than 10^3 cfu/g. Not more than 10^2 cfu/g. Absent.	Yes*	Release and stability testing requirement. The presence of microbial growth could affect patient safety. However, there is no history of failure for this product at 25 °C/60% RH. In the stability data reviewed 4 failures were observed in metalized lay flats at 30 °C/75% RH. The product is packed in various packaging material and metallised lay flats are the least protective. The product is not marketed in any territories that require these storage conditions. Microbial growth is considered to be CQA for this product; however, process variables are unlikely to affect microbial growth. As part of the control strategy, testing will be performed at batch release and at the start and end of stability trials as per the specification. For this reason this CQA will not be discussed further in this Quality Risk Assessment.
* Formulation and process variables are unlikely to impact the CQA. Therefore the CQA will not be investigated or discussed in detail in the subsequent risk assessment. However, the CQA remains a target element of the QTPP and is ensured through the product and process design and the control strategy.			

For Product X, assay, dissolution, and related substances were identified as the CQAs that had the potential to be impacted by the formulation and/or process variables.

4.3 Identification of Knowledge Baseline

4.3.1 Evaluation of Product and Process Knowledge

A review of the latest Product Quality Review Report available for Product X was conducted. During the review period, a total of 50 deviations were initiated. There were 43 minor, 6 major, and 2 that were withdrawn. The largest amounts of deviations were in compression as a result of poor granule flow. During the review period, 6 batches were rejected as they could not be compressed. Fungal contamination was observed in 4 batches packed in metallised layflats, otherwise known as 'patient ready packs', stored at 30 °C/75% RH. This packaging is not sold in territories where long term storage is required at 30 °C/75% RH, and there is no fungal contamination observed at 25 °C/60% RH. Despite batches being rejected because they could not be compressed, all of the process specifications evaluated as part of the annual product quality review had a CpK of greater than 1.33, except for assay, which had a CpK result of 0.61. This indicates that the process is not capable because it does not

meet the target of 1.33 for CpK. Despite the high variability, only one batch was rejected with a low assay result. Assay results for all other batches fell within the 5% specification limits.

In addition to reviewing the latest available Product Quality Review, a review of the currently registered product dossier, validation and stability data was also conducted. The current commercial manufacturing process for Product X was validated in 2011. The compression machine speed of 162 000 tablets per hour (60 rpm) was achievable at the time of validation. Despite a compression machine speed of 162 000 tablets per hour being validated, the actual average compression machine speed during the review period was only 72 000 tablets per hour, and ranged between 45 000 and 162 000 tablets per hour. The average bulk and tap density was obtained for four commercial batches prior to compression. Using the average bulk and tap density the current commercial product had a Carr and Hausner ratio of 28 and 1.4, respectively.

The pharmaceutical development report which details the optimisation studies that were conducted at the outsource development facility was also reviewed. Optimisation activities conducted at the development site involved laboratory scale batch manufacture with the following process and formulation changes being proposed:

- Change in the order of addition of one of the pharmaceutical ingredients.
- Change in the quantity of granulating medium.
- Change in the processing speed and timing during batch manufacture.
- Specific API supplier to be used for the development that has a particle size distribution in the range of 90 % of the particles between 40 – 70 µm and a tapped density within a range of 0.55 – 0.90 g/ml.

No changes to the manufacturing process control strategy were proposed by the outsource development facility. Prior to commencing QbD activities, a production scale development batch was manufactured implementing the changes proposed by the outsource development facility. A suitable granule was obtained and no tablet defects were observed during the compression process. However, granule flow during compression was very poor. Tablet mass and hardness were extremely variable as a result of the poor granule flow. The formulation changes proposed by the outsource development facility were used as the

starting point for subsequent development activities at the Port Elizabeth site with an additional excipient being added to the formulation to improve granule flow.

Small scale formulation trials were conducted at the Port Elizabeth Site using granules produced from an unsuccessful production scale development batch whereby 1 % colloidal silicone dioxide was added to the extra-granular phase of the formulation. Good compression characteristics were obtained and good granule flow was observed. The bulk and tap densities were measured for both batches. The batch with colloidal silicone dioxide included in the formulation had a Carr Index and Hausner ratio of 14 and 1.1, respectively. This indicates good to excellent granule flow properties. Granule flow for the batch manufactured without colloidal silicone dioxide displayed poor flow properties with a Carr and Hausner Ratio of 26 and 1.3, respectively. Comparative dissolution profiles in the batch release and Biopharmaceutics Classification System (BCS) media were generated and Product X with colloidal silicone dioxide included in the formulation compared favourably to the current commercial product. Based on the improved granule flow and compression performance, a decision was made to include colloidal silicone dioxide to the formulation. The revised product manufacturing process flow is shown in Figure 4.1.

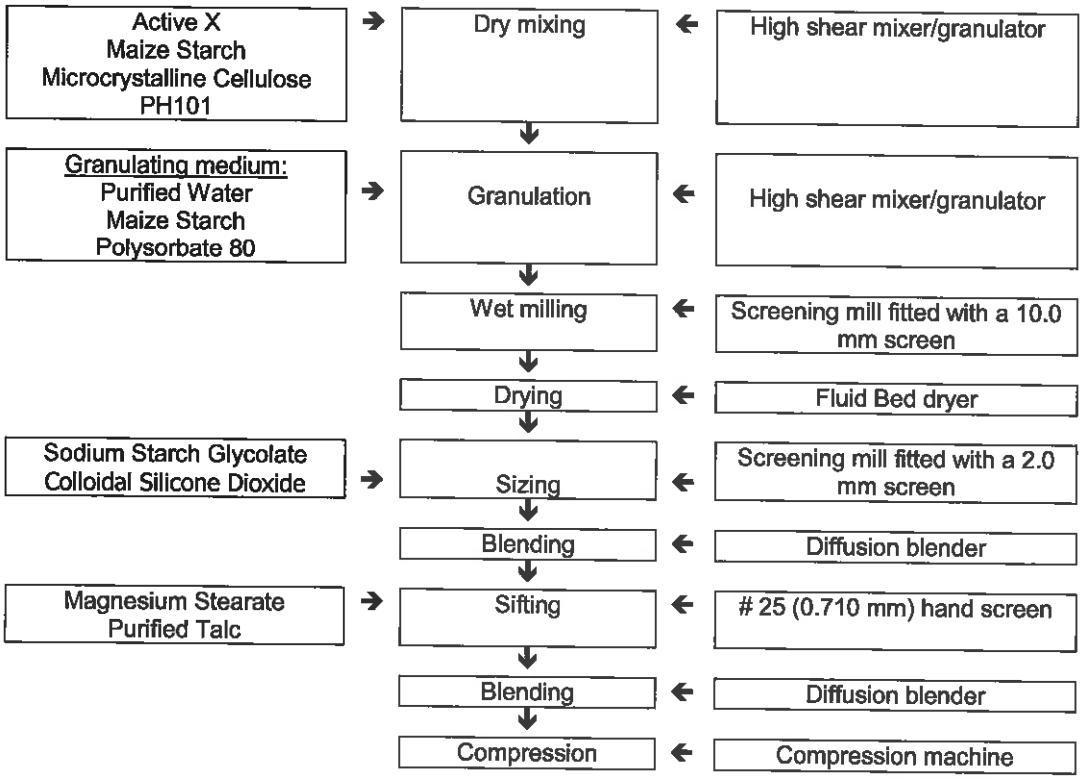

Figure 4.1: Proposed manufacturing process flow for Product X

4.3.2 Quality Risk Assessment

A quality risk assessment was performed for Product X. Material attributes for the API's and IPI's, as well as the manufacturing processing parameters, were evaluated in order to determine their effect on the identified CQAs for Product X. An informal risk ranking system was used for the purposes of the risk assessment. The risk to the product CQAs were ranked as being low, medium or high and were justified by evaluating the knowledge base available for Product X. A summary of the outcome of the quality risk assessment is shown in Tables 4.7, 4.8, and 4.9.

4.3.2.1 Active Pharmaceutical Ingredient Risk Assessment and Justification

Table 4. 7: Risk assessment and justification for API

API Attribute	CQA	Justification
Solid state form: Appearance Identification Polymorphism	Assay	Assay should not be affected by solid state form. The solid state form of the API is controlled by the supplier. The risk is low.
	Dissolution	Active X shows polymorphism. The presence of a different polymorph could influence dissolution and bioavailability. Active X, which is manufactured by the registered supplier, conforms to the polymorphic Form – III. The elucidation of the polymorphic form has been performed through x-ray powder diffraction (XRPD) technique. X-Ray diffractograms confirming the consistency of the pattern for three commercial batches have been provided as part of the suppliers Drug Master File for Product X (Amoli Organics Private Limited, 2014). The risk is low.
	Related substances	Solid state form will not impact degradation products. API lots will be tested prior to release and will be required to meet the in-house and pharmacopeial specifications. The risk is low.
Solubility	Assay	Solubility does not affect assay. The product formulation and manufacturing process have been designed to achieve the desired finished product performance. The risk is therefore low.
	Dissolution	API solubility can influence dissolution. The optimised product has been designed to compare to the registered reference product in the batch release medium as well as BCS conditions. With an established formulation and process that achieves dissolution requirements, solubility poses a low risk to dissolution, as release and BCS profiles for laboratory scale batches were compared to the registered reference product and were found to be similar.
	Related substances	Solubility does not affect related substances. The product formulation and manufacturing process have been designed to achieve the desired finished product performance. The risk is therefore low.
LOD	Assay	LOD is controlled by the API supplier by means of the raw material specification. A potency adjustment calculation will be performed prior to dispensing whereby the quantity of API dispensed may be adjusted depending on the assay and LOD result. The risk to assay is low.
	Dissolution	LOD is controlled by the API supplier by means of the raw material specification. LOD is required to meet the raw material specification prior to raw material release. The risk to dissolution is low.
	Related substances	Moisture content has the potential to affect degradation products. LOD is controlled by the API supplier of the raw material. The product is fluid bed-dried and the desired moisture is targeted at this stage. Chemical stability data available from the API supplier confirms that the product is stable at long term and accelerated conditions (Amoli Organics Private Limited, 2014). The risk is low.

Table 4.7: Risk assessment and justification for API (continued)

API Attribute	CQA	Justification
Related substances/Process impurities	Assay	Related substances and process impurities are controlled by the API supplier's specification. Stability data available for the registered reference product confirms that assay results were not affected for batches where related substance failures were observed. The API will be stored as per the supplier recommendations. Stability of the finished product will be monitored for out of specification results. The risk to the assay is low as related substances and process impurities are controlled within the API.
	Dissolution	Related substances and process impurities are controlled by the API supplier's specification. Stability data available for the registered reference product confirms that dissolution results were not affected for batches where related substance failures were observed. Stability of the finished product will be monitored for out of specification results. The risk to dissolution is low.
	Related substances	Related substance failures were observed during stability on two batches in the 2014 to 2015 review period. Related substances and process impurities in the drug substance can affect related substance results in the finished product. Related substances and process impurities are controlled by the API supplier's specification. Chemical stability data available from the API supplier confirms that the API is stable at long term and accelerated conditions (Amoli Organics Private Limited, 2014). Stability of the finished product will be monitored for out of specification results. The risk is medium.
Assay	Assay	Assay requirements for the API are 98 to 102 % (on a dried basis) (Amoli Organics Private Limited, 2014). Finished product specification limits for assay are 95 to 105% (Aspen Phamacare, 2016b). API assay is required to meet the supplier specification prior to release. A potency adjustment is performed if the 'as is' potency is less than 100 %. Active content is 72.2% of the final tablet mass, therefore if assay is within specification it is unlikely that problems will be observed. The risk is low.
	Dissolution	Active X is only slightly soluble in water. However, the product has been formulated and processed in order to be comparable to the registered reference product. API assay should not affect dissolution, provided that assay meets the supplier specifications. The product will be required to meet the dissolution requirements for the finished product prior to batch release. The risk is low.
	Related substances	A low assay result could occur as a result of related substances. Assay, degradation products, or impurities will be required to meet the relevant in-house and pharmacopeial specifications. Stability of the finished product will be monitored for out of specification results. The risk is low.

Table 4.7: Risk assessment and justification for API (continued)

API Attribute	CQA	Justification
Tap density	Assay	A low tap density can result in incomplete granulation end-points resulting in a high amount of fines being generated. This can cause poor granule flow during compression and incomplete die filling. Tablet assay may therefore be affected. The outsource development facility performed small scale trial batches which proved that, if a tap density of 0.55 – 0.90 g/ml is targeted, a reproducible granulation end point and a blend with good flow characteristics would be produced (Alphamed Formulations PVT Ltd, 2015). The risk is low.
	Dissolution	A low tap density can result in incomplete granulation end-points which could potentially affect dissolution. The outsource development facility performed small scale trial batches which proved that if a tap density of 0.55 – 0.90 g/ml is targeted a reproducible granulation end point will be achieved (Alphamed Formulations PVT Ltd, 2015). The risk is low.
	Related substances	Tapped density will not influence related substances; the risk is low.
Residual solvents	Assay	Residual solvents are controlled in the API by means of the specification provided by the supplier. Residual solvents will be required to meet the raw material release specification prior to material release; therefore the risk of affecting product CQAs is low.
	Dissolution	
	Related substances	
Particle size distribution (PSD)	Assay	The particle size distribution can influence blend flowability which could result in assay failure in severe cases. Although the product has a history of flow problems, the API accounts for 72.2% of the final tablet mass. The finished product has a high active content and it is unlikely that particle size could result in assay failures. This is supported by batch release and stability data available for the product. The risk is low.
	Dissolution	Particle size can affect dissolution. The current particle size specification for the API is less than 75 µm. The wide particle size distribution may influence the granulation characteristics of the product. A history of over-granulation has been noted for this product that may be attributable to particle size. This in turn may impact the dissolution behaviour of the final product. The outsource development facility evaluated the effect of particle size and proposed a particle size distribution of 90 % of the particles ranging between 40 – 70 µm. Dissolution studies were conducted by the outsource development facility, and it has been demonstrated that dissolution performance will not be adversely affected if the API PSD falls within the range of 40 – 70 µm. The risk is low.
	Related substances	Particle size is unlikely to affect degradation products. Material will be tested according to in-house and pharmacopeial requirements and degradation products will be tested as part of batch release and on stability for the finished product. The risk is low.

4.3.2.2 Inactive Pharmaceutical Ingredient Risk Assessment and Justification:

Table 4.8: Risk assessment and justification for excipients

Formulation attributes	CQA	Justification
Starch maize grade	Assay	Starch maize is used both as a binder as well as an intra-granular filler/disintegrant. A change in the grade of starch maize could impact the flow properties of the granule, which could in turn impact assay. A change from the current grade of starch maize (food grade) to a pharmaceutical grade is proposed as part of this development. Small scale trials have been performed utilising the new grade of excipient and no impact on assay has been noted. Ensuring that the correct grade of starch maize is utilised in the formulation will be ensured by the company's vendor management system. The risk is low.
	Dissolution	Since starch maize plays a role as a binder in the formulation, a change in grade may impact the quality and density of the granules, which can influence its dissolution properties. Small-scale trials performed using the new grade of starch maize have not shown any adverse effects on the dissolution performance of the finished product. The risk is low.
	Related substances	Screening stability studies performed at laboratory scale have shown a relatively low increase in related substances. No link can be determined between the grade of starch maize and the formation of degradation products. The risk is therefore low.
Starch maize LOD	Assay	The loss on drying specification of not more than 15.0 % is controlled by the product manufacturer (Alphamed Formulations PVT Ltd, 2015). The same limit is set for both grades of starch maize. Based on historical data and laboratory-scale development trials on the reformulated product, no assay or dissolution problems have been noted for this product. The risk is therefore low.
	Dissolution	
	Related substances	The impact of varying moistures of starch maize on the degradation of the final product is unknown. The LOD is controlled via the product manufacturer. Degradation profiles have been generated on the reformulated product with no problems being noted (Alphamed Formulations PVT Ltd, 2015). The risk is low.

Table 4.8: Risk assessment and justification for excipients (continued)

Formulation attributes	CQA	Justification
Microcrystalline cellulose (MCC) 101 grade	Assay	MCC 101 has been moved from the extra-granular phase to the intra-granular phase, which could impact the flowability of the resultant granule. This could then affect assay. The influence of varying grades of MCC has not been evaluated, but small scale trials utilising MCC 101 has shown no impact on assay of the final product (Alphamed Formulations PVT Ltd, 2015). Ensuring that the correct grade of MCC is utilised in the formulation will be ensured by the certificate of the MCC 101. The risk is low.
	Dissolution	The impact of different grades of MCC on compression is unknown and would need to be evaluated in terms of its effects on tablet hardness/compressibility, which could in turn affect dissolution. The grade of MCC 101 is controlled by the supplier. The control strategy will be responsible for ensuring that the correct grade MCC is utilised in the formulation. Prior history and testing of the reformulated product has shown no impact on dissolution for this product (Alphamed Formulations PVT Ltd, 2015). The risk is low.
	Related substances	The influence of different grades of MCC on the formation of degradation products has not been evaluated. Screening stability studies performed at laboratory scale have shown a relatively low increase in related substances (Alphamed Formulations PVT Ltd, 2015). The risk is low.
Microcrystalline cellulose 101 particle size distribution (PSD)	Assay	Particle size distribution of MCC 101 could affect the uptake of water used in the granulating medium during wet granulation and also influence the flowability of the resultant granules. This can occasionally impact assay. MCC 101 is specifically marketed based on its particle size characteristics and is controlled by the supplier via a multi-tiered specification. The risk to assay is low.
	Dissolution	A finer or coarser PSD may influence the uptake of water during granulation and thereby impact granule density and resultant dissolution. Results of dissolution testing on the reformulated product utilising MCC 101 have shown comparable dissolution profiles to that of the currently registered product in release and BCS media (Alphamed Formulations PVT Ltd, 2015). The PSD of the MCC 101 is controlled by the supplier; hence the risk to dissolution is low.
	Related substances	The PSD of MCC 101 will not influence related substances. The risk is low.

Table 4.8: Risk assessment and justification for excipients (continued)

Formulation attributes	CQA	Justification
Microcrystalline cellulose 101 LOD	Assay	The LOD specification is controlled via in-house limits of not more than 7.0% m/m (Aspen Phamacare, 2016a). The supplier also controls the LOD to tighter limits of not more than 6.0% (Gujarat Microwax PVT. Ltd, 2016). The risk is low.
	Dissolution	
	Related substances	The impact of varying moistures of MCC PH 101 on the degradation of the final product is unknown. The LOD is controlled via the supplier and in-house limits. Degradation profiles have been generated on the reformulated product with no problems noted (Alphamed Formulations PVT Ltd, 2015). The risk is low.
Microcrystalline cellulose 101 water/ether soluble substances	Assay	The presence of water-soluble and ether-soluble substances would not have an influence on the assay of the final product. The risk is low.
	Dissolution	Water-soluble and ether-soluble substances present in the MCC 101 could have an influence on dissolution and absorption of the final product. However, these substances are controlled by the supplier to limits of not more than 0.25% and 0.05%, respectively (Gujarat Microwax PVT. Ltd, 2016). The risk is low.
	Related substances	The presence of water-soluble and ether-soluble substances would not have an influence on the degradation of the final product. Current screening stability data has shown no impact on related substances for this product (Alphamed Formulations PVT Ltd, 2015). Hence the risk is low.
Polysorbate 80 composition of fatty acids	Assay	The composition of fatty acids in polysorbate 80 will not impact the assay of the final product due to the small concentrations in the final dosage form. The risk is low.
	Dissolution	The composition of fatty acids can affect the wetting capability of polysorbate 80, which in turn can influence the dissolution of the active ingredient from the final dosage form. The composition and ratios of the fatty acids present in polysorbate 80 are controlled by the supplier specification. The risk is low.
	Related substances	The composition of fatty acids will not influence the formation of degradation products as determined from acceptable results after screening stability studies (Alphamed Formulations PVT Ltd, 2015). The risk is low.

Table 4.8: Risk assessment and justification for excipients (continued)

Formulation attributes	CQA	Justification
Sodium starch glycollate Loss on drying	Assay	Loss on drying is controlled by the supplier to a limit of not more than 10% m/m (Amishi Drugs and Chemicals Pvt Ltd, 2014). Based on historical data, no assay problems were noted for this product. The risk is low.
	Dissolution	The loss on drying of sodium starch glycollate should not impact the dissolution of the final product. The risk is low.
	Related substances	The impact of varying moistures of sodium starch glycollate on the degradation of the final product is unknown. The LOD is controlled by the supplier. Degradation profiles have been generated on small scale during stability testing with no problems being noted (Alphamed Formulations PVT Ltd, 2015). The risk is low.
Sodium starch glycollate Bulk density	Assay	Sodium starch glycollate is present as a disintegrant in a small concentration of 3.61% m/m of total tablet mass. As the quantity is controlled in the BMR, the effect of bulk density on assay should be minimal. The risk is low.
	Dissolution	The bulk density may influence the wicking and swelling properties of sodium starch glycollate, which could impact disintegration and dissolution. The bulk density is controlled by the company to a limit of 0.839 – 0.993 g/ml. No historical dissolution problems have been noted for this product as a result of changes in sodium starch glycollate density, hence the risk is low.
	Related substances	Bulk density will not influence related substances. The risk is low.
Purified talc Water-soluble substances	Assay	The presence of water-soluble substances would not have an influence on the assay of the final product. The risk is low.
	Dissolution	Water-soluble substances present in purified talc could have an influence on dissolution of the final product. However, these substances are controlled by the supplier to limits of not more than 10 mg (0.2%) and 5 mg (0.1%). This complies with the pharmacopeial limits for this material (Imerys Talc Italy S.p.A, 2015). The risk is low.
	Related substances	The presence of water-soluble substances would not have an influence on the degradation of the final product. Current screening stability data has shown no impact on related substances for this product (Alphamed Formulations PVT Ltd, 2015). Hence the risk is low.

Table 4.8: Risk assessment and justification for excipients (continued)

Formulation attributes	CQA	Justification
Magnesium stearate Specific surface area	Assay	The surface area of magnesium stearate is unlikely to affect the assay of the final product.
	Dissolution	A large specific surface area may result in increased efficiency in the coating of the granules during blending. This may retard dissolution of the final drug product as a result of the hydrophobic nature of magnesium stearate. The specific surface area is controlled by the supplier. No dissolution problems have been noted on laboratory-scale developmental trials performed on the reformulated product (Alphamed Formulations PVT Ltd, 2015). The risk is low.
	Related substances	The specific surface area of magnesium stearate will not influence related substances. The risk is low.
Colloidal silicon dioxide Specific surface area	Assay	A low surface area of colloidal silicon dioxide may not adequately improve granule flow which may lead to poor die filling and resultant impact on assay of the final product. The specific surface area is controlled by the supplier to a limit of 200 m^2/g (175 – 225 m^2/g) and hence should not negatively impact assay (Evonik Industries, 2016). The risk is low.
	Dissolution Related substances	The specific surface area of colloidal silicon dioxide will not influence dissolution or related substances in the final formulation. The risk is low.
Colloidal silicon dioxide Loss on drying	Assay	Loss on drying is controlled by the supplier to a limit of not more than 7.0 % m/m, but a more stringent in-house control of not more than 2.5 % m/m is implemented by the company (Evonik Industries, 2016). Loss on drying is therefore unlikely to impact assay and the risk is low.
	Dissolution	The loss on drying of colloidal silicon dioxide should not impact the dissolution of the final product. The risk is low.
	Related substances	The impact of varying moistures of colloidal silicon dioxide on the degradation of the final product is unknown. The LOD is controlled by the supplier as well as the company. The risk is low and will be monitored pending the outcome of stability studies.
Colloidal silicon dioxide Bulk density	Assay	Colloidal silicon dioxide is present as a glidant in a small concentration of 1 % m/m of total tablet mass. The effect of bulk density on assay should be minimal. The risk is low.
	Dissolution	The effect of bulk density on dissolution on the active ingredient is minimal. The bulk density is controlled by the company to a limit of 0.049 – 0.066 g/ml (Aspen Phamacare, 2015a). The quantity will be controlled by the BMR as per the control strategy. The risk is low.
	Related substances	Bulk density will not influence the formation of degradation products or related substances. The risk is low.

Table 4.8: Risk assessment and justification for excipients (continued)

Formulation attributes	CQA	Justification
Colloidal silicon dioxide quantity	Assay	Colloidal silicon dioxide is used as a glidant and present in a low quantity in the formulation (1 % m/m of total core mass). It is unlikely to impact assay or dissolution. The risk is low.
	Dissolution	
	Related substances	The impact of the presence of colloidal silicon dioxide on the formation of degradation products in the formulation is unknown. However, colloidal silicon dioxide is present in the innovator product, and should therefore pose a low risk to related substances. This will be monitored during stability testing.

4.3.2.3 Manufacturing Process Risk Assessment and Justification

Table 4.9: Risk assessment and justification for the manufacturing process

Formulation attributes	Finished Product CQAs	Justification
Dry mix	Assay	The quantity of dry powders that are dispensed is controlled by means of the BMR. Active X accounts for 72.2 % w/w of the intra-granular formulation. Similar processing speeds and times will be used during scale up from development to the commercial manufacturing scale. The risk to assay is low.
	Dissolution	Dry mixing variables do not impact dissolution and hence the risk is low.
	Related substances	Dry mixing of the powders may generate heat. However, the amount of heat produced would be much less than that required to degrade the active (Amoli Organics Private Limited, 2014). Stability data generated on previous batches have been found to be acceptable, hence the risk is low (Alphamed Formulations PVT Ltd, 2015).
Starch paste preparation	Assay	The quantity of starch paste is specified in the BMR. Development batches with the reformulated product as well as historical data show that the preparation of the starch paste does not impact the assay of the product. The risk is low.
	Dissolution	A starch paste that is too thick or too thin may impact the quality and density of the resultant granules. This in turn could impact dissolution of the tablets. The method of starch paste preparation specified is identical to that implemented during laboratory-scale development batches and will be controlled in the BMR for production-scale batches. The impact on dissolution will therefore be low.
	Related substances	Laboratory-scale stability trials have shown satisfactory results with regard to formation of degradation products (Alphamed Formulations PVT Ltd, 2015). The preparation of the starch paste is therefore assigned a low risk.

Table 4.9: Risk assessment and justification for the manufacturing process (continued)

Formulation attributes	Finished Product CQAs	Justification
Dosing	Assay	The granulating medium is dosed via a pipe clamped to the mixer/granulator. No loss of dry powders will occur during dosing of granulating medium and hence the risk to assay is low.
	Dissolution	The rate of addition of the granulating medium may produce a denser granulate that could impact dissolution. The risk is high.
	Related substances	The rate of addition of the granulating medium will not impact the formation of degradation products in the formulation. The risk is low.
Wet mix	Assay	Insufficient wet mixing time may lead to variations in granule size. This could cause segregation problems during compression and hence affect assay of the final tablets. The presence of a large amount of active in the formulation would reduce this risk. The risk to the assay of the final dosage form is therefore medium.
	Dissolution	Prolonged wet mixing may produce a denser granulate that could impact dissolution. The risk is high.
	Related substances	Wet mixing may increase the contact time of the water with the active. However, the contact time is brief and fluid-bed drying will evaporate most of the water. Release testing will ensure that that any degradants are identified. Small-scale studies have shown satisfactory stability results (Alphamed Formulations PVT Ltd, 2015). The risk is therefore low.
Wet milling	Assay	Wet milling is a deagglomeration step before drying that ensures even drying and avoidance of large lumps which may remain relatively wet in their core. It is a non-critical step that will not impact assay of the final product. The risk is low.
	Dissolution	As wet milling is a deagglomeration step where wet granule is passed through a large diameter (10 mm) screen. In some instances, a rapid mill speed may result in densification of the granulate, which could impact disintegration and dissolution. The wet mill speed will be controlled as per instruction in the BMR. Wet milling is therefore considered to be a low risk to dissolution.
	Related substances	Although the screen may heat up during the milling process, the dwell time is brief. Wet milling is unlikely to impact degradation products. The risk is low.

Table 4.9: Risk assessment and justification for the manufacturing process (continued)

Formulation attributes	Finished Product CQAs	Justification
Fluid-bed drying	Assay	The wet granules are suspended and agitated in a warm air stream in a constant state of motion. This results in constant mixing occurring during fluidisation. However, a long drying time might generate excessive fines. This can cause poor granule flow with resultant uniformity of mass violations and hence assay failures. The moisture will be controlled to a limit of 1.0 – 2.0%, as determined through previous batch history and laboratory-scale trials (Alphamed Formulations PVT Ltd, 2015). The drying time is therefore dependant on the air flow, inlet temperature, product temperature end-point, and LOD. No previous history of assay failures has been noted for the product. Hence fluid-bed drying poses a medium risk to assay.
	Dissolution	Over-drying may result in the formation of excess fines which could impact the rate of dissolution of the active. Over-drying may also result in the formation of hard granules which could retard the release of the drug substances from the final dosage form. However, previous batch dissolution data suggests that the influence of drying on the dissolution of the active is a low risk (Alphamed Formulations PVT Ltd, 2015).
	Related substances	The inlet air temperature could influence the degradation of the active. However, the product will be in a constant flow of motion and the temperature of the product is lower than the inlet temperature. In addition, a high moisture after drying could also impact the formation of degradation products. The LOD limit is controlled to 1.0 – 2.0%, similar to that of Laboratory-scale batches. Screening stability studies also revealed a satisfactory degradation profile for the product; hence the risk will be low (Alphamed Formulations PVT Ltd, 2015).
Dry milling	Assay	The milling step controls the final granule size distribution. A sub-optimal distribution may affect flow, causing variable tablet weight and assay during compression. A 2.0 mm screen is set for dry milling and hence the risk to final granule size distribution is low.
	Dissolution	A large amount of fines may impact tablet hardness and dissolution. Previous reference batch characterisation has found the dissolution rate to be fast and hence the milling step should not negatively impact tablet dissolution. The risk is low.
	Related substances	Although the screen may heat up during milling, the dwell time is brief. Milling is unlikely to impact degradation products. The risk is low.

Table 4.9: Risk assessment and justification for the manufacturing process (continued)

Formulation attributes	Finished Product CQAs	Justification
Blending	Assay	Active X makes up 72.2% of the final tablet mass. Previous batch blending data has shown no assay problems. The risk of failures from blending is low.
	Dissolution	Granule density, which impacts dissolution, will be controlled in previous steps (granulation and drying). Blending of the un-lubricated granule will not impact dissolution of the drug substances. The risk is low.
	Related substances	Blending process variables are unrelated to degradation of the product. The risk is low.
Lubrication	Assay	Under-lubrication may result in poor flow, resulting in segregation. It could thus impact the assay of the final tablets. Lubrication optimisation has been performed on laboratory-scale batches by Alphamed Laboratories and was found to be suitable in forming tablets (Alphamed Formulations PVT Ltd, 2015). The risk of assay failures is therefore low.
	Dissolution	Over-lubrication due to an excessive number of revolutions may impact hardness, disintegration and hence dissolution. Lubrication optimisation has been performed on laboratory-scale batches by Alphamed Laboratories and a lubrication time of 5 minutes was found to be satisfactory in producing adequate hardness, disintegration and dissolution of the final tablets (Alphamed Formulations PVT Ltd, 2015). The risk is low.
	Related substances	Blending process variables are unrelated to degradation of the product. The risk to related substances is low.
Compression	Assay	Uniformity of mass variability has historically been noted. High/low feeder speeds combined with poor granule flow could therefore impact uniformity of mass and resultant assay. The presence of 72.2% active content would negate this effect to a certain extent. The risk is medium.
	Dissolution	Tablet hardness can potentially affect dissolution. Average tablet hardness levels have been assessed at a laboratory scale by Alphamed Laboratories and were found to not impact dissolution results (Alphamed Formulations PVT Ltd, 2015). High feeder speeds may result in over-lubrication of the granules which can impact dissolution. The risk is high.
	Related substances	Compression is unlikely to impact related substances. The risk is low.

Based on the manufacturing process risk assessment, dosing, wet mixing, and compression were deemed to be high risk in their potential to affect dissolution performance. Dosing, wet

mixing and compression were further evaluated using DoE. Low and medium risk items were not investigated because they were either deemed to have no effect on the product CQAs, or the current in-process and release specifications mitigates the risk.

4.4 Application of Design of Experiments

In order to develop product and process understanding, the following critical process parameters were identified for the DoE studies at 10 L laboratory scale:

- Dosing impeller speed during granulation (80 rpm to 120 rpm).
- Dosing time in granulation [300 s (240 s + 60 s) to 420 s (300 s + 120 s)]. Dosing time includes the total time to dose the starch paste (16 ml polysorbate 80, 122.36 g starch maize, 975 ml purified water) as well as a set additional quantity of purified water (100 ml).
- Wet mix time in granulation (60 s to 120 s).
- Feeder speed in compression (20 rpm and 50 rpm).

4.4.1 Screening Trial

A screening trial was performed to assess the main effects of the four factors which were identified as CPPs. A 2-level full factorial design with centre point was chosen to assess how each individual factor affects the responses. The experimental runs were randomised in order to prevent bias. The processing parameters which were not identified as being critical were kept constant for all the batches. Results of the screening trial are shown in Table 4.10.

Table 4.10: Stepwise regression – screening trial

Response	Factor	p-value	R^2
Torque after wet mix	3-way interaction Dosing impeller speed * Dosing time * Wet mix time	0.022	49.95%
LOD after lubrication	No factors affecting outcome	N/A	N/A
Flowdex	Main effect Feeder speed 2-way interaction Dosing impeller speed * Feeder speed	 0.033 0.02	85.56%
Bulk density	Main effect Wet mix time Feeder speed	 0.024 0.005	75.57 %
Hausner ratio	2-way interaction Dosing impeller speed * Feeder speed	 0.023	37.59%
Carr index	2-way interaction Dosing impeller speed * Feeder speed	 0.017	39.28%
Particle size distribution % less than 0.105 mm	Main effect Wet mix time 2-way interaction Dosing impeller speed * Wet mix time	 0.026 0.011	73.13%
Particle size distribution % greater than 0.105 mm	Main effect Wet mix time 2-way interaction Dosing impeller speed * Wet mix time	 0.025 0.011	73.05 %
Fill depth	Main effect Feeder speed 2-way interaction Dosing time * Wet mix time	 0.000 0.020	94.56%
Compaction force	Main effect Feeder speed 2-way interaction Dosing impeller speed * Dosing time	 0.034 0.029	64.08%
Average % RSD compaction force	Main effect Feeder speed	 0.002	86.04%
Ejection force	No factors affecting outcome	N/A	N/A
% RSD of tablet mass	Main effect Feeder speed 2-way interaction Dosing impeller speed * Feeder speed	 0.038 0.002	86.39%

Table 4.10: Stepwise regression – screening trial (continued)

Response	Factor	p-value	R^2
Average tablet thickness	Main effect		97.70 %
	Dosing impeller speed	0.002	
	Wet mix time	0.02	
	Feeder speed	0.002	
	2-way interaction		
	Wet mix time * Feeder speed	0.000	
	3-way interaction		
	Dosing impeller speed * Wet mix time * Feeder speed	0.02	
Dissolution	No factors affecting outcome	N/A	N/A

Dissolution was not considered to be a CQA because it was within the required specification. It was therefore not considered in further investigations.

For the factors and monitored responses R^2 values ranging from 37.59 to 97.70 % were obtained. The higher R^2 values indicate that the model is a good fit for the data (Frost, 2013). The lower R^2 values indicate that the model may demonstrate non-linear behaviour and therefore a CCD design was used to confirm this relationship.

Based on the screening trial results, the following factors were identified as having an effect on the responses measured:

- Dosing impeller speed: average tablet thickness.
- Wet mix time: bulk density, particle size distribution (less than and greater than 0.105 mm), and average tablet thickness.
- Feeder speed: flowdex, bulk density, fill depth, compaction force, average % RSD compaction force, relative standard deviation (RSD) of tablet mass, and average tablet thickness.

In addition, 2-way and 3-way interactions were also identified where all factors played a role in the outcomes.

4.4.2 Pivotal Study

Based on the outcome of the screening trial, dosing impeller speed, wet mix time, and feeder speed were shown to have a significant impact on the CQAs for Product X. In order to investigate these factors further, a pivotal study using a surface response methodology

approach with a central composite design was performed. All of the processing parameters with the exception of dosing impeller speed, wet mix time, and compression feeder speed were set at a predetermined value.

Table 4.11: Stepwise regression – pivotal trial

Response	Factor	Model	p-value	R^2
% RSD of tablet mass	Feeder speed	Linear	0.019	71.94%
	Wet mix time * Wet mix time	Square	0.045	

Based on the outcome of the screening trial, dissolution was not affected by any of the factors. For this reason, responses with no potential impact on dissolution were excluded from the pivotal study. The results from the pivotal trial indicated that both wet mix time during granulation and feeder speed in compression significantly affected percentage RSD of tablet mass (p-value = 0.045 and 0.019, respectively). The relationship between feeder speed and percentage RSD of tablet mass is described as a linear model. The relationship between wet mix time and percentage RSD of tablet mass is described by a quadratic model. All other factors were not found to statistically impact the responses. Figure 4.2 illustrates the contour plot that was generated to show % RSD of tablet mass as a function of wet mix time and feeder speed.

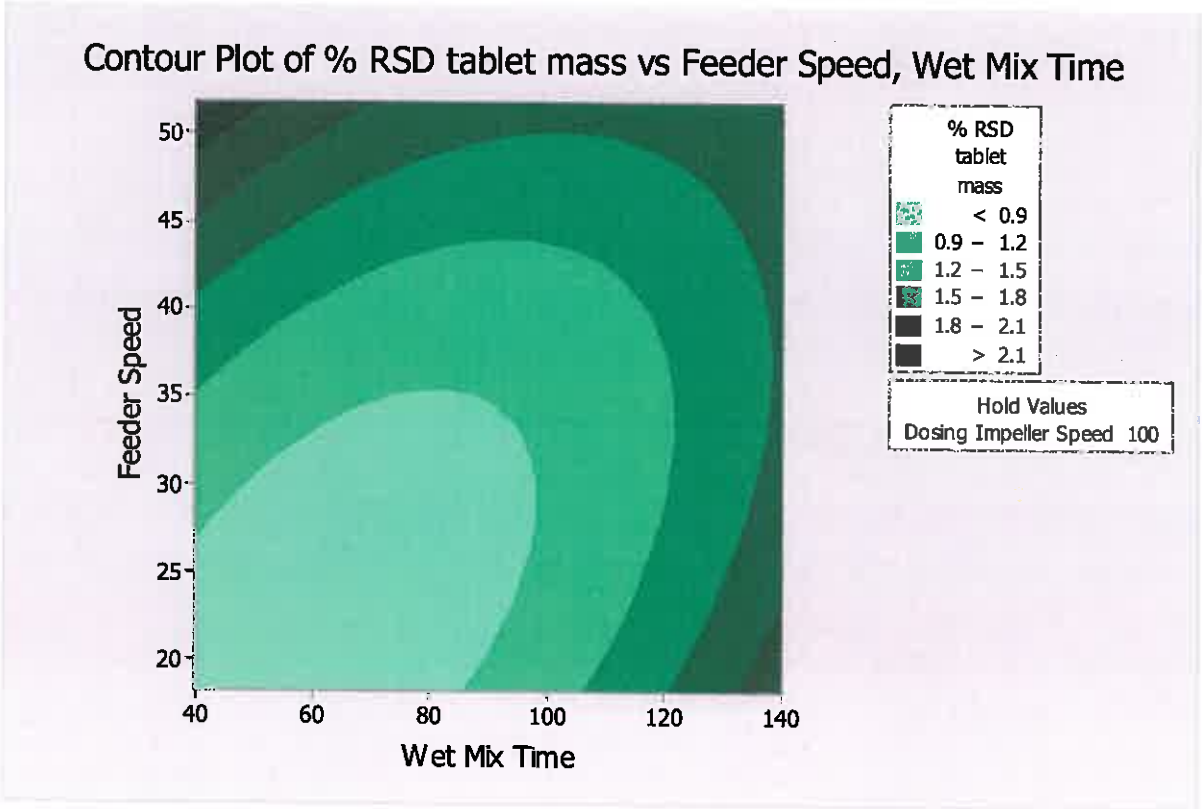

Figure 4.2: Contour plot showing % RSD of tablet mass vs. wet mix time and feeder speed

At lower wet mix times and feeder speeds, the % RSD of the resultant tablets decreased to less than 0.9%. For all experiments the maximum % RSD recorded was 2.08%, implying that tablet mass was relatively well controlled. Thus from all factors analysed the employed ranges would result in good tablet mass control and a robust design space was achieved. The current specification for tablet mass allows tablets to be within 5% of the nominal value.

4.4.3 Verification

Based on pivotal study results, the Minitab® response optimiser was used to identify the optimal parameters for wet mix time and feeder speed to achieve a 95 % confidence interval on % RSD of tablet mass.

A 10 L verification batch was manufactured using a wet mix time of 62 seconds and a feeder speed of 22 rpm. The % RSD of tablet mass achieved for this batch was 0.96 %. This falls within the 95 % Confidence Interval of 0.301 to 1.154 % as calculated by Minitab®. Based on these results the design model has been verified.

4.5 Development of a Control Strategy

The initial risk assessment that was conducted highlighted the dosing, wet mixing, and compression stages of batch manufacture as having a high risk in influencing the dissolution behaviour of Product X. Following the outcome of the DoE studies, the quality risk assessment was reassessed. The revised risk assessment is shown in Table 4.12 below.

Table 4.12: Revised risk assessment for the manufacturing process

Formulation attributes	Finished Product CQA	Justification
Dosing	Assay	Employing a dosing time of 300 – 420 seconds and a dosing impeller speed of 66 – 134 rpm showed no influence on any physical characteristic that could impact assay of the final product. The risk is reduced to low.
	Dissolution	Employing a dosing time of 300 – 420 seconds and a dosing impeller speed of 66 – 134 rpm showed no impact on dissolution rate. Therefore the risk has been updated to low.
Wet mix	Assay	The wet mix time was found to significantly impact the % RSD of resultant tablet mass, which could influence assay. However, at the times employed during the study (40 – 140 seconds), the % RSD was still well within acceptable uniformity of mass limits, and the risk can be reduced to low.
	Dissolution	At the employed range of 40 – 140 seconds the wet mix time was found to not impact any physical characteristic that could influence dissolution rate. The risk is thus reduced to low.
Compression	Assay	The feeder speed was found to significantly impact on the % RSD of the tablet mass, which could influence assay. However, at the range employed of 18 – 52 rpm the % RSD was still well within the acceptable uniformity of mass limits for the product. The risk is reduced to low.
	Dissolution	At the range of 18 – 52 rpm the feeder speed was not found to significantly impact any physical characteristic that could influence dissolution rate. The risk is reduced to low.

Based on the DoE study, wet mix time in granulation and feeder speed in compression was found to impact % RSD of tablet mass and could thus affect UOM and result in poor compression performance. The current control strategy, which includes IPC's during granulation and compression as well as the finished product specifications used for batch release and stability testing, is suitable for the reformulated product. Granulation time must be be optimised during scale up from laboratory to production scale. Once the manufacturing process of the optimised product has been finalised at the products commercial batch size, the manufacturing recipe will be set for the high shear mixer/granulator. The batch manufacturing recipes are product specific and, once selected, run in automatic mode. At present the compression machine feeder speed is usually only monitored and not controlled during routine production. The range for compression feeder speed identified in the pivotal DoE study will be evaluated at a production scale and a recommended feeder speed range will be included in the batch manufacturing record.

4.6 Evaluation of the Project and Business Case

4.6.1 Determining whether the application of QbD resulted in an optimised product or process

The formulation and processing changes proposed in the QbD approach appear to have resolved the over-granulation and compression issues with no instances of over-granulation or tablet defects being observed at a laboratory scale.

A production scale trial batch manufactured as per the method proposed by the outsource development facility without colloidal silicone dioxide included in the formulation displayed poor flow properties. The granules also had a Carr Index and Hausner ratio of 26 and 1.3 respectively. The results obtained for the trial batch are similar to the average bulk and tap densities obtained for the commercial batches which have an average Carr and Hausner ratio of 28 and 1.4 respectively. Evaluation of the bulk and tap densities of the DoE pivotal study experimental batches where colloidal silicone was included in the formulation had Carr Indices ranging between 16 – 22 and Hausner ratios ranging between 1.2 – 1.3. Based on these results, the application of a QbD approach has improved granule flow at a laboratory scale. A production scale development batch using the DoE study learnings must still be performed in order to evaluate the flow properties of the granule.

4.6.2 Comparison of the control strategies between the QbD and traditional development approaches

The control strategies between the traditional and QbD approaches remain the same, except that the QbD approach will include a control strategy for compression feeder speed once scale up of the product has been completed. The optimal compression feeder speed range will be determined during the scale-up process. Once determined the optimum compression feeder speed range will be specified and the BMR and monitored during tablet compression.

4.6.3 Determining the actual cost of the QbD activities

Prior to embarking on the project, a project quote was generated using standard rates in the unit activity cost model. Activities related to the QbD approach included time spent manufacturing the QbD batches and the cost of the material needed to manufacture small scale batches.

The unit activity cost model that was used to generate the preliminary project costing budgeted R 25,309.08 for labour related to the QbD activities. This value was the standard cost reflected in the template when the project costing was performed before embarking on the QbD project. The timesheets for the employees who were involved in DoE batch manufacture for Product X were reviewed and the actual labour costs were calculated. It was not possible to isolate the actual activities, such as time spent by the formulation scientist drafting the production control sheets, due to the manner in which the timesheet system is configured. For comparative purposes, activities for each job description were totalled and compared. A breakdown of the budgeted labour cost for the time spent by personnel versus the actual cost of QbD-related activities is shown in Table 4.13.

Table 4.13: Comparison of budgeted cost versus actual cost of QbD-related activities

QbD-related activities	Cost as per project quote (ZAR)	Actual Cost (ZAR)
Labour costs for QbD batch manufacture	25,309.08	404, 225.46
Material costs	106,798.34	106,798.34
Analytical costs	501,604.67	40,773.00
Total costs	633,712.09	551, 796.80

The actual labour costs related to QbD batch manufacture were much higher than the cost that was budgeted for in the costing model. A total of 37 batches were manufactured as part of this study. Because the full scope of the DoE trial design had been finalised at the time of quote generation, the standard value was used for the purposes of the quote. The template used to generate the project costing budgeted for 30 batches. Despite the fact that more batches were manufactured in this study, the difference does not justify the large difference in labour costs. The main reason for the cost difference is that the costing model quote is not realistic in terms of the hours allocated for the DoE-related activities. When this activity was costed as part of the unit activity model the formulation team did not have much experience with conducting DoE studies. Therefore theoretical times were proposed for each activity. The costing model was reviewed in 2016 and the hour allocation has subsequently been revised based on feedback from the employees involved in DoE batch manufacture. Labour for DoE batch manufacture was based on an average of 30 batches. Following the 2016 costing model update, QbD-related activities were costed at R 362,944.07. This standard cost is more in line with the actual cost of labour for DoE batch manufacture for Product X.

When the project quote was generated, the analytical costs to test Product X allowed for full testing as per the finished product specification. This resulted in a very high value in terms of analytical costs. Based on the outcome of the risk assessment it was only necessary to perform very limited chemical analytical testing in the company's technical laboratory. Release dissolution profiles were generated for the 17 screening trial batches, which amounted to R 40,773.00. Further chemical testing was not required when conducting the pivotal study because the screening trial revealed that no factors significantly affected dissolution. The cost of material remained the same because material was specially procured for the DoE trials. The under spend in terms of the actual analytical cost offset the over spend in terms of the actual labour costs and resulted in the actual cost of the DoE batches amounting to a grand total of R 551,796.80. This resulted in the actual cost of QbD-related activities being R 81,915.29 less than originally budgeted for.

4.6.4 Calculating the projected Return on Investment (ROI) and payback period

In order to evaluate the profit margins for Product X the total revenue and cost of sales for Product X was requested from the company's finance department. The total volume required in order to satisfy the 2018 market demand is 2,987,483 units, which resulted in a nett profit of R 20,870,713.00. The development spend required in order to optimise the product can be justified based on the high nett profit for Product X.

Although the product optimisation will not influence market demand and sales volumes, the proposed changes are expected to resolve the granulation and compression problems experienced with Product X based on the results of the laboratory scale trials. Due to the fact that the manufacturing process must still be up-scaled to manufacture submission batches at a production scale, the financial benefit in terms of improved compression machine speeds cannot be calculated at this stage. During the review period, 6 batches could not be compressed and had to be discarded. The cost of these batches amounts to a total of R 1,203,780. Based on the assumption that a minimum of 6 batches of Product X will continue to be 'written off' due to granulation and compression issues without the intervention, the reduction in financial losses due to batch failures can be considered to be a direct financial gain. Based on this assumption, the estimated savings due to the reduction in batch write-offs were used in order to calculate the ROI. The cumulative savings based on batch rejections was extrapolated over a 5 year period, working on the assumption that without the

intervention a minimum of 6 batches would continue to be rejected per annum. The projected ROI over as 5 year period is shown below in Table 4.14.

Table 4.14: Projected return on investment

	Development Cost Based on Quote	Development Cost including actual labour & analytical cost	Estimated saving due a reduction in batch write-off's
Spend in ZAR	2,843,592.31	2,761,677.02	
Estimated ROI for Year 1	- 58%	- 56%	R 1,203,780.00
Estimated ROI for Year 2	-15%	-13%	R 2,407,560.00
Estimated ROI for Year 3	+ 27%	+ 31%	R 3,611,340.00
Estimated ROI for Year 4	+ 69%	+ 74%	R 4 815,120.00
Estimated ROI for Year 5	+ 112%	+ 118%	R 6,018,900.00

A positive ROI can be expected during the third year following implementation of the proposed changes.

The payback period was also calculated based on the actual time spent on QbD-related activities. The payback period in order to recover the costs incurred as a result of the development activities for the QbD approach is shown in Table 4.15.

Table 4.15: Projected payback period

	Development Cost Based on Quote	Development Cost including actual labour & analytical cost
Spend	R 2,843,592.31	R 2,761,677.02
Estimated saving due a reduction in batch write-off's	R 1,203,780	R 1,203,780
Payback period in years	2.5 years	2.5 years

CHAPTER 5 – CONCLUSION & RECOMENDATIONS

Product X was selected for optimisation because it was highlighted as a high volume problem product. The product required optimisation in order to improve granulation and compression performance and stop costly batch write-offs as a result of compression issues.

Product X is an existing product and therefore there was a great deal of existing information and product knowledge available when establishing the QTPP, CQA's, and knowledge baseline for the product. Product X was selected for optimisation because it was highlighted as a high volume problem product. Product X required optimisation in order to improve granulation and compression performance and eliminate costly batch write-offs. The registered product dossier, as well as the development, validation, and latest product quality review data were reviewed. This information assisted in justifying the CQA's based on actual product knowledge and experience. This resulted in fewer CQA's needing to be investigated when performing the risk assessment. Additional studies for the API and IPI were not required as sufficient data was already available to determine that their effects on the Product CQAs were low risk.

Risk assessments performed for the manufacturing process identified dosing, wet mixing, and compression to be high risk in terms of their effect on the Product CQA's. A screening and pivotal DoE study was planned focussing on these areas. A full factorial design was selected for the screening trial; in hindsight it would have been more valuable to have examined additional factors at a lower resolution; that is, a fractional factorial design. In addition, assay should have been tested as one of the responses. Despite the high content of API in the dosage form, the batch release assay results that formed part of the quality review period calculated CpK of less than 1.33, this indicates that the process is not capable. While the effect of the processing parameters adversely affecting assay was justified as low risk because the active makes up such a large portion of the finished product dosage form, the low process capability would warrant that assay be evaluated as part of any future studies. Notwithstanding the above shortfalls, the screening trial study was able to identify significant factors that could be further evaluated via a pivotal study.

The pivotal study revealed that wet mix time during granulation, as well as compression machine feeder speed, had a significant effect on % RSD of tablet mass, which can be

regarded as an indicator of tablet uniformity of mass. Compression machine feeder speed is usually a parameter that is monitored but not controlled. Thus, the application of QbD has also additionally identified the need to implement a control strategy for compression machine feeder speed. The application of QbD has therefore successfully resolved the granulation and compression issues experienced with Product X. In addition, it has provided statistical data which supports the product's current design space with the proposed formulation and process changes without negatively affecting the safety, efficacy, or quality of Product X.

The methodology proposed by Christopher Potter (2009) for applying QbD principles to optimise an existing product was therefore successfully implemented for Product X on a laboratory scale. Due to time constraints, the scale-up activities for Product X were outside the scope of this study. The learnings from the laboratory scale DoE studies will be applied when manufacturing the scale-up submission batches in order to determine the optimal wet mix duration and compression machine feeder speed. Although no other changes in the control strategy were proposed, the positive outcome was that no further regulatory changes would be required for Product X and the justification to support the control strategy is supported by the DoE studies. This additional data will support the post-registration amendments as justifications will be based on a science- and risk-based approach and could assist in preventing costly bioequivalence studies.

Despite the actual labour costs related to DoE batch manufacture being grossly understated in terms of the initial project costing, the actual analytical costs for testing of the DoE trials were much lower than originally anticipated. This resulted in the actual cost specifically related to DoE batch manufacture being less than expected. The hours allocated in the costing template for QbD batch manufacture have subsequently been updated. After reviewing the actual labour costs incurred for Product X, the theoretical cost in the updated costing model now appears to be more in line with what was observed during this study.

In terms of development project spend the application of QbD principles to optimise Product X increased the total cost of the project by about 20 %. Despite the additional spend, the return on investment in terms of total project cost was very good due to the fact that Product X is such a high volume product. The ability to successfully upscale the small scale process to production scale will resolve the granulation and compression issues and eliminate batch

write-offs. Based on the number of batches written off during the review period, development spend will be recovered within a period of less than 3 years.

There is no doubt that application of a QbD approach adds extra costs to an optimisation of an existing product, but the gain in institution knowledge may warrant the additional spend provided that the product generates sufficient profit. Due to the vast amount of information available it would be possible to apply a QbD approach to optimise an existing product without having to perform extensive DoE studies, which should theoretically reduce the cost of QbD-related activities.

Based on the outcome of the laboratory scale batches, it appears that the adoption of a formalised approach when embarking on a QbD improvement project for an existing product proves that the development cost and the gain in institutional knowledge would support the business case.

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